DEATH BY NEUROLOGICAL CRITERIA: A REVIEW OF DIAGNOSTIC PRACTISE, AIMED AT PROPOSAL OF A STANDARDISED PROTOCOL AT KNH.

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A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT FOR THE AWARD OF MASTER OF MEDICINE IN NEUROSURGERY AT THE UNIVERSITY OF NAIROBI.

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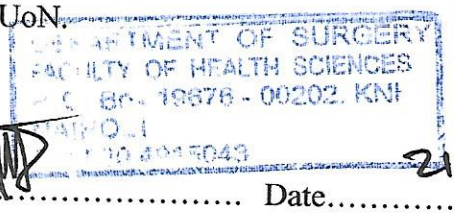

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DEDICATION

This research is dedicated to all critically ill patients in the Intensive Care Units and their loved ones. Your well-being is of utmost importance to us.

LIST OF ABBREVIATIONS AND ACRONYMNS

AAN: American Academy of Neurology

A-a: Alveolar-Arterial gas gradient

AAP: American Academy of Pediatrics

ABA: American Bar Association

ABGs: Arterial Blood Gases

ACLS: Advanced Cardiac Life Support

AMRC: Academy of Medical Royal Colleges

ANOVA: Analysis of Variance

ANZICS: Australian and New Zealand Intensive Care Society

BD: Brain Death

BI: Brain Injury

BP: Blood Pressure

CBF: Cerebral Blood Flow

CCU: Critical Care Unit

CD: Circulatory Death

CDC: Centre for Disease and Control

CBIG: Catastrophic Brain Injury Guidelines

CKD: Chronic Kidney Disease

CNS: Central Nervous System

CPAP: Continuous Positive Airway Pressure

CPP: Cerebral Perfusion Pressure

CPR: Cardiopulmonary Resuscitation

CTA: Computed Tomography Angiography

CT Scan: Computed Tomography Scan

DT: Delphi Technique

DI: Diabetes Insipidus

DICG: Declaration of Istanbul Custodian Group

DNC: Death by Neurologic Criteria

DOD: Determination of Death

EAANS: East African Association of Neurological Sciences

ECG: Electrocardiogram

ECMO: Extracorporeal Membrane Oxygenation

EEG: Electroencephalogram

FiO_2: Fraction of Inspired Oxygen

GBS: Guillaine barre Syndrome

GODT: Global Observatory on Donation and Transplantation

HDU: High Dependence Unit

HICs: High Income Countries

ICU: Intensive Care Unit

ILCOR: International Liaison Committee on Resuscitation

ISN: International Society of Nephrology

IVF: Intravenous Fluids

KNBTS: Kenya National Blood Transfusion Service

KNH: Kenyatta National Hospital

KTTA: Kenya Tissue and Transplant Authority

LICs: Low Income Countries

LMICs: Lower Middle Income Countries

MAP: Mean Arterial Pressure

MO: Medical Officer

MRI: Magnetic Resonance Imaging

MV: Mechanical Ventilation

NCCUSL: National Conference of Commissioners on Uniform State Laws

NCDs: Non-Communicable Diseases

NMBAs: Neuromuscular Blocking Agents

OCHA: United Nations Office for the Coordination of Humanitarian Affairs

OPTN: Organ Procurement and Transplantation Network

$PaCO_2$: Partial Pressure of CO_2

PEEP: Positive End Expiratory Pressure

PICU: Pediatric Intensive Care Unit

RLCs: Resource Limited Countries

ROSC: Return of Spontaneous Cardiac & Respiratory Activity

RRA: Resuscitation Room A

RRB: Resuscitation Room B

SBP: Systolic Blood Pressure

SD: Standard Deviation

SOL: Space Occupying Lesion

SpO_2: Percentage Oxygen Saturation in Blood

SRTR: Scientific Registry of Transplant Recipients

SSA: Sub-Saharan Africa

SSEPs: Somato-Sensory Evoked Potentials

TBI: Traumatic Brain Injury

TCAs: Tri-Cyclic Antidepressants

TTS: The Transplantation Society

UDDA: Uniform Determination Death Act

UON: University of Nairobi

UK: United Kingdom

US: Ultrasound Scan

USA: United States of America

WHO: World Health Organization

OPERATIONAL DEFINITIONS

Ancillary Test: An alternative or supplementary test to the neurological clinical exam for BD determination, which could not be reliably done.

Adult: A subject who is >18 years

Brain Death: A state of irreversible injury to the brain from which a patient cannot recover and is deemed to no longer be alive

Children: Pediatric patients between the ages of 1 to 18 years

Coma: A state of unresponsiveness to a strong noxious stimuli

Circulatory Death: A state in which the patient is confirmed to have lost life by virtue of absent cardio-Respiratory activity

Critical Care Unit: An Intensive care unit in a hospital, where critically ill patients are treated

Child: A person less than 18 years of age

Determination of Death: A method of evaluation by which a doctor that the patient is no longer alive

Delphi Technique: A qualitative method data collection on complex multidisciplinary topics in which a coordinator recruits relevant experts and sends them questionnaires online to capture their unique views

Delphi Panel: A group so experts so empaneled by the coordinator

Ethnicity: A Kenyan tribe from which the subject hails

Expert Panel: Same as a Delphi panel

Indisposed kin: A potential subject of the study, admitted to CCU and on a MV and DNC, on behalf of whom informed consent is signed by the Next of Kin.

Infant: Pediatric patient between the ages of 1 month to 1 year

Neurological Death: Similar to Brain death

Next of Kin: A close relation of the patient who has been determined DNC & a subject of this study

Premature Neonate: A baby bone before 37 weeks of Gestation and is less than 30 days of life

Term Newborn: A pediatric patient born at ≥ 37 weeks of Gestation, aged 1 to 30 days of life.

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ABSTRACT

Introduction: The definition and diagnosis of death has become more complicated because of the advancement in critical care medicine especially advanced respiratory and cardiac support.[1] Early on, death was only diagnosed with the cessation of cardiorespiratory activity. It was noted however that some patients who had sustained fatal brain injury would remain in irreversible coma despite respiratory system being supported by MV.[1] The Concept of Brain Death thus was born. In developed countries, there has been a concerted effort to more clearly define the concept and develop guidelines on its diagnosis. Advance in transplant medicine and advantages of deceased donors have contributed the need for stronger legislative regulations. This study has reviewed the practice in KNH, identified gaps in practice and recommended a standardized protocol for DNC.[2]

Study Title: Death by Neurological Criteria: A review of diagnostic practice, aimed at proposal of a standardized protocol at KNH

Study Design: Descriptive Cross-Sectional

Broad Objective: To review the practice of determining Death by Neurological Criteria at KNH

Study Area: Critical Care Units in KNH

Study Population: All patients diagnosed with BD in KNH during the study

Sample Size: Thirty eight patients

Data Collection: Used a Data collection tool developed from AAN/AAP checklist on diagnosing BD

Data Analysis: SPSS v29.0 Used. Univariate analysis was done using Measures of central tendency & dispersion. Bivariate analysis using Chi-Square and Fishers Exact Test, ANOVA.

Study Results: During the study period (July-December 2022), a 38 patients were recruited into the study. Age range was 9 months to 82 years with a mean and median of 41 years. Adults were 84%. Patients were distributed in 6 CCUs, with Main CCU having 18 (47%). The initial DNC exam was done > 24hours after severe TBI or a CPR event, for all patients and all had acceptable inter-exam interval for age. All patients had a pre-exam GCS of 2T and had a radiologically confirmed cause of irreversible coma. Severe TBI was the commonest cause of Coma (44.7%) Co-morbidities were noted to contribute negatively to the disease process of the patient. Confounders to BD evaluation accounted for included: Temperature, Blood pressure, CNS

Depressants and metabolic disorders. All subjects had a core temperature > 35^0C. About 29% of patients had a pre-exam SBP below 2 SD age in the intial DNC exam. Prior to 1st DNC, 84% of patients were on a CNS depressant. The figure was 52.6% for the 2nd exam. The most common CNS depressant was Phenytoin. Drug levels were not measured prior to BD exam. Severe metabolic disorders were noted prior 1st (39.5%) and 2nd (17%) BD exam. The commonest of these was severe metabolic acidosis. Neurologic examination was the most consistently done aspect of BD exam. All brainstem reflexes were done in most patients. Oculovestibular reflex was not done in patients with otorrhea. Pupillary size varied from 4-8mm. Apnoea test was done only 10 out of 62 exams. No documented reason was given for not doing it. Where it was done, the standard procedure was followed. The test was aborted in 5 examinations due to bradycardia and desaturations. No ancillary test was done for any patient. BD exams were largely done by resident doctors especially in neurosurgery, followed by anesthesia. Post DNC diagnosis, MV settings and medical treatment were de-escalated. Supportive care was generally maintained. CPR was noted to have been done for all patients at asystole, inspite of BD. No deceased organ donation was reported. No formal documentation structure or checklist for BD evaluation was available.

Conclusion: The practice of BD evaluation in KNH is not yet standardized. Different examiners may leave out certain sections of the exam. Some confounders were not completely corrected prior to a few of the examinations. Apnoea test, a crucial part of the exam, was not consistently done. Having a standardized protocol and checklist will ensure adherence to the process and improve documentation.

CHAPTER 1.0: INTRODUCTION

1.1: BACKROUND

In the course of patient care, some patients recover whilst others die. Death is a common medical occurrence with legal, religious and socio-cultural implications that require standardized clinical practices for its diagnosis and legal regulation.[3] Doctors play a critical role in certifying death, especially in Hospital settings.[4,5] Death was once understood to mean "The loss of life; the act of ceasing to be; is described by specialists as the complete elimination of blood circulation and the animal's subsequent loss of vital processes like respiration, pulse, etc."[6–8] In the era of advancement in medical technology, especially in critical care, wide availability of mechanical ventilators meant that the patient's cardiorespiratory activity could be supported even after cessation of brain function.[9,10] As a result, it became necessary to expand the definition of death to include a neurologic standard.[7,9] Conceptually, "brain death (BD)" is described as "irreversible brain function loss including the brainstem".[7] Consequently, death can be determined or diagnosed via two main mechanisms.[10] First is "Circulatory death" (CD), characterized by an unresponsive patient, not breathing and lacks cardiac or circulatory activity. Second, "Death by Neurologic Criteria" (DNC), also called "Brain Death" (BD), is characterized by a comatose patient, evaluated to be devoid of brain function including brainstem and inability to maintain spontaneous breathing.[11]

There is paucity of legal guidelines in most of Sub-Saharan Africa (SSA) regarding BD. In Resource Limited Countries (RLC) such as Kenya, several barriers to establishment of BD laws exist and include: Ethno-cultural and religious plurality which creates a complex view regarding death. This negatively impacts development of uniform guidelines in relation to BD.[7] The definition of BD must be agreed upon by the medical community and the general public before BD legislation can be developed. Major advantages would follow such legislative policy, including: Standardized clinical practice as it relates to diagnosis & certification of death; limit futile and prolonged medical interventions to BD patients in the Intensive Care Units (ICU); enhance judicious allocation of limited resources for critical care especially in RLCs.[7,8]

The oldest and largest referral hospital in East and Central Africa, Kenya's Kenyatta National Hospital (KNH), was founded in 1901 and is located in Nairobi. With more than 1,800 beds, it can accommodate an average of 700,000 inpatients each year. Open heart surgery,

neurosurgery, orthopedic surgery, reconstructive surgery, burns management, new-born services, ophthalmology (cornea transplant), oncology, palliative care, and renal services (including kidney transplants) are just a few of the specialty services it provides.[12] According to United Nations Office for the Coordination of Humanitarian Affairs (OCHA), in 2020, Kenya had a total of 518 ICU bed capacity, 55 of which were based in KNH.[13]

Kamithu, 1986, in his thesis titled *"The Brain Death Syndrome in the Intensive Care Unit, Kenyatta National Hospital"*, did a 10 year retrospective study on 30 'brain-dead' patients in ICU at KNH.[14] According to his research, the two most frequent causes of brain death comprise, head injury (43.4%) and brain tumors (13.4%). In diagnosing brain death, all patients had none-reacting, dilated pupils. None of the patients had any motor response along the cranial nerves. The caloric reflex was tested in twelve (40%), Doll's eyes was tested in six (20%) and the oropharyngeal reflex was tested in eight patients (26.6%). Four patients (13.3%) had the atropine test, whilst the apnoea test was not performed on the others.[15] After diagnosis of BD, confirmatory tests were done in 50% of the patients: Electroencephalogram (EEG) in 14 patients, while 1 patient underwent carotid angiography.[14] Notably, no protocol on determination of Brain death was reported to have been followed.[2] It was not clear either why some brainstem function tests were used in some patients and omitted in others.[8]

After BD diagnosis, mechanical ventilation was continued for all patients until asystole. In 50% of the patients, medication was continued unchanged. In eleven patients (36.7%), all medication was stopped, leaving intravenous fluids. In four patients (13.3%), the number of drugs were reduced.[14]

This study reviews the current practice in KNH ICUs regarding DNC, aimed at proposing a standardized protocol for all critical care units. This hopefully, will inform practice not only in KNH but also nationally, regionally and in other LRCs. It also aims to inform legislative policy discussion and framework, to increase legal clarity in practice related to DNC on issues including but not limited to: Limiting prolonged and futile interventions; deceased organ donor transplant programmes and termination of mechanical ventilation after DNC.[7]

This is a descriptive cross-sectional study, undertaken in the critical care units in KNH between June and December of 2022.

1.2: JUSTIFICATION OF THE STUDY

Kenyatta National Hospital in Kenya, provides important health care services, including critical care to a large catchment area- Eastern Africa and beyond.[12] Being in the SSA, a region with LMICs and LICs, judicious use of Health resources is very important.[7] Because of the high demand of critical care services and especially mechanical ventilation (MV), it is desirable that only patients who stand to benefit are placed and maintained on MV. Patients who have been determined to be dead either by CD or DNC, and remain on MV, receive costly but futile care at the expense of critically ill patients with a good chance of survival.[7]

Kenyatta National Hospital currently lacks an articulated protocol for diagnosis of BD, with notable lack of uniformity in DNC.[2,14] It is important to have a standardized protocol on diagnosis of BD and articulate clearly post BD handling of such patients.[10] Transplant surgeries are increasing in Kenya and SSA region. KNH is a major transplant centre in the region.[105] Clear and protocolized DNC can spur discussion on deceased organ donation and therefore alleviate organ donor shortages.[88]

The study aims to spur mainly national but also regional discussion on streamlining the legal and policy framework around BD, organ and tissue transplantation.[41]

CHAPTER 2.0: LITERATURE REVIEW

2.1: DETERMINATION OF DEATH (DOD)

In a variety of settings, including those involving a natural process and those involving artificial interventions maintaining cardiorespiratory activity in the absence of a patient's capacity to breathe on their own, the evaluation and proof of death are necessary.[16] Since the 14th-16th century, it was a common practice for the dead to be observed for 2-3 days undisturbed, to be sure that they were not alive.[17] Traditionally, death had been defined using the common law definition as stated in **Black's Law Dictionary** as, "*The loss of life; the act of ceasing to be; is described by specialists as the complete elimination of blood circulation and the animal's subsequent loss of vital processes like respiration, pulse, etc.*"[6,7,17] The use of mechanical breathing and cardiovascular support in intensive care units rose in the later part of the 20th century.[18] In patients with severe brain injuries, cerebral circulatory arrest, no encephalic functions, and a lack of spontaneous breathing, this procedure allowed maintenance of heart activity.[11]

Defining the precise moment of death was therefore difficult yet important because it helped avoid usage of pointless medical procedures on people who had already passed away.[11] It became scientifically evident that death resulted from the irreversible loss of brain function, either from an extra-cranial cause—lack of circulation—or from an intra-cranial cause—devastating brain injury.[11] Dr Harvey Cushing, in 1902, was the first to report cessation of cerebral blood flow (CBF), occasioned by a raised intracranial pressure (ICP) that exceeded the mean arterial pressure in monkeys.[19] He also noted a case where MV was able to prolong cardiac function for 23 hours after cessation of spontaneous breathing in a brain tumor patient.[17,20] In 2014, a World Health Organization (WHO) Technical Expert Consultation on ***Clinical Criteria for the Determination of Death,*** noted that: There were many different ways to pass away, but only one way to be dead. For this reason, it was crucial to reach international agreement on the clinical criteria for the determination of death in order to uphold public confidence and to advance ethical practices that upheld peoples' basic rights and promoted the quality of life.[11]

2.2: ALGORITHMS ON CLINICAL DOD

WHO Expert consultation on clinical criteria for DOD, based on Cochrane review, developed two classic algorithms DOD, viz: **"brain death"** (BD) and **"circulatory death"** (CD) and that whichever of the 2 was used, would result in a single end-point identified as "death".[10] The team noted that: the same definition of death should apply everywhere; the process of DOD should not change depending on patient's organ donation status; the algorithms needed to identify the tests required at each stage of the process and would be applicable to both adults and children.[11,21]

2.3: DOD BY CARDIOCIRCULATORY DEATH

According to the International Liaison Committee on Resuscitation's (ILCOR) recommendations, cardiocirculatory arrest has the following characteristics:[22,23] (1) Lack of response (2) absence of circulation, (3) no breathing or only sporadic gasps. The process of DOD won't begin for a patient who has been successfully revived from a cardiocirculatory arrest unless either (1) cardiopulmonary resuscitation (CPR) is not tried, or (2) CPR is attempted but fails.[11,22–24] The next step is to use clinical and, occasionally, instrumental tests to confirm that there is no circulation. Clinical evidence that there is no circulation includes the following: (1) no central pulse on palpation; (2) no heart sound on auscultation; (3) no breathing; and (4) no pupillary reactions to light. If necessary, the following instrumental exams should be carried out to demonstrate: (1) asystole, or pulseless electrical activity, on a continuous ECG display; (2) absence of pulsatile flow during intra-arterial pressure monitoring; (3) absence of cardiac contractile activity using echocardiography. However, it is not required to use instrumental tests.[11,22–24]

It is crucial to wait several minutes after the clinical and/or instrumental examinations are finished, to be sure there hasn't been a spontaneous recovery of cardiac or respiratory function (ROSC). The bare minimum wait time should be five minutes, however nations, hospitals, and CCUs are free to set their own waiting times. The DOD is made after the waiting period has elapsed with no ROSC.[11,22–24]

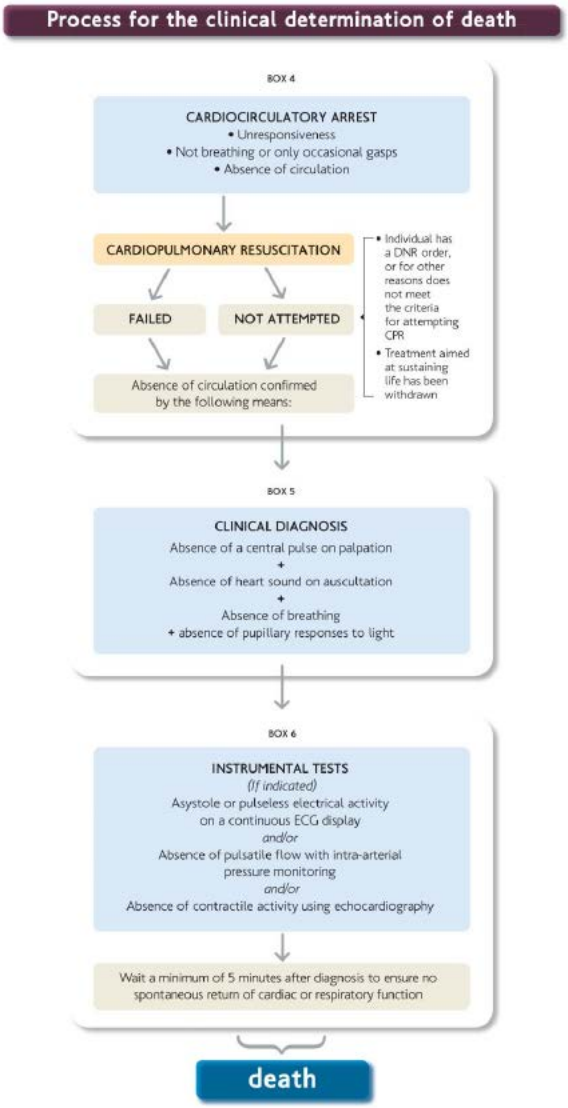


Fig. 1: Algorithm on Cardiocirculatory death.[11]

2.4: DOD BY NEUROLOGIC CRITERIA (DNC)

2.4.1: EVOLUTION OF PRACTISE RELATED TO DNC

2.4.1.1: Internationally

The term "**coma dépassé**" (or "irreversible coma") originally appeared in the medical literature thanks to Mollaret and Goulon, who presented the first description of 23 patients with this clinical state in 1959 at the 23rd International Neurological Meeting.[9,10,25–27] This state went beyond the most severe kind of coma and involved the "complete and definitive elimination of vegetative functions."[25,28–31] Unresponsiveness and lack of receptivity were included to the definition of irreversible coma in 1968 by an **ad hoc committee at Harvard Medical**

School.[30,31] This group was generally credited for drawing the attention of the American medical community to the legal and scientific difficulties surrounding BD.[30]

The committee took note of how death was defined, which is "*The loss of life; the act of ceasing to be; is described by specialists as the complete elimination of blood circulation and the animal's subsequent loss of vital processes like respiration, pulse, etc*" according to the Black's Law Dictionary.[6,28,32] The Committee promoted the idea that advancements in critical care treatment had made it possible for people to survive who had suffered severe brain injuries that were previously always fatal. However, these individuals were left with irreparable damage to their entire brains, lacking even vestiges of their former abilities. As a result, it suggested developing a brand-new category of physical death called BD that might be used in cases where complete brain function had been lost. It defined BD as *"All brain functions, including those of the brainstem, are permanently lost characterized by a coma, the lack of brainstem reflexes, and apnoea."*[29,30,33,34]

Different DNC-related legislation achievements were noteworthy in numerous different nations. The first state statute in USA was passed by Kansas in 1970. Mohandas and Chou reaffirmed the brainstem's importance in brain damage and demise in 1971.[25,28,29] Professors Capron and Kass further honed the ideas and legal standards in 1972.[7,29] The BD laws passed by more than a dozen states varied significantly. The American Bar Association (ABA) Law and Medicine Committee addressed the need for uniformity in guidelines in 1975 when it created the definitions and guidelines that would later serve as the Model Definition of Death Act.[10,29,35] The Uniform Brain Death Act was created in 1978 by the National Conference of Commissioners on Uniform State Laws (NCCUSL), in an effort to reduce the legal uncertainty surrounding DOD. The law was updated in 1981 to become the Uniform Determination of Death Act (UDDA), and most US States and the District of Columbia have since ratified it.[7,9,35,36]

The UDDA made a two-part statement, first restating the common law understanding of what constituted death and, crucially, expanding this definition to encompass people who had "*irreversible loss of all brain function, including that of the brain stem.*"[35] Similar recommendations regarding pediatric BD have been released by both the AAP and the AAN.[10,37–39]

A definition of BD was created by consensus among experts in the UK to answer concerns about "when to turn off the ventilator" in the era of "intensive care procedures and their widespread availability."[40] The report concluded that *"it is agreed that brain death is the permanent functional death of the brain stem and that further mechanical support is futile and should be withdrawn once this has occurred."*[6,28,40] Even though there isn't a statute in the UK that defines death, BD is protected by common law and is a recognized definition of death in the country.[16,40]

2.4.1.2: Sub-Saharan Africa & Kenya

There is no Kenyan law that clearly defines death or attempts to interpret BD, according to a study of the Kenyan Law Database.[41] The **Human Tissue Act**, an Act of Parliament that governs the use of dead persons' body parts, offers the closest resemblance to a definition (The Republic of Kenya, 1967).[7,42] Even in these situations, the Tissue Act does not define death; it only states that a licensed physician must "*satisfy themselves by firsthand assessment that life is extinct*".[7,43]

2.4.2: GUIDELINES IN DIAGNOSIS OF DNC

Drake et al, 2017, recommends that every hospital providing critical care for patients with severe brain injury should have a policy for BD determination.[28] Multiple criteria on DNC have been developed over time in various countries and jurisdictions.[36] They include **USA:** The Harvard Criteria[30], The Minnesota Criteria, Philadelphia Criteria, AAN, AAP among others[37,38]; **Great Britain:** Guidelines by Academy of Medical Royal Colleges (AMRCs).[16] **Other Jurisdictions:** Argentina, Australia, Canada, Czechoslovakia, Finland, France, Greece, Norway and Spain etc, have unique DNC guidelines.[7,10,26,29,32,44–50] AMRCs and The Japanese Ad Hoc Commission on Brain Death and Organ Transplantation in 1991, have recommended that irreversible brainstem dysfunction is sufficient to diagnose death.[17]

2.4.2.1: WHO Expert consultation on clinical criteria for DOD – commentary on DNC[11,51]

Its purpose is to clarify how death can be evaluated in situations including "neurological arrest," in which case the conventional cardio-circulatory DOD criteria cannot be applied.[11] The method consists of three main parts: (1) the fundamental conditions that must be met in order for the algorithm to be activated; (2) examination and then diagnosis clinically; and (3) confirmation tests to guarantee irreversibility. [11] The fundamental requirements are a diagnosis of neurological

arrest and any concomitant evaluations meant to rule out the presence of any confounding factors for the neurological state. The rest of the DNC evaluation proceeds systematically as shown in the figure below.[11,51]

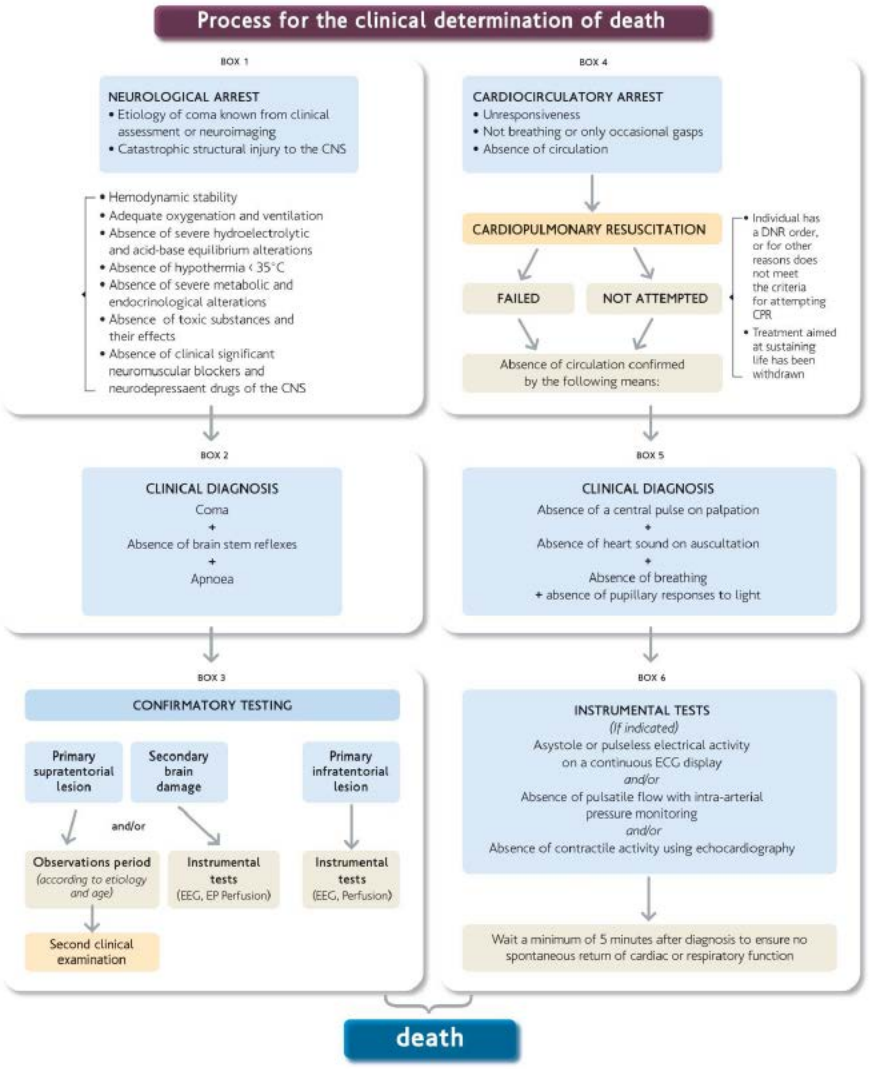


Fig. 2: Summary of clinical DOD: Two different workflows, but common endpoint- Death.[11,51]

2.4.2.2:The Harvard Criteria[30]

Published by the *Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death.*[7,36,52] It formed the foundation upon which many criteria on DNC were developed and improved around the world. The committee's goal was to establish an irreversible coma as the new standard for death.[30,52] This was necessitated by increased resuscitative and

technological advancement in critical care, which translated to patients with fatal brain injuries with vital cardiorespiratory functions sustained artificially.[5] Additionally, the prevailing *Heart-Lung Criteria* for defining death, was controversial for purposes of obtaining transplant organs.[30,52]

Harvard criteria	**Minnesota criteria**	**Philadelphia criteria.**
1. Unreceptivity and unresponsiveness	1. Known but irreplaceable intracranial tension	1.Absence of responsiveness to internal and external environment
2. No movements	2. No spontaneous movements	2.No spontaneous breathing for more than 3 min
3. Apnoea	3. Apnoea	3.Absence muscular movements with generalized flaccidity
4. Absence of elicitable reflexes	4. Absence of brain stem reflexes	4.Absence of reflexes and responses
5. Isoelectric electroencephalogram		5. Arterial pressure lowering without medications or other interventions
Two separate teams must independently announce these results, with a 6-hour gap between each declaration.	For a period of 12 hours, all results must remain constant.	6. An isoelectric electroencephalogram that was spontaneously recorded while being stimulated by touch and sound

Table 1: Summary components of various DNC guidelines[5,7,10,29,32,46–50]

2.4.2.3: AAN Guidelines (See Appendix III)

It's the main authority in guidelines regarding DOD in the USA. Initial guidelines developed in 1995, with an update in 2010 focused on DOD by DNC in adults.[53,54] The goals of the 2010 update were to provide evidentiary answers to five fundamental questions regarding these guidelines[55] i.e. whether any patients who met the clinical criteria for BD ever experienced neurologic function recovery; what the right observation period was to ensure that the cessation of neurologic function was irreversible; whether complex motor movements were occasionally seen in BD; the safety of the techniques used to determine apnea; and whether newer ancillary tests could identify BD patients.[55]

2.4.2.4:AAP guidelines[37] (See Appendix IV)

Initially developed in 1987 and revised in 2012.[37–39] It streamlined DOD by Neurologic criteria in pediatric patients and developed recommendations and a checklist to be utilized in the process.[37,38,56] Below is a summary algorithm of DNC evaluation in pediatrics as recommended by AAP.

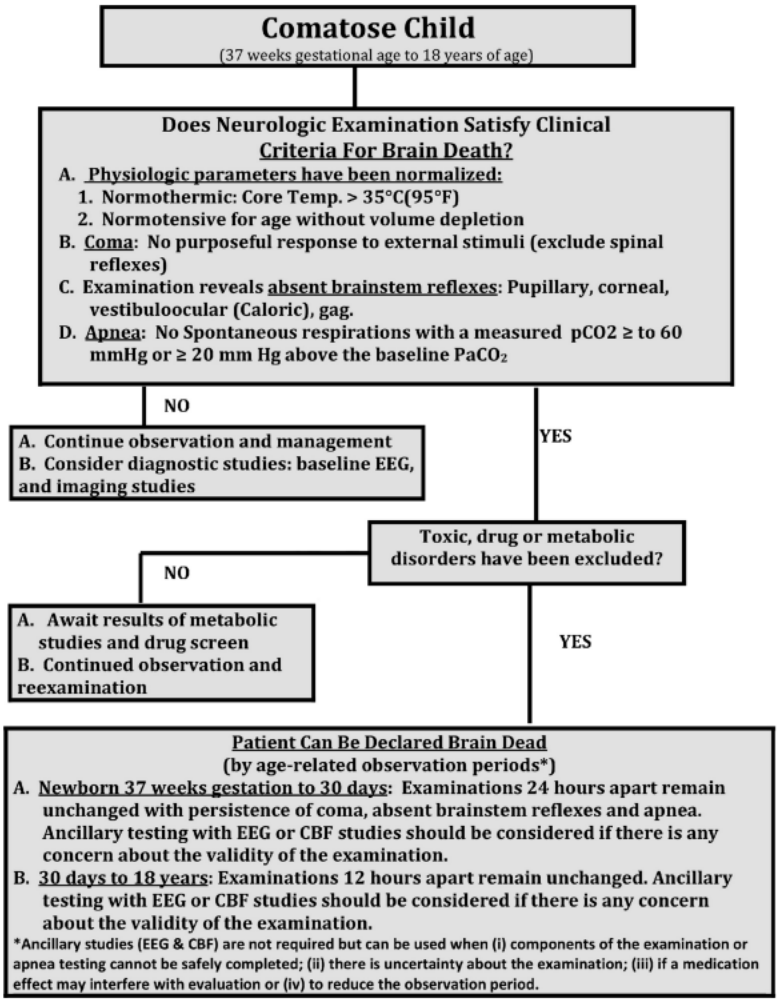


Fig. 3: Algorithm to Diagnose Brain Death in Infants and Children[37,38,56]

2.5: IMPORTANT COMPONENTS OF DNC GUIDELINES [5,7,17,18,25,26,28,29,49,50,55–62]

The steps for making the diagnosis of BD in a comatose patient (See Appendices III & IV)[49,63] are as follows: (A) Prove that the cause of the coma is a disorder that can result in permanent BD; (B) Rule out reversible causes; and (C) Show the absence of all testable cranial nerve and brainstem responses.[60] Before making a diagnosis of BD based on clinical tests, the conditions in A) and B) must be met.[33,64]

2.5.1: AGE OF RELIABILITY OF DNC

The age criteria is not controversial in DNC guidelines for adult patients.[10,21,48] Diagnosis of BD in newborns evokes some controversy, primarily because of paucity of literature on the subject. It is unclear how physiologic variations in infant brain metabolism, CBF, and damage response may influence BD evaluation.[37,38] DNC is complicated by maturational lag in newborns, and usually unreliable in preterm infants.[1,33,56] The AAP indicates that term neonates and babies can be diagnosed with BD if the doctor is aware of the limits of DNC examination and auxiliary tests in this age bracket.[37,38] It is advised to wait 24 hours before assessing the term newborn for BD. Lack of adequate studies and data precludes making DNC recommendations for preterm infants.[1,33,37,38,56]

2.5.2: TIMING OF EXAMINATION FOR DNC

2.5.2.1: Observation period.

The first formal examination can be performed once the patient satisfies the criteria in A) and B) and cranial nerve and brainstem responses have been absent for at least 4 hours.[64] Brainstem testing shouldn't be done until at least 24 hours following ROSC if cardio-respiratory arrest is what caused the coma. There is paucity of high quality data on the most ideal timing to start evaluation for BD.[64] The Harvard criteria required an observation period of at least one hour for spontaneous muscular or respiratory movements, whilst patients on MV, would require 3 minutes of observation after the ventilator was turned off.[30,52]

2.5.2.2: Inter-Examination period.

The *Committee for Determination of Brain Death in Infants Children* upheld the 1987 BD guidelines that recommended the conduct of two BD exams, each followed by an observational period.[30,52] ***Drake et al, 2017,*** however notes that, little evidence exists indicating superiority of 2 clinical examinations to 1, even though most hospitals and states statutorily require 2.[28] AAP guidelines recommends an inter-examination 24 hours of surveillance for newborns and 12 hours for children and infants.[30,52] The objective of the initial (first) examination is to certify that the patient satisfies the BD neurologic examination requirements. The second (final) examination confirms DNC on the basis of unchanged neurological findings and irreversibility of the patient's condition.[30,52] The inter-examination period can be reduced by use of an ancillary study.[30,52,56]

2.5.3: PREREQUISITES FOR DNC

Establishment of irreversible and proximate cause of coma

There is a general agreement across different BD guidelines regarding antecedent requirements to BD evaluation.[48,59,65] These principles are derived from the UDDA definition of BD, "*stoppage of all brain activities, including those of the brain stem,"* and presuppose that the doctors will evaluate for the existence of unresponsive coma, the lack of brainstem reflexes, and the lack of airflow limitation with hypercapnia.[31,48] In the Harvard Criteria, the ad hoc committee noted that for all intents and purposes, a brain or other organ is dead if it no longer works and has no chance of ever doing so.[52]

Determining the characteristics of patients with permanently non-functioning brain, the patient would fulfill the following conditions[30,52]: 1) ***Unreceptivity and Unresponsitivity***- utter unresponsiveness and total unawareness to both inner need and externally imposed, very unpleasant stimuli.[48,59,65] This defined irreversible coma.[30,52]Coma is assessed by inducing a noxious stimulus to all 4 extremities (nail beds), trunk (sternum), and head (supraorbital nerve or temporomandibular joint).[28] 2) ***No movements or Breathing***: Required observations by a physician for a period of at least one hour for spontaneous muscular or respiratory movements. For patients on MV, the ventilator would be turned off for 3 minutes whilst observing for spontaneous respiration.[30,52] 3) ***No Reflexes***: It was noted that irreversible coma with abolition of

CNS activity was demonstrated partially by a lack of elicitable reflexes.[30,52] 4) ***Flat Electroencephalogram (EEG):*** A flat or isoelectric EEG was of high confirming significance.

The cause of coma will mostly be derived from the history, physical examination, neuroimaging, and a battery of laboratory tests.[55] Conditions that are reversible and may result in the loss of brainstem reflexes such as poisoning, brainstem encephalitis, Guillain-Barré syndrome (GBS), and others must be ruled out[37,38]. A firm diagnosis must be made of the neurological illness causing the severe brain injury. A CT scan, angiography, or MRI scan must show neuroimaging evidence of significant structural brain damage consistent with substantial and irreversible loss of brain function.[57,60] Repeat scans may be necessary to firm up presence of irreversible brain injury.[37,38,57,60]

2.5.4: CONFOUNDERS TO BD DIAGNOSIS

Brain death determination is based fundamentally on neurological examination.[10,55] It should therefore be performed under normal, age-appropriate physiologic parameters. Many factors may potentially influence and must therefore be corrected prior to DNC examination to avoid false positive or false negative outcomes.[10,48,55,66] Across many centers, main areas of persistent practice variance include the exclusion of confounders of BD determination.[57,66] A recent survey done by ***Wang et al, 2017,*** showed that of the hospitals surveyed, only 56% excluded hypotension and only 79% excluded hypothermia, during DNC evaluation.[28] Important confounding factors include:

2.5.4.1: Shock or persistent hypotension

AAP BD guidelines advise that SBP or MAP be within acceptable range based on age.[37,38] It is advised to use an indwelling arterial catheter for the twin purpose of monitoring BP and ABGs during the DNC examination.[37,38] Systolic Blood pressure should be > 90mmHg, with a MAP > 60mmHg. For blood pressure maintenance during DNC examination, fluid infusion and vasopressors may be employed.[1,66]

2.5.4.2: Hypothermia

Hypothermia is a CNS depressant and may result in a false BD diagnosis.[37,38] It also alters metabolism and clearance of CNS depressant medications. Different DNC guidelines differ slightly on definition of hypothermia. AAP and AAN guidelines recommend that a core body temperature of >35^{0}C (95^{0}F) is mandatory during the DNC examination.[37,38] Other guidelines indicate hypothermia as being a temperature below 32.2 ^{0}C.[30,52] Hypothermic patients must be rewarmed prior to the exam.[37,38] Therapeutic hypothermia can slow down the metabolism of sedatives and neurological recovery. After cardiac arrest, brainstem testing should continue unless the temperature recorded has been below 35°C for more than 6 hours continuously [67]; this necessitates a delay of 24 hours before clinical tests for BD. After therapeutic hypothermia to 32-34^{o}C, the return of motor reflexes may take up to 5 days, therefore brain stem testing should be similarly postponed.[67]

2.5.4.3: Severe Metabolic Anomalies

They include reversible conditions like severe electrolyte, pH anomalies, hyper- and hypoglycemia, severe hepatic or renal failure, endocrine disorders eg Hypothyroidism, pan-hypopituitarism, adrenal dysfunction or inborn errors of metabolism.[37,38] It's vital to identify and treat these conditions before DNC evaluation. This is especially relevant where clinical history does not provide clarity on the cause of coma.[37,38] Hypernatremia, typically brought on by diabetes insipidus, is the most prevalent metabolic anomaly in BD patients. For brainstem testing, serum sodium levels between 130-155 mmol/L are acceptable ranges. Blood levels of magnesium, phosphate, and glucose shouldn't be severely out of range.[1,66]

2.5.4.4: Drug Intoxications and Poisoning

They must be ruled out as causes of coma.[11] The commonly used offending drugs include: Neuromuscular Blocking Agents (NMBAs), opioids, sedatives, barbiturates, intravenous and inhalational anesthetics, antiepileptic agents, and alcohols.[1,11,66] They're CNS depressants hence interfere with BD examination.[37,38] If the drugs were recently ingested or administered, their serum levels should measured. AAP and AAN guidelines recommend that drug levels in a low to mid therapeutic range are allowable prior to DNC examination.[37,38] Clearance of the drug based on patient age, weight, organ dysfunction, drug elimination half-life, amount of drug

administered, and presence of known active drug metabolites, must be borne in mind during this evaluation.[37,38] Adequate clearance of NMBAs once stopped, can be evaluated using a nerve stimulator, assessing the neuromuscular junction activity and twitch response.[37,38,56]

Toxins, poisons and drug overdose may cause coma. Good history is vital. Obtain a toxicology screen where applicable.[1,11,66] Before determining whether someone has brain death, their level blood alcohol should be under the threshold for driving (0.08%).[1,11,66]

2.5.4.5: Post-CPR DNC Examination

Most BD guidelines recommend deferral of DNC examination by at least 24 hours following successful CPR after a cardio-pulmonary arrest.[67] Neurologic evaluation has been found to be unreliable immediately post CPR or after acute brain injury.[29,37,38]

2.5.4.6: High Spinal Cord Injury

May reduce the validity of DNC examination due to inability of spontaneous breathing efforts. It also precludes use of Oculocephalic reflex in neurologic examination. Use of Oculovestibular reflex and/or ancillary test may be justifiable in this circumstance.[37,38] Chest wall and lung injury will also preclude aspects of BD examination such as apnoea testing.

2.5.4.7: Severe Neuromuscular Disease

Some disease conditions eg Guillain Barre Syndrome (GBS), mimic coma but are reversible.[1,66] It is advisable to postpone the DNC examination, continually observe the patient until these conditions resolve. Additionally, an ancillary study may be used to ensure false positive or false negative BD diagnosis is avoided.[37,38]

2.5.5: NEUROLOGIC EXAMINATION

2.5.5.1: Coma

AAP and AAN guidelines, define coma as a state in which the patient exhibits vocalization, full loss of consciousness, and volitional activity.[37,38] A Glasgow Coma Scale (GCS) score of 3/15 or 2T/15 (for patient on MV), is definitive for this state (See Appendix V).[37,38] For purposes of DNC evaluation, patients who are unconscious must show no signs of

response. With the exception of spinally mediated reflexes, there is no eye opening or movement in response to painful stimuli.[37,38]

2.5.5.2: Neurological Responses: Loss of Brainstem Reflexes

The minimal number of brainstem reflexes that must be examined has not been documented or subject to agreement (although apnoea testing is essential). A helpful generalization found in the Australian and New Zealand Intensive Care Society (ANZICS) Guidelines is that you should be able to examine *'at least one eye and at least one ear'*.[44,60]

2.5.5.2.1: Pupillary Reflexes

The cranial nerves II and III carry the reflex arc. The results of this test may be impacted by past eye surgery (such as iridectomy) or a history of pre-existing pupillary abnormalities. Use a bright light in the examination room and muted lighting to examine each eye. Rapid pupil constriction is the typical response.[1,11,66] Round, oval, or asymmetrical pupils can indicate BD. In most BD patients, the pupils are fixed, in mid position or fully dilated (4-9mm) and unresponsive to bright light bilaterally. If uncertain of the pupillary response, a magnifying glass should be used.[37,38]

Major intoxication can result in false positive pupillary reflexes. However, severe barbiturate overdose can cause loss of pupil response to light. After poisoning with antihistamines, tricyclic antidepressants (TCAs), amphetamines, cocaine, phenylephrine, and other sympathomimetic drugs, mydriasis (8 or 9 mm) or mid-position pupils (6 or 7 mm) are observed. Miosis (1-2 mm) is a sign of the presence of drugs that inhibit cholinesterase, as well as opioids, pilocarpine, barbiturates, and baclofen.[1,19,49]

2.5.5.2.2: Absence of Motor Response (Bulbar Musculature including Facial muscles).

Cranial Nerves V and VII mediate this response. Examine whether there is any movement of the limbs or facial muscles in response to painful stimulation in the trigeminal nerve distribution (such as grimacing).[1,11,66] Since a high cervical injury may cause a painful stimulus not to be felt when applied peripherally, stimulation must be carried out within the trigeminal nerve's distribution. Deep pressure is used to stimulate either the condyles at the level of the temporo-mandibular joint or the supraorbital notch.[37,38]

2.5.5.2.3: Absent Corneal Reflex

Corneal reflex is mediated via Cranial nerves V, VII. It is demonstrated by dabbing a dab of tissue paper, a strand of cotton wool, or a stream of water on the cornea. Watch out for blinking.[1,11,66] If this is unsuccessful in getting a reaction, a stronger stimulus is used, such as a sterile throat swab and strong exertion of force directly. There should be no eyelid movement. Be careful not to harm the cornea when doing tests.[37,38]

2.5.5.2.4: Oculocephalic Reflex (Doll's Eye Phenomenon)

Mediated through Cranial nerves VIII, VI, and III. The patient's head is suddenly shifted to the side while the examiner keeps their eyes open.[1,11,66] When the reflex is functioning properly, the eyes appear to lag behind the head movement as it turns in the opposite direction. The response is missing when the eyes move with the head but do not move inside the orbit. The neuronal pathway used by this test and the caloric reflex are similar. Patients who have had an unstable cervical spine injury should not undergo this test.[1,11,66]

2.5.5.2.5: Oculovestibular Reflex (Caloric Testing)

Like the oculocephalic reflex, it's mediated by Cranial nerves VIII, VI, and III. Before testing, an auroscope is used to check both ears to make sure the tympanic membrane is intact and the external auditory canal is not blocked by wax or other materials.[1,11,66] The test should not be conducted on that ear if the external auditory canal contains blood, CSF, or brain tissue due to a damaged base of the skull. The patient is positioned supine with their head in the midline and 30 degrees elevated.[1,11,66] By ensuring the lateral semi-circular channel is vertical, the responsiveness is maximized. While an assistant holds the eyes open, a soft catheter is inserted into the external auditory canal for a slow, gentle irrigation with at least 50ml of chilled water (one ear at a time). In children, 10-50ml of ice-cold water is used. After the irrigation is finished, the eyes need to be monitored for a minute.[1,11,66]

An intact oculovestibular reflex leads the eyes to slowly deviate in the direction of the irrigated ear in a patient who is unconscious. A diagnosis of BD is ruled out by any eye movement, whether conjugate or not, in one or both eyes. When there is no reflex, the eyes stay fixed. With a few minute break, both sides are tried.[1,11,66]

2.5.5.2.6: Pharyngeal (Gag) Reflex

Mediated by Cranial nerves IX, X. Each side of the oropharynx is stimulated with a tongue depressor or suction device, and the patient is watched with a torch for any pharyngeal or palatal movement. There should be no response in BD.[1,11,66]

2.5.5.2.7: Laryngeal (Cough) Reflex

It's mediated by Cranial nerves IX, X. The carina is stimulated by inserting a suction catheter far enough into the endotracheal or tracheostomy tube. The patient is watched for any coughing reaction or chest or diaphragm movement. The reflex is absent in BD.[1,11,66]

2.5.5.2.8: Absent Sucking, and Rooting Reflex

Sucking and rooting reflexes for part of primitive neonatal reflexes which are automatic movements that start around 25-26 gestational weeks and are mediated via the brainstem.[37,38] Normally, they do not persist beyond 6 month of age. Rooting reflex is usually well established by 32-34 weeks of Intra-Uterine life. It is elicited when the cheek of a newborn is stroked on the side of the mouth. Normally, the child turns his head towards the stimulated side and starts to suckle.[68–72]

Sucking reflex is normally present by 28 weeks of gestation and well established by 32-34 weeks of gestation. It disappears by 2 years post-partum.[68–72] It's closely associated with the rooting reflex and breast feeding. Normally, anything touching the roof of the child's mouth, will reflexively stimulate sucking action. In BD, these two reflexes are absent.[68–72]

2.5.5.2.9: Absence of Response to Atropine

It's rarely used. In an intact brainstem, administration of 1-2mg of atropine is expected to elicit an increase in the heart rate of > 5beats per minute. This is due to the anticholinergic effects of atropine, mediated via the vagus nuclei. This response is absent in BD.[21]

2.5.5.3: Flaccid Tone and Absence of Spontaneous or Induced Movements

Examine the patient's extremities for tone via passive range of motion activity. Keep an eye out for any unintentional or forced movements in the patient. Exclude spinal cord reflexes such as reflex withdrawal or spinal myoclonus if aberrant movements are observed.[37,38] The following observations have been noted to be compatible with a BD diagnosis: Spontaneous movements or

those elicited by stimulation eg Arm flexion or extension; leg movements; head rotation; body movement to sit up to 45° (Lazarus sign); sweating; blushing; and tachycardia. Patients that meet the clinical criteria for BD have spinal reflexes regularly reported, which is supported by the absence of intracranial blood flow.[1,11,66] The following observations are however incompatible with a BD Diagnosis: Decerebrate or decorticate posturing; Facial movement and Seizures.[1,11,66]

2.5.6: APNEA TEST

The diagnosis of BD requires this test. It should be performed after determining that all other brain-stem reflexes are absent.[1,11,66] The test is performed similarly in term newborns, infants, children and adults. Prior to the test, ensure a core temperature of $>35^0$C, normotensive for age, normal ABGs and no factors that would affect respiratory effort are present.[73] Pre-oxygenate the patient using 100% O_2 about 10 minutes, targeting a PaO_2 of 200mmHg. Switch off the MV. Deliver oxygen via the C-circuit at a rate of 7L/min with the valve fully open.[1,11,66] In order to maintain the airways open and maximize oxygenation, a suitable Continuous Positive Airway Pressure (CPAP) valve can be fitted. Additionally, a CPAP valve may stop atelectasis and help prepare the lungs for transplantation by enhancing lung health.[1,11,66]

Continuously monitor the patient's pulse rate, BP, SPO_2 and observe for spontaneous respiratory effort during the procedure. After 8-10minutes, do ABGs; if the $PaCO_2$ is ≥60mmHg (≥8.0 kPa) or ≥20mmHg above the baseline, and associated acidaemia has developed (pH<7.30), yet no respiratory effort is observed, the apnea test is positive i.e., consistent with brain death.[37,38] Monitor respiration via examination of the reservoir bag of the breathing circuit; chest and abdominal movement as necessary. Minimal movement synchronized with heartbeat may be visible upon visual examination of the chest and belly. The patient's diminished sensitivity to a high PaC02 must be taken into account if they have a history of chronic respiratory illness. Occasionally, the necessary changes in pH and PaCO2 take longer than 10 minutes. If during the test SPO_2 fall below 85%, patient develops hemodynamic instability, or a $PaCO_2$ level of ≥60mmHg cannot be achieved, patient should be reconnected to the MV and stabilized to achieve normoxia, normocarbia and restore hemodynamic stability. The test is therefore aborted, to be attempted later or an ancillary study is used assist with determination of DNC. The test is stopped, and MV assistance for the patient is restored because there is proof of any respiratory

effort, which is incompatible with brain dead. Up to the conclusion of the second DNC examination and the apnea test that confirms brain death, other care is continued.[37,38]

Most guidelines recommend that Apnea test be done with every DNC evaluation in all patients unless medically contraindicated.[37,38] Some conditions make the test unsafe for the patient or invalid and therefore should not be done e.g.: high cervical spine injury; high oxygen requirements on ventilator settings. Under such settings an ancillary study is recommended to augment DOD by neurological criteria.[37,38]

Inadequate Preparation for the Apnea Test

Pre-oxygenation with a FiO2 of 100% for 10 minutes is mandatory to clear nitrogen in the alveoli and the diffusion of oxygen. If the patient has a substantial A-a gradient because oxygen cannot cross the alveolar blood barrier, the test will fail. The probability of a failed apnea test is further exacerbated by the presence of chest tubes (such as traumatic pneumothorax) and chest injuries. Oxygen desaturation when positive end-expiratory pressure (PEEP) is reduced to 5 cm of H_20 is a predictor of O_2 desaturation when the ventilator is disconnected during the apnea test.[1,66]

2.5.7: ANCILLARY TESTS[44,60,74]

Some BD protocols recommend that ancillary (also referred to as Instrumental) tests are mandatory under certain circumstances such as, cases involving a primary infratentorial lesion, where the test is needed to prove that the hemispheric regions have no function.[11,57] They claim that since clinical examination focuses solely on the brain stem, it does not capture evidence of injury to the hemisphere.[44,60] Clinical testing is the established international standard for BD diagnosis.[44,60] Testing all of the brainstem reflexes may be impossible in cases of severe head and facial injuries. Testing pupillary and corneal reflexes may be hampered by periorbital enlargement or direct eye damage.[75] Similar to CSF otorrhoea, external auditory canal blockage can prevent caloric testing of the oculovestibular reflex. Apnoea testing may not be possible due to cervical cord lesions, severe respiratory illnesses, and other problems.[44,60] Since full brain death must occur in these circumstances, clinical examination alone is insufficient to determine if the requirement has been satisfied.[11,29]

AAP and AAN guidelines recommend that ancillary investigations are not required to establish DNC and cannot be used in place of the recommended neurologic evaluation.[37,38] The utility of Ancillary tests is in helping the examiner make the diagnosis of DNC in case: aspects of the neurologic examination cannot be done or are unreliable; components of the apnoea test cannot be completed safely; the effect of confounders e.g. CNS depressants is noted and finally, to reduce the inter-examination observation period. This tests also help the family members better understand the BD diagnosis made for their patient.[37,38]

The aim of these studies is to show electro-cerebral silence or lack of cerebral blood flow in BD. The gold standard for demonstrating absence of CBF is the **Four-vessel cerebral angiography**.[37,38,53] Under strong pressure, the contrast material should be injected into the aortic arch in order to reach the anterior and posterior circulations.[44,60] At the point where the carotid or vertebral artery enters the skull, no intracerebral filling should be seen. The circulation around the external carotid should be clear.[44,60] There may be a delay in the superior longitudinal sinus filling.[53] The downsides are that, it's not readily available in many institutions, requires moving the patient to the Angiography suite and can be difficult to perform in infants and small children.[37,38,53]

Electroencephalography (EEG) documents electro-cerebral activity and the test must be in accordance with standards established by the American Electroencephalographic Society.[37,38] EEG should show no response to strong somatosensory or audiovisual stimuli. (Electro-cerebral silence).[53,74]

Cerebral scintigraphy (technetium Tc 99m hexametazime(HMPAO)[53] determines CBF and must be carried out in compliance with standards published by the American College of Radiology and the Society of Nuclear Medicine. After reconstitution, the isotope needs to be injected within 30 minutes. There should be various time intervals where anterior and both lateral planar image counts (500,000) of the head are obtained: immediately, between 30 and 60 minutes later, and after 2 hours. Additional liver pictures showing uptake can be used to verify an IV injection was administered properly (optional).[45,61] There was no radioactive localization in the cerebral hemispheres' basilar artery, middle cerebral artery, or anterior cerebral artery areas (hollow skull phenomenon). Superior sagittal sinus has no tracer.[37,38,53] These 2 (EEG & Radionuclide study), are the most commonly used ancillary studies in diagnosis of BD among

infants and children.[37,38] Where they're used, only one test is considered necessary. The choice of test is dependent on the context, pathology, and resources available.[11,47]

Hemodynamic and core body temperature parameters must be within normal range during these studies. Some drugs may affect the tests, thus must be discontinued and their serum levels measured. Radionuclide CBF study can be performed with a high-dose barbiturate treatment, whilst EEG is reliable at low to mid therapeutic levels of barbiturates.[37,38] A repeat radionuclide CBF study, if necessary, requires a waiting period of 24 hours, to allow for clearance of Tc-99m.[37,38] Available studies show that ancillary tests are less sensitive in newborns compared to older children, hence longer periods of observation and repeat neurologic examinations required prior to BD diagnosis.[37,38,57]

Additional ancillary studies include: transcranial Doppler (TCD), CT angiography (CTA), CT perfusion using arterial spin labeling, nasopharyngeal Somatosensory Evoked Potentials (SSEPs), Magnetic Resonance Angiography (MRA), and perfusion MRI.[75] These studies have not been validated for use in diagnosis of BD in infants and children and therefore are not recommended as ancillary studies in pediatric patients currently.[37,38,53]

Over-reliance on Ancillary Tests

Misinterpretation of ancillary tests, can lead to errors in DNC. Studies of cerebral blood flow (CBF) rely heavily on cerebral perfusion pressure (CPP). Low CPP causes no flow; if CPP is not very low, some CBF may still be present and be seen in people who are clinically dead. There are frequently differences between CBF investigations and EEG. In the ICU, the EEG is highly prone to artifacts. Pumps, ventilator, or complex set-ups e.g. ECMO, make the interpretation of EEG difficult[1,33,56]

2.5.8: DECLARATION OF DEATH

Death by Neurologic Criteria, is declared when the second neurologic examination including apnea test, confirm an unchanged and irreversible brain injury.[37,38,61] Where ancillary tests are utilized, the second completed neurological examination, must remain consistent with BD.[61] Both the 1st and final DNC evaluation must be meticulously documented. The time of brain death, corresponds to: the time the arterial $PaCO_2$ is confirmed to reach the target value or when the ancillary test is officially interpreted, where it's used.[37,38]

2.5.9: CADRES OF EXAMINERS

Drake et al, 2017, in their article *"Brain Death"*, advocates for a hospital-based BD policy that specifies the roles of doctors who determine BD and how they should be trained, credentialed and which precise criteria of DNC evaluation they ought to use.[28,47] The AAP guidelines, recommended that attending physicians participating in the care of the child could perform the DNC examinations.[37,38] Numerous medical and surgical specialists would be among them. It was found that if at least two distinct attending physicians were involved in the BD evaluation, the patient and family were well served.[37,38] This made sure that the DNC evaluation adhered to the most recent established standards, that there were no conflicts of interest while making the BD diagnosis, and that clinicians all agreed that the BD criteria had been satisfied.[4,74] Additionally, it was highlighted that the apnoea test, which is objective, would be conducted by the same attending physician, preferably one who was in charge of the patient's ventilator management.[37,38] ***Power et al, 1995***, suggests performing two sets of tests, one by a consultant and the other by a physician (registered by a recognized institution for a minimum of five years).[59] Both should be actively involved in providing care and have knowledge of BD testing. The medical professionals BD-certifying should not participate in the transplant procedure if organ donation is being discussed.[1,48,56]

Numerous guidelines suggest that DNC examinations be conducted by seasoned doctors familiar with newborns, babies, and have received special training in neurocritical care, and are skilled in the interpretation of auxiliary testing.[37,38] According to AAP standards, these medical professionals include pediatric neonatologists, pediatric neurologists, pediatric trauma surgeons, and pediatric anesthesiologists with critical care experience. According to AAN standards, professionals should have the necessary neurologic and critical care skills to diagnose BD when evaluating DNC in adults.[37,38] The AAN guidelines declare *"It appears appropriate to demand that all physicians rendering a decision of BD be thoroughly versed with BD criteria and have shown competency in this complicated examination"*.[1,66]

2.5.10: DOCUMENTATION

The findings of each of the formal sets of tests in DNC must be fully documented, ideally in a checklist form and summarized in the medical records.[62] If both sets of tests show no evidence of brain-stem function and the preconditions for a clinical diagnosis of BD are satisfied, Brain Death is diagnosed and documented.[37,38] Use of checklists (See Appendices III & IV), provides a standardized documentation system for DNC.[37,38,73]

2.5.11: POST DNC MANAGEMENT

Once the patient has been confirmed dead by neurologic criteria, how are they/should they be managed? In the USA, the physician is required by the federal and state law to promptly contact an organ procurement organization.[37,38,76] Brain death is physiologically catastrophic and is associated with profound dysfunction of other body organs.[77] The BD patient will inevitably deteriorate in cardiorespiratory function leading to asystole.[28,58] The period between confirmation of BD and subsequent asystole is generally short, numbered, at most, in days.[58] In jurisdictions that allow disconnection of the ventilator, the family must be handled sensitively and with respect. Where appropriate, the next of kin may be allowed to attend while the ventilator is disconnected.[21,47]

There are systematic changes known to occur to the patient in the setting of BD. Cerebral ischemia progresses rostro-caudally leading to vagal activation which results in bradycardia and a hypotensive state.[28] This if followed by pontine ischemia, which stimulates the Cushing's response ie a sympathetic stimulation with associated parasympathetic modulation leading to moderate hypertension and bradycardia.[28,58] Progressive uncal herniation causes ischemia of the upper medulla leading to a sympathetic stimulation without a parasympathetic challenge. This is referred to as a sympathetic storm, which causes severe hypertension and tachycardia and this may lead to neurogenic pulmonary edema and myocardial dysfunction. Finally, as herniation of the cerebellar tonsils (coning) takes place, compression and ischemia of the lower medulla and upper cervical spinal cord leads to autonomic paresis.[28,58,73] The associated pathophysiological sympathectomy, vasopressin deficiency hence diabetes insipidus and left ventricular dysfunction leads to hypovolemia and hypotension.[28,58] Other physiological anomalies associated with brain death include: Cardiac Arrhythmias, Hypernatremia, Endocrine deficiency, Hypothermia (rarely hyperthermia), Hyperglycemia, Coagulopathy and Cyto- and endothelial dysfunction. If

aggressive management is not instituted, the deterioration of the cardiovascular dysfunction in these patients results in cardiac arrest.[28,46,58]

In jurisdictions where deceased organ donation is practiced, aggressive resuscitation, including Advanced Cardiac Life Support (ACLS) and blood transfusion are done.[76] There is evidence supporting prevention of the sympathetic storm, as a way to reduce cardiac and pulmonary injury associated with BD.[28,58,62] There are established guidelines on treatments used to ensure optimization of salvageable organs for transplant purposes. ***Salim et al, 2006,*** in a series of BD patients, noted that 97.1% needed vasopressors, whilst about 50% of them developed coagulopathy, thrombocytopenia, and DI.[28,46] Other therapies for potential deceased donors include: Thyroid hormone, steroids, ECMO, etc. Many institutions have Catastrophic Brain Injury Guidelines (CIBG) which provide a road-map of hemodynamic, hormonal support and complication management for BD patients prior to organ harvesting. A simple algorithm such as the *"Rule of 100s"*can be used. I translates to maintenance of SBP at >100mmHg, PaO2 >100mmHg and urine output about 100mL/h. The Society of Critical Care Medicine recommends a target urine output of 1mL/Kg/Min and a MAP of 60mmHg.[28,46,58,73]

2.6: BRAIN DEATH & ORGAN DONATION

Many diseases especially non-communicable diseases (NCDs) culminate in end-stage organ failures; the preferred treatment for most end-stage organ diseases is transplantation.[43,78]A Transplantation programme is a complex healthcare service which entails huge costs and requires highly skilled health professionals, complex infrastructure and equipment, and well-articulated legal frameworks to enable its operationalization.[78,79] This programmes are therefore better developed countries e.g. North America and western Europe.

The concept of BD wasn't developed for purposes of organ transplantation.[80] As the historical analysis done by ***Machado et al, 2007*** demonstrates, the two had separate historical developments, but became interlinked in the 1960s, when the first kidney transplant was performed using a BD donor.[80,81] **Sub-Saharan Africa (SSA),** occupying about **80%** of the African continent is a heterogeneous region with estimated population of 1.1 billion people in 47 countries.[43,82,83] Most belong to the **low resource countries (LRCs).** The need for appropriate interventions for organ failures in sub-Saharan Africa (SSA) is underscored by the high prevalence of **end-organ diseases** such as chronic kidney disease (CKD), chronic liver disease (CLD)[15], chronic lung and heart diseases, which cause increased morbidity and mortality.[26,78,82,84]

2.6.1: Prevalence of Transplantation

The WHO in collaboration with the *Organización Nacional de Trasplantes* of Spain set up the **Global Observatory on Donation and Transplantation (GODT)**, mandated to document the distribution of organ transplantation programmes in the countries that report their data to the Observatory and to evaluate the access of transplantation activities worldwide.[43] According to the GODT database, 139,024 solid organ transplants were reported globally in 2**017**: 90,306 kidney (36% from living donors), 32,348 liver (19.0% from living donors), 7881 heart, 6084 lung, 2243 pancreas and 162 small bowel transplants. Africa, notably, contributed the least number of transplant activity per continent and SSA the least number per WHO World regions.[43,78,84]

In the Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) 2016 annual data report (***Israni et al, 2017***) of deceased organ donation in the USA, about 1.07 million death or imminent death referrals were made to the

organ procurement organizations.[85] Approximately 23,000 of these, met donor eligibility criteria. Deceased donors constituted about 9900, a number that had continually increased since 2010.[85]

The first organ transplantation in Africa was kidney transplant performed by **Thomas Starlz** and colleagues in **1966** at Wills Donald Gordon Medical Centre, Johannesburg, South Africa. This was followed in **1967** by the first successful heart transplant performed in the world at Groote Shuur Hospital, Cape Town, South Africa by **Christian Barnard**. From **1968 to 1983**, they engaged in research on cardiac transplantation and advanced the concept of BD, organ and tissue donation, and ethical issues in transplantation. **Kenya** started kidney transplantation in 2009 and by 2019 had performed 200 transplants.[78,86]

2.6.2: Stratification of Transplant Programmes

Programmes are classified into different stages of development of transplant services, with those from **HICs** better developed than those from **LMICs** and **LICs.** Kenya falls in the second stage of transplant strata.[78,86]

Stage	Characteristic	Country
I	No existing transplant programme with little or no posttransplant and post-donation care. Transplant tourism is rife.	The poorest countries of the world
II	Faltering or poorly developed transplant programme offering only living-related donation, no nationally structured transplant program, and often no legislation. There is nonexistent deceased-donor program and proliferation of transplant tourism with little or no posttransplant and post-donation care.	Countries in sub-Saharan Africa and many other low- and middle-income countries
III	Fairly developed transplant programme offering mostly living-related donation with rudimentary deceased-donor program. Poorly developed kidney paired exchange and organ sharing programs, often with poor posttransplant and post-donation care. Some level of transplant tourism and moderate to long wait time.	Many countries in Asia, Central and South America, the Middle East, and North Africa
IV	Well-developed structured transplant programme and accompanying legislation offering deceased donation, kidney paired exchange, and organ sharing programs with good posttransplant and post-donation care. Little transplant tourism and short to moderate wait times for transplant.	Many of the developed economies belong to this stage
V	Highly developed and structured transplant programme and accompanying legislation offering mostly deceased donation, advanced donation/kidney paired exchange, and organ sharing programs with excellent posttransplant and post-donation care. There is no transplant tourism and short or no wait times for transplant.	Utopian

Table 2: ***Proposed staging for transplant stratification model (transplant transition)***

2.6.3: Shortage of Organs

Scarcity of organs for transplantation is a multi-factorial global problem. Living donors remain the major source of organs for transplantation in SSA with **largely non-existent deceased donor programmes.**[87,88] This has resulted in the persistent dearth of organs in the face of continuous rise in demand. Unavailable storage facilities, poor knowledge about transplantation, socio-cultural and religious beliefs (which discourage living organ donation, view deceased organ donation as a taboo or an act of mutilating the dead with violation of the person's dignity) are contributory factors.[78] ***Chatterjee et al, 2015***, in their article *"The Effect of State Policies on Organ Donation and Transplantation in the United States"*, concluded that only state based revenue policies enacted within the past 20 years, had a positive impact on national increase of transplants from deceased donors.[89]

2.6.4: Legal and Regulatory Policies

The weak regulatory frameworks observed in SSA countries e.g. Kenya, are often insufficient to ensure the effective oversight needed for the implementation of quality standards for organ transplantation.[7] In 2008, The Transplantation Society (TTS) and the International Society of Nephrology (ISN), in a summit in Istanbul, developed principles aimed at preventing unethical practices in organ transplantation.[87] In 2010 the two bodies created the Declaration of Istanbul Custodian Group (DICG) which was updated in July 2018 in Madrid.[87] Among other principles, DICG recommended that every country develop and implement policies and legislation that would oversee the retrieval of organs from deceased and living donors and ensure practice of transplantation, consistent with international standards.[87]

2.7: LEGAL AND POLICY ENVIRONMENT

Increasing availability of critical care services, expanding need of transplant services, organ donation and BD are closely interlinked. A robust regulatory framework is required at international, regional, national and institutional level, in order to maximize benefits to patients and eliminate any unethical practices.[90] Since the first transplant surgery in 1954, transplants have continued to be successful with better graft and overall survival rates.[91] Countries around the globe are coming up with new laws and policies or advancing the ones in existence as a way of formalizing, organizing and regulating organ donation and transplantation. This is gradually

enhancing the practice and rendering it more equitable and safer thus creating more trust among the public.[15,32,43,79,81,85,89,91–93]

These law and policy changes, notably, around donor consent systems and adoption of allocation priority are therefore also intended to increase the pool of donor organs.[91] Countries in the United Kingdom, Singapore, Israel, Chile, Spain etc., have resolved to shift their consent system from an **opt-in system** to an **opt-out system** in order to increase the number of donor organs.[90,91] Spain for instance, in the year 2017, recorded 5,260 transplant surgeries and they had **2,183 deceased donors**.[91]

2.7.1: Legal Frameworks Governing Organ Donation and Transplantation in Kenya

2.7.1.1: Human Tissue Act Cap 252 [41,42,94,95]

This law repealed the Corneal Grafting Act and it makes provision for deceased donation of whole body or any specified body parts for therapeutic purposes and purposes of medical education and research. This Act provides that a person permitted by law to practice medicine must satisfy himself by a personal examination of the body that life is extinct before removal of specified body parts. The Act fails to define a criterion to determine that indeed life is extinct. It also allows the doctor determining death to take part in the removal of the body parts, which is contrary to the World Health Organization (WHO) Guiding Principles on Human Cell, Tissue and Organ Transplantation,[78,82,91] which provides that physicians determining the death of potential donor should not be directly involved in the removal of cell, tissue or organ removal or subsequent transplantation procedures.[94]

2.7.1.2:The Constitution of Kenya, 2010[95]

It is the supreme law of Kenya and binds all persons and all State organs. The constitution recognizes any treaty or convention ratified by Kenya and takes such to form part of the Laws of Kenya. This way, the country can use the international guidelines and regulations it has ratified in relation to organ donation and transplantation to act as a guide while formulating its own specific laws and policies. The right to health is contained in the ***Bill of Rights***. Under ***Article 43 (1) (a)***, *'every person has the right to the highest attainable standard of health, which includes the right to health care services including reproductive health care'*.[95] The right to health is essentially connected to the right to life, provided for under Article 26 of the constitution. Attaining the highest attainable standard of health is beneficial to living a life in

dignity and in the context of organ failure, acquiring an organ transplant may offer a higher quality life as compared to the alternatives, say dialysis, for patients with kidney failure. It does not explicitly define death and also does not prescribe how death should be determined.[43,95]

2.7.1.3: Health Act, 2017[42,96]

Kenya enacted the Health Act on 21st August 2017 with an aim to establish a unified health system, coordinate the inter-relationship between the national government and the county government health systems, provide for regulation of health care service and health care service providers, health products and health technologies.[42] The Act incorporates donation and transplantation services into Kenya's healthcare system by virtue of **Part XI**, which provides for human organs, human blood, blood products, other tissues and gametes.[42] This Act made sale of organs illegal. This Part is further divided into six sections as follows: Section 80 on human organ transplantation; Section 81 on making of Wills; Section 82 on donation purposes; Section 83 on revocation of a donation by a donor; Section 84 on postmortem; and Section 85 on Kenya National Blood Transfusion Service.[42]

2.7.1.4:Kenya Tissue and Transplant Authority (KTTA)[97]

On 1st of August 2022, the KTTA was established by special gazette notice by president Kenyatta.[97] KTTA replaces the Department of the National Blood Transfusion, Tissue and Human Organ Transplant Services. The authority is mandated to regulate all services relating to human cells, tissue and organ transplant in accordance with the Health Act, 2017, register and license facilities and establishments dealing with human cells, tissues and organs and transplant services, maintain a registry of transplant service providers, donors and recipients as well as establish an equitable mechanism for matching and allocation of cells, tissue and organs.[97] Kenya has also developed the ***Kenya Policy on Donations, Transfusion and Transplant of Human derived medical products***, the first integrated policy on blood, cells, tissues and organs in Eastern, Central and Southern Africa.[98]

		Kenya	South Africa	UK
1.	The law on organ and tissue donation and transplantation	Less robust. KTTA newly established	More robust and progressive	Very robust
2.	Human Tissue Acts	Enacted *Health Act 2017*, but *Human Tissue Act of 1966* not repealed	Enacted *National Health Act 2003* & repealed *Human Tissue Act of 1983*	Human Tissue Authority
3	Definitions of Death in relation to organ donation	Not done	Done	*A code of practice for the diagnosis and confirmation of death*- by AMRCs
4.	Procedure to be followed in DOD of a potential organ donor	Not outlined	Clearly outlined	*A code of practice for the diagnosis and confirmation of death*- by AMRCs
5	Donor- Donee matching programme	Lack of a donee renders the donation null	Aggressive matching thus optimal use of donor organs	Opt-Out system. Human Tissue Authority centrally manages
6.	Specific institutions in charge of living & deceased donations	Health Act 2017 only establishes KNBTS. No organ donation & Transplant service KTTA to replace KNBTS starting 2022	Has established institutions	Human Tissue Authority regulates Organ donation & Transplant activities
7	Protected populations e.g. mentally ill	Only "competent person" can donate. Needs further clarity	SA Mental Health Act, 2002 protects the mentally ill from donating.	Good legal framework of protection
8	Donor consent system	Opt-In	Opt-In	Opt-Out
9	Commercialization of donor organs	Criminalized in principle- not robust	Criminalized, more robust	Very robust

Table 3: Comparative analysis of Legal Framework governing Organ Donation & Transplant Activity between Kenya, South Africa and UK, [7,8,16,41,43]

2.8: PRACTISE IN KENYA AND KNH

Kenyatta National Hospital (KNH), established in 1901, is currently the largest referral hospital in East and Central Africa, based in Nairobi, Kenya. It has a capacity of over 1,800 beds and attends to an annual average of 700,000 inpatients.[12,99,100] It offers specialized services include open heart surgery, neurosurgery, orthopedic surgery, reconstructive surgery, burns management, critical care services, new born services, ophthalmology (cornea transplant), oncology, palliative care and renal services (including kidney transplantation), among others.[12] According to United Nations Office for the Coordination of Humanitarian Affairs [13](OCHA), in 2020, Kenya had a total of 518 ICU bed capacity, 55 of which were based in KNH ***(OCHA, 2020) (number-of-icu-beds-per-county n.d.)*** [99,100]

Kamithu, 1986, in his thesis titled "*The Brain Death Syndrome in the Intensive Care Unit, Kenyatta National Hospital,"*[14] did a 10 year retrospective study on 30 'brain-dead' patients in ICU at KNH. He found that the two most common causes of brain death were, head injury (43.4%) and brain tumors (13.4%). In diagnosing brain death, all patients had none-reacting, dilated pupils. None of the patients had any motor response along the cranial nerves. The caloric reflex was tested in twelve (40%), Doll's eyes was tested in six (20%) and the oropharyngeal reflex was tested in eight patients (26.6%). Four patients (13.3%) had the atropine test, whilst the apnoea test was not performed on any of the patients.[14] After diagnosis of BD, confirmatory tests were done in 50% of the patients: Electroencephalogram (EEG) in 14 patients, while 1 patient underwent carotid angiography.[14] Notably, no protocol on determination of Brain death was reported to have been followed. It was not clear either why some brainstem function tests were used in some patients and omitted in others.[14]

After BD diagnosis, mechanical ventilation was continued for all patients until asystole. In 50% of the patients, medication was continued unchanged. In eleven patients (36.7%), all medication was stopped, leaving intravenous fluids. In four patients (13.3%), the number of drugs were reduced.[14] In 2004, KNH ICU/HDU users committee prepared a ***KNH ICU/HDU Protocols Booklet,*** guidelines to daily management of patients in KNH CCUs.[2] No guideline on DOD either by CD or DNC was included. No further update of the protocols has been made to date.

2.9: PROTOCOL ADOPTION

There is generally, a widespread move towards developing and use of clinical practice guidelines, designed to improve the quality of health care, reduce the use of unnecessary, ineffective or harmful interventions, and to facilitate the treatment of patients with maximum chance of benefit, with minimum risk of harm, and at an acceptable cost.[101] The World Brain death Project (***Greer et al, 2020***), empaneled an international multidisciplinary expert team and made a special communication on BD/DNC.[10] They recommended: adoption of a minimum criteria in BD/DNC protocols worldwide to harmonize this diagnosis; all hospital policies were advised to adopt the most updated guidelines on BD/DNC and that clinical checklists for BD/DNC were to be used routinely.[10]

This proposed research aims to propose a model protocol for DOD in our CCUs using DNC. **Delphi method** of protocol development can be employed over time to improve on the proposed protocol. ***Delphi technique (DT)*** was developed by Dalkey and associates in the 1950s at the Rand Corporation. It was named after the ancient Greek temple where the oracle was found.[102] It is well suited for researching complex issues to help the researcher understand subtle expert opinion. It does not offer the rigor of clinical testing or quantitative analysis, but it provides a scientific methodology that is appropriate for issues that require the insights of subject matter experts.[102]

The DT requires knowledgeable and expert contributors individually responding to questions and submitting the results to a central coordinator, who processes the contributions, looking for central and extreme tendencies, and their rationales. The results are then fed back to the respondents, who are then asked to resubmit their views, assisted by the input provided by the coordinator. This process repeats until the coordinator sees that a consensus has formed. The technique was intended to remove the bias that is possible when diverse groups of experts meet together. In the Delphi technique, the experts do not know who the others experts are during the process.[102–104] Studies had been undertaken to test Delphi against other group judgment techniques, with indication that the DT offers superior accuracy (Riggs, 1983).

The DT may be employed to refine the proposed protocol over time by empaneling local expertise from clinical, legal, religious, academia, and lay sections of the society.

CHAPTER 3.0: METHODOLOGY

3.1: STUDY QUESTION

How is Death by Neurologic Criteria, determined in the Critical Care Units in KNH?

3.2: STUDY HYPOTHESIS (NULL)

Determination of Death by Neurological Criteria in the CCUs at KNH, does utilizes a standardized protocol.

3.3: STUDY OBJECTIVES

3.3.1: BROAD OBJECTIVE

To review the practice of determining Death by Neurological Criteria at KNH

3.3.2: SPECIFIC OBJECTIVES

1. To identify the steps in determination of Death by Neurologic Criteria at KNH
2. To identify the intra/inter-CCU variance in the steps of determination of DNC at KNH
3. To identify the gaps in the KNH process of DNC in comparison to AAN and AAP guidelines
4. To determine the management of BD post DNC evaluation at KNH
5. To propose a KNH-based standardized protocol for determination of Death by Neurologic Criteria

3.4: STUDY DESIGN

A Descriptive Cross-Sectional study design was be employed in carrying out this research.

3.5: STUDY AREA

Key Critical Care Units (CCUs) in Kenyatta National Hospital were identified and used. These included: The Main CCU, Wards 4c, Level 7 & 8 CCUs, Pediatric ICU (PICU), GFB-CCU and Resuscitation Rooms A&B (RRA/B) at the Accident and Emergency Unit.

3.6: TARGET POPULATION

All patients admitted to the CCUs at KNH during the study period

3.7: STUDY POPULATION

Patients admitted to KNH CCUs, on mechanical ventilation, and were diagnosed with brainstem death or BD.

3.7.1: Inclusion Criteria

Patients fulfilling the following characteristics were included in the study:

- ✓ Pediatric patients: Term Neonates to 18 years old
- ✓ All adult patients: >18 years old
- ✓ Had to be admitted to any of the KNH CCUs
- ✓ Had to be on Mechanical Ventilation at the time of DOD
- ✓ Had to have had at least one Death by Neurological Criteria (DNC) evaluation done.

3.7.2: Exclusion Criteria

Patients with the following characteristics were excluded from the study:

- ✓ Premature Neonates
- ✓ Death occurred in CCU with no DNC evaluation
- ✓ Not on Mechanical Ventilation at the time of death.

3.8: SAMPLE SIZE DETERMINATION.

The Cochran/Fisher's Formula will be utilized as follows:

$$n0 = \frac{Z^2 pq}{e^2}$$

$$n0 = \frac{1.962\ x\ 0.025x0.975}{0.0025}$$

n0= 37.5= 38

Where:
$n_{0=}$ Sample Size
Z= Z-score at 95% Confidence Level (1.96)
p= Variability/Standard deviation in study population from previous study (2.5%)
q= 1-p
e= Level of precision (5%)

3.9: SAMPLING AND RECRUITMENT PROCEDURE

Non-Probabilistic purposive sampling technique was employed as follows:

- ✓ During the period of the study running from July to December 2022, all eligible subjects were recruited to the study consecutively and progressively, until the sample size of 38 was reached.
- ✓ Upon identification of an eligible subject, Informed Consent (see Appendix I) was sought from the next of Kin listed in the patient's file, who would sign it after a clear explanation, in either English or Swahili language.
- ✓ The patient (subject) was then be assigned a unique identification code, which was used for purposes of data collection, recording and analysis during the study.
- ✓ The researcher then proceeded to review the patient's records and images, to elucidate the process of DNC evaluation.
- ✓ The researcher followed up the patient monitoring subsequent DNC evaluation and post-DNC care, until the patient went into cardiac arrest and was removed from MV.
- ✓ The information gathered for each subject was entered in the Data Collection Tool (see appendix II)

3.10: VARIABLES

The Data generated was categorized as per the table below:

Variable	Type	Values
Demographics		
Patient Serial No.	Numeric	Unique Serial Number starting 01
Age	Categorical	<18yrs and >18years
Date & Time of Examination	Numeric	Both 1st & 2nd
Timing of 1st DNC Exam	Catergorical	<24hrs and >24hrs
Variable	**Type**	**Values**
Prerequisites		
GCS	Discrete	3-8, Not Indicated
Primary Dx	Categorical	Indicated/ Not documented
Knowledge of cause of coma	Categorical	Yes/No
Neuroimaging Done	Categorical	CT/MRI/CTA/Others
Confounders		
CNS Depressants	Categorical	Yes/No
Drug Level Measurement	Categorical	Yes/No
Presence of Metabolic Derangements	Categorical	Yes/No
Body Temperature	Numerical	$\leq 35^0$C, $> 35^0$C
Blood Pressure	Numerical	SBP/MAP
	Categorical (SBP for Age)	Yes/No
Neurologic Examination		
Pupillary reactivity	Categorical	Present/Absent/Not done
	Discrete	Pinpoint- 9mm
Corneal reflex	Categorical	Yes/No
Oculocephalic Reflex	Categorical	Yes/No
Oculovestibular Reflex	Categorical	Yes/No
Facial movement to Noxious stimuli	Categorical	Yes/No
Gag Reflex	Categorical	Yes/No
Cough Reflex	Categorical	Yes/No
Motor Response	Categorical	Yes/No
Apnea Testing	Categorical	Done/Not done/Not documented
Rooting/Sucking Reflex	Categorical	Yes/No
Apnea Testing	Categorical (if done)	Yes/No
	Continuous (Pre- & Post-test **$PaCO_2$)**	Specific value
	Categorical (Resp. efforts)	Yes/No

	Categorical (Abandoned)	Yes/No
Ancillary testing		
Done	Categorical	Yes/No
Reason for Test	Categorical	Yes/No
Which Test	Categorical	EEG/CBF study
Results	Categorical	Yes/No
Cadre of Examiners		
Same for Exam 1& 2	Categorical	Yes/No
Qualification	Categorical	MO/Resident/Consultant
Post DNC Patient Management		
MV Disconnected	Categorical	Yes/No
Care De-Escalated	Categorical	Yes/No
Care Sustained	Categorical	Yes/No
Organ Donation	Categorical	Yes/No
Time to Asystole	Numerical	In Hours

Table 4: Study Variables

3.11: CONFOUNDERS

The following factors confounded the data collected in this research:

- ✓ Poor and incomplete documentation
- ✓ Lack of availability of tests e.g. drug level measurements.

3.12: DATA COLLECTION

- Once the researcher was aware of an eligible case, and consent duly signed by the next of keen, the patient's file and imaging was retrieved and the DNC process as documented, was reviewed accordingly.
- Radiological images were reviewed and discussed with a neuro-radiologist accordingly to confirm the neuroradiological diagnosis.
- Direct observation of the DNC evaluation process, where possible was also done. The subject was the followed up until eventual disconnection from MV.
- The data collected was duly recorded in the Data Collection Tool (See Appendix II) and collated in an Excel spreadsheet in preparation for analysis.

3.13: QUALITY ASSURANCE

Data quality was ensured through triangulating review of patient's file, direct observation of the DNC evaluation process and follow-up of the patients until asystole. Radiological imaging was discussed with a neuro-radiologist to assure diagnostic accuracy. Methodology development and execution was discussed and guided by a statistician ensuring quality data was collected. The Data collection tools was cleaned up before uploading onto the Excel spreadsheet, to weed out notable errors.

3.14: ETHICAL CONSIDERATIONS

The following ethical considerations were woven into the study:

- ✓ This research is a non-interventional study and therefore posed no physical risk to the patient or next of kin
- ✓ A detailed informed consent from the next of kin was sought and obtained, prior to co-opting the subjects into the study.
- ✓ The consent signee was free to withdraw their Kin from the study at any time and without need for an explanation during the period of the study.
- ✓ Patient's identity was masked by use of a unique numerical identifier and any records involved in the study were be treated with utmost confidentiality.
- ✓ Approval to proceed with the study was sought and obtained from the KNH-UoN Ethics and Research Committee before commencement.

3.15: DATA MANAGEMENT

- ✓ Data was collected using the Data collection Tool (See Appendix II).
- ✓ Data check and clean-up for errors and completeness was then done
- ✓ Data entry into Microsoft Excel Spreadsheet 2021, and export to Statistical Package for Social Sciences version 29.0 for analysis, was then done.
- ✓ Continuous data was analyzed and summarized using descriptive statistics eg measures of central tendency such as Means and measures of dispersion e.g. Standard Deviations.
- ✓ Categorical data will be analyzed and displayed in charts by use of frequencies and proportions.
- ✓ Chi-square test and Fisher's Exact Test were used for bivariate analysis, to establish the correlations between incidence of BD and the clinic-demographic characteristics of the study population.
- ✓ Analysis of variance (ANOVA) was used to establish association between quantitative and other clinic-demographic parameters.
- ✓ A ***P value*** of less than 0.05 form the cutoff for statistical significance.

3.16: LIMITATIONS OF THE STUDY

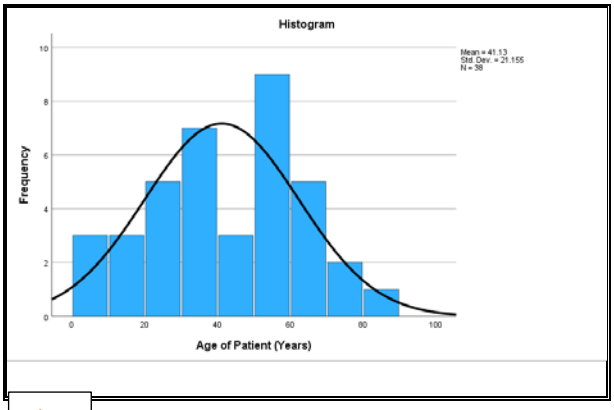
- ✓ A Review of records was an important design aspect of data collection. Gaps in documentation were notable and affected the quality of data collected. Triangulation of information gathering including discussing with Examining physicians, and direct observation and follow-up of the patient once the process of DNC evaluation was initiated, mitigated against this limitation.
- ✓ The study period was limited to a few month, which was a constraint on data collection. The study design and sampling technique however enabled the researcher achieve the required study subjects within the available study period.

✓ Associated cost did not affect data collection analysis and other aspects of the research project. The researcher bore all the cost of the project and therefore had no external funding to declare.

CHAPTER 4.0: STUDY RESULTS

4.1: DEMOGRAPHICS

Over the study period spanning July to December 2022, a total of 38 patients who met the study inclusion criteria were enrolled. The patients' ages ranged from 9 months to 82 years (see fig.4), with a median and mean age of 41 years. Eighty four % of these were adults (> 18years) whilst the remainder were children (Fig.5). No term newborns or neonates were recruited. Majority of the study population were males (71.1%) (See fig.7).



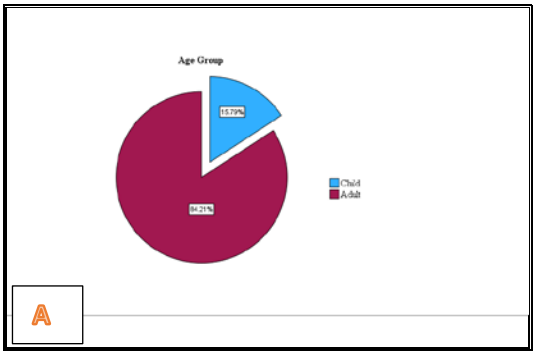
A

Parameter	Value (Years)
N=38	
Min. Age	9/12
Max. Age	82
Mean	41.13
Median	41.00
SD	21.16
Variance	447.53
Range	81

B

Fig.4: Showing a Histogram (A) and Table (B), Descriptive Summary Statistics of Age of Patients in Years.

Six CCUs in KNH formed the study areas. Most of the patients (47.4%) were from the Main ICU. The least number of patients (2= 5.3%) on the other hand were from the Medical CCU (see Fig.6)



A

Age Group

	N	%
Child	6	15.8%
Adult	32	84.2%

B

Fig.5: Showing (A), a Pie Chart and (B), a table of Age Group Distribution

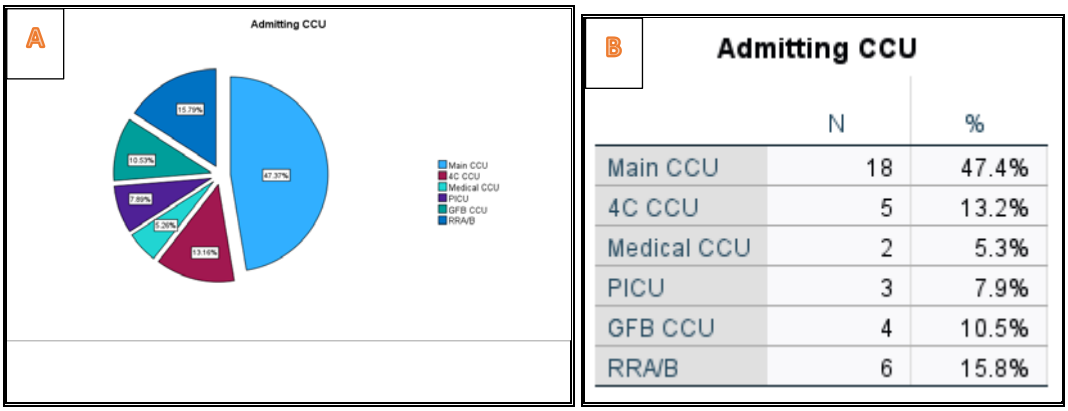
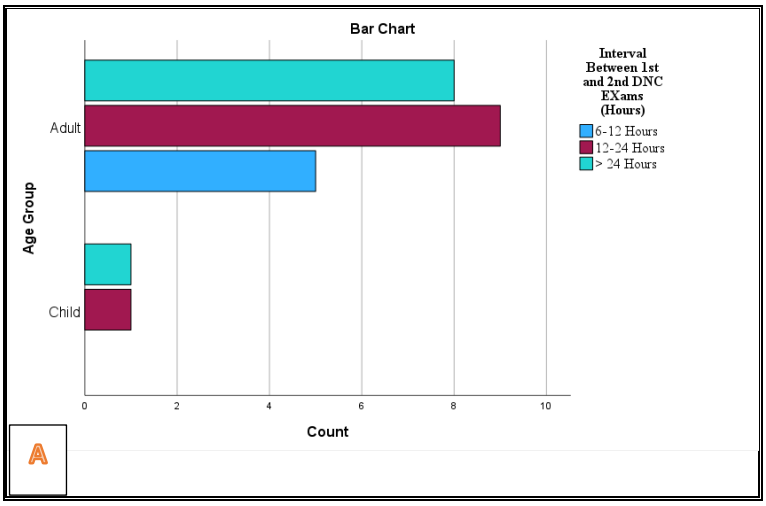


Fig.6: Showing (A), a Pie Chart and (B), a table of Admitting CCUs

Fig.7: Showing (A), a Pie Chart and (B), a table of Patient Gender Distribution

4.2: TIMING OF BRAIN DEATH EXAMINATION

All patients had an initial DNC evaluation more than 24 hours after severe brain injury or resuscitation following a cardiac arrest event (See Fig.8). A second DNC examination was done on 24 (63.2%) of the patients. In total, 62 DNC examinations were carried out on these patients. Of the remaining 14 (36.8%) patients, 8 (21.1%) had early asystole while 6 (15.8%), lacked a documented reason for not undergoing a second DNC examination. Of the patients who underwent a 2nd DNC evaluation, 2 were children while the remainder were adults. The interval between 1st and 2nd DNC exam was ≥ 12hours for 19 (50%), of these patients (see Fig.8).



B

Interval Between 1st and 2nd DNC EXams (Hours)

	N	%
6-12 Hours	5	13.2%
12-24 Hours	10	26.3%
> 24 Hours	9	23.7%
Not Applicable	14	36.8%

Fig.8: Showing (A), a Bar Chart and (B), a table of Interval Between 1st & 2nd DNC Exams

4.3: PRE-REQUISITES FOR BD EXMINATION & APNEA TEST

4.3.1: Coma Evaluation

Pre-evaluation GCS was 2T/15, and was documented for all (100%) the DNC examinations done. All patients had at least one neuro-radiological study done, with a documented radiological diagnosis (See Fig.9).

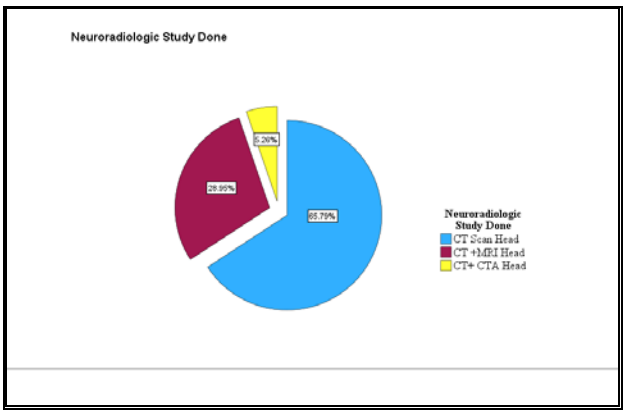


Fig.9: A Bar Chart Showing Neuroradiologic Studies Prior to DNC Exams

The most common cause of irreversible coma, identifiable radiologically was severe Traumatic Brain Injury, and had a prevalence of 44.7% (See Fig.10). Infra-tentorial Brain Tumors had the least diagnostic prevalence radiologically at 5.3% among these patients.

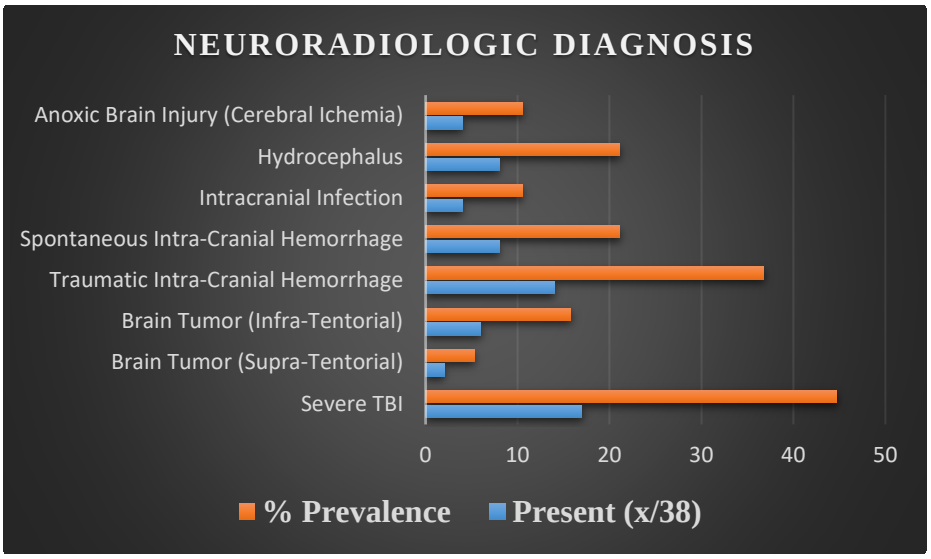


Fig.10: A Bar Chart Showing Frequent Neuroradiologic Diagnoses among the Patients

4.3.2: Co-Morbidities

Sixty-three percent of these patients had comorbidities, in addition to their primary neurological diagnosis (See Fig.11). The commonest comorbid conditions included: Severe metabolic disorder (34%), Septic shock (13.2%), severe anemia and coagulopathy (10.5% each). Others included: Acute Kidney Injury (AKI) (4%), Severe Pre-Eclamptic Toxemia (SPET) & HELLP (7.9%). Three (7.9%) of these patients, also had Multi-Organ Dysfunction Syndrome (MODS).

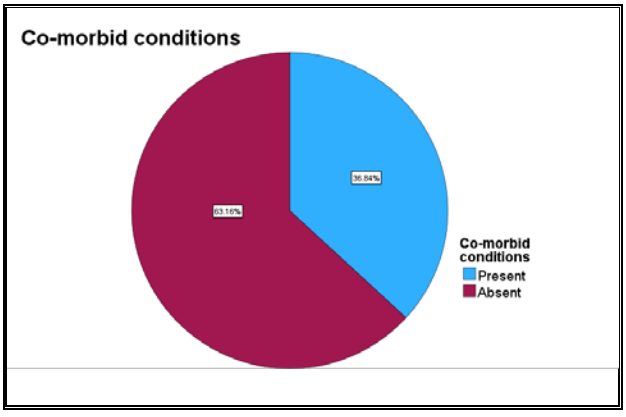


Fig.11: A Pie Chart Showing Prevalence of Comorbidities in Study Population

4.4: CONFOUNDERS TO BD EXAMINATION

4.4.1: Core Temperature and Blood Pressure

Pre-examination core temperature was documented and was > 35^{o}C, prior to all DNC evaluation done. Blood pressure likewise was documented prior to every DNC evaluation. (See the fig.12) Below, illustrating the recorded pre-DNC exam SBP and MAPs in relation to the acceptable cut-offs.

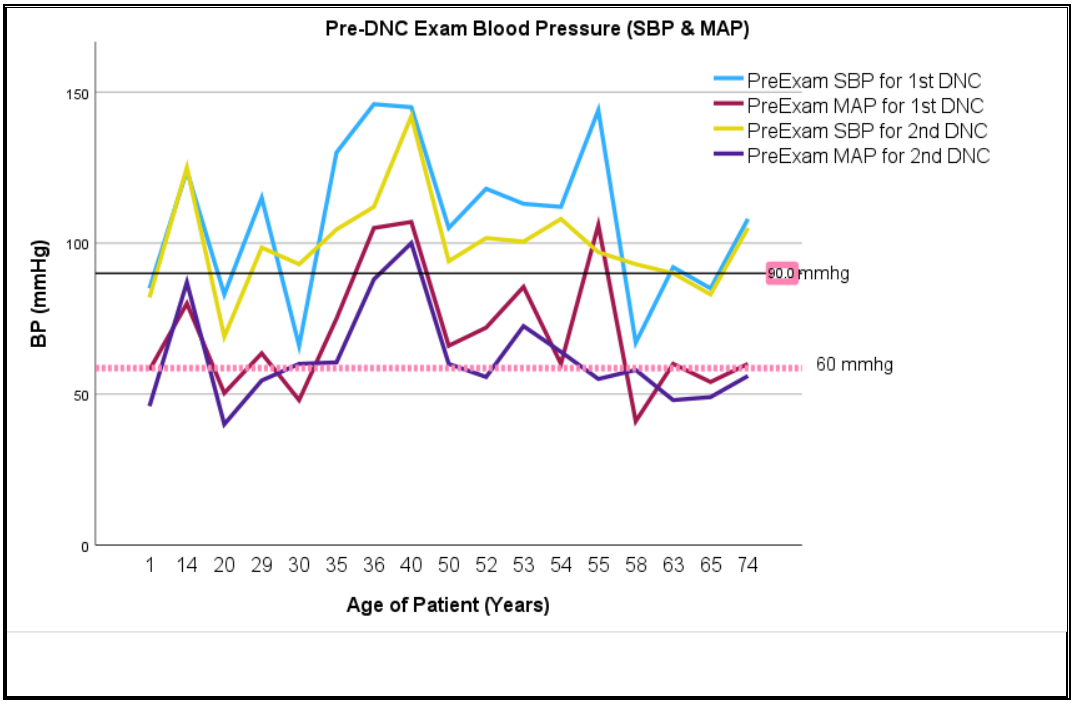


Fig.12: A Multiple line Graph Illustrating the Pre-Exam SBPs and MAPs Against their Ages in Years. Note the Reference Lines for Minimum Acceptable SBP (Black), and MAP (Pink), for Adult Patient.

Overall, prior to 1st DNC exams, SBP for 27 (71.1%) of patients were within, while the remainder (28.9%) fell below the 2 SD for age (See Fig.13). Systolic BPs prior to 2nd DNC exam on the other hand, had 15.79% of the measurements, below 2SD for age (See Fig.13).

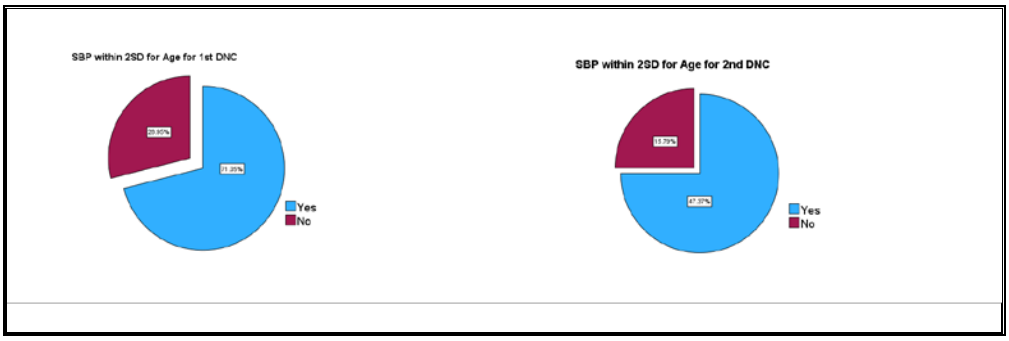


Fig.13: Pie Charts Showing Whether the Pre-DNC Exam SBP of the Study Population Fell Within 2 SD of Acceptable SBP for Age.

4.4.2: CNS Depressants

Prior to 1st and 2nd DNC exam, 84.21% and 52.63% of the patients respectively, were on a CNS depressant medication (See Fig.14).

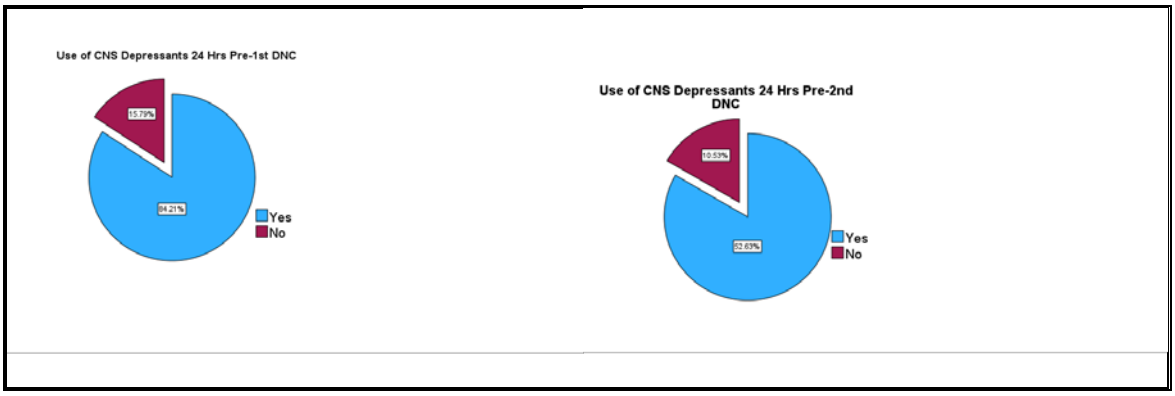


Fig.14: Pie Charts Showing The Use of CNS Depressants 24 Hours Prior to BD Exam

Anticonvulsants, was the commonest group of CNS depressant used- in 27 (71.1%) in 1st and 85% in 2nd DNC examinations. Phenytoin particularly, was the commonest anticonvulstants in use (Table 5). Other drugs in use included: Dexmedetomidine, Tramadol, Morphine etc. Of the 32 patients who were on these medications within 24 hours of the DNC exam, none had the drug levels measured.

CNS Depressants used Pre-1st DNC

	N	%
Opioids	1	2.6%
Anticonvulsants	27	71.1%
Opioids + Anticonvulsants	3	7.9%
Anticonvulsants + Sedatives	1	2.6%
None	1	2.6%
Not Applicable	5	13.2%

Drug Name of CNS Depressant Used Pre-1st DNC

	N	%
Phenytoin	27	71.1%
Morphine	1	2.6%
Phenytoin + Morphine	3	7.9%
Phenytoin + Dexmedetomidine	1	2.6%
Not Applicable	6	15.8%

Table 5: Showing The Use of CNS Depressants Within 24 Hours Prior to 1st BD Exam

4.4.3: Metabolic Disorders

About 39.5% of the patients prior to 1st DNC exam, and 17% those who had a 2nd DNC exam, had a severe metabolic disorder (See Fig.15).

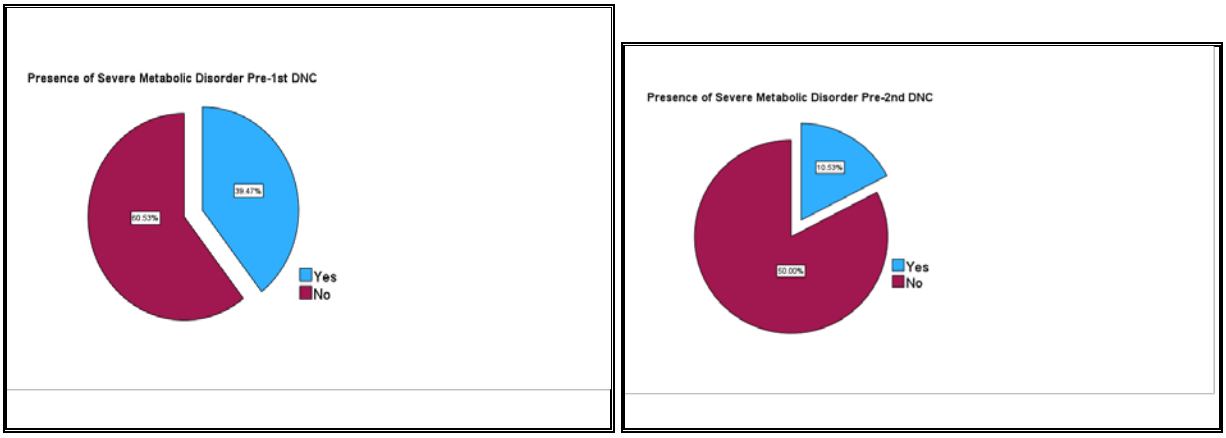


Fig.15: Pie Charts Showing the Presence of Metabolic Disorders pre-DNC Exam

As is evident in the Bar Chart (See Fig.15) below, severe metabolic acidosis was the most prevalent metabolic disorder among these patients (28.9%). Most of the metabolic disorders were corrected, either fully or partially by the time BD exam were performed.

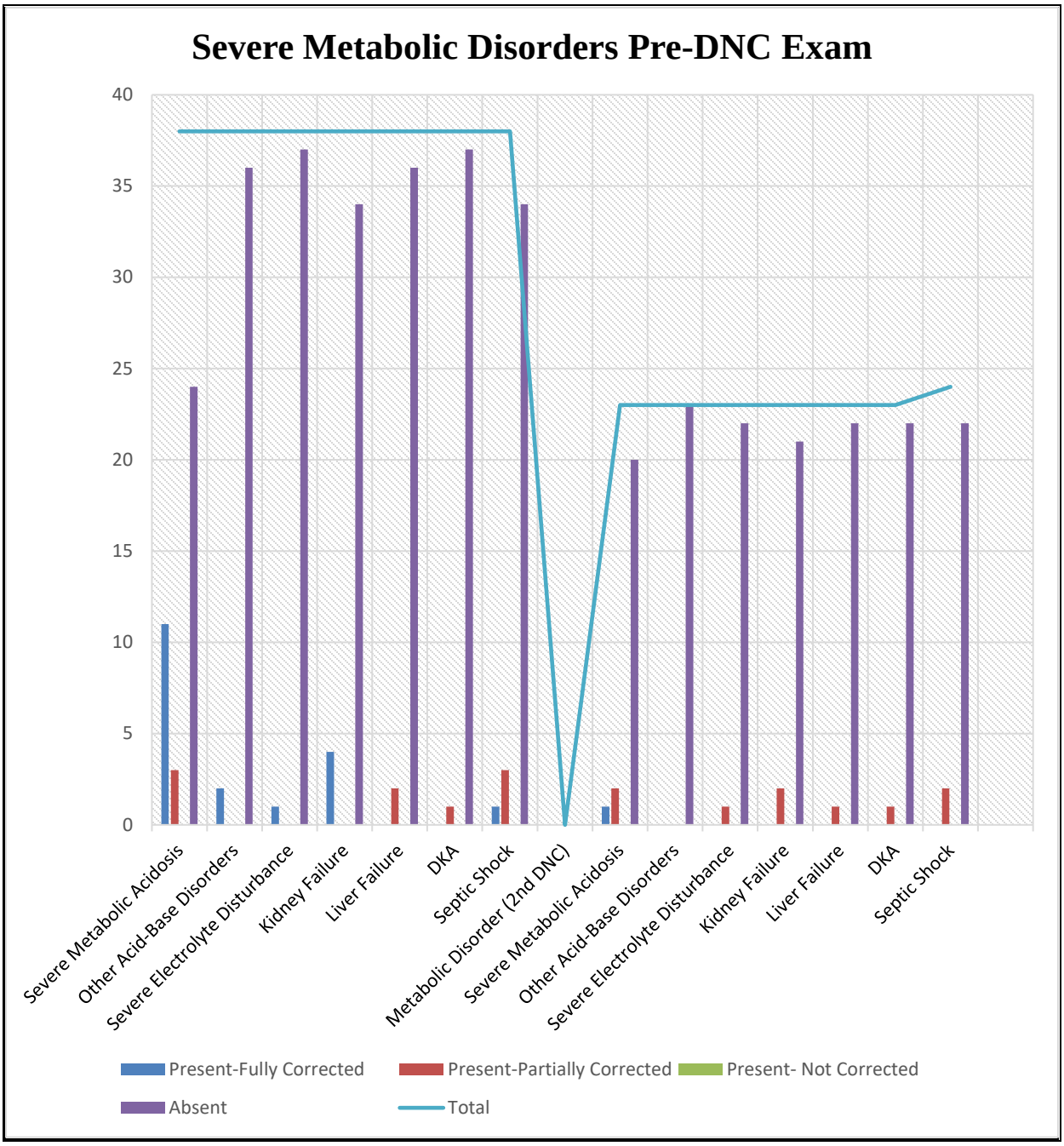


Fig.16: A Clustered Bar Graph Showing Prevalence of Severe Metabolic Disorders Prior to the BD Exam.

4.5: NEUROLOGIC EXAMINATION

4.5.1: Summary Responses on Brainstem Reflex Exam

Most brainstem reflexes were tested in most of the patients and documented. All tested reflexes were absent except for cough reflex, which was present in the 1st DNC in one patient (See Fig.17). Sucking and Rooting reflex was done in infants only. There was no documentation of oculocephalic reflex in 4 (10.5%) patients in 1st DNC and 2 (9%) patients, in the 2nd DNC. Oculovestibular reflex also lacked documentation for 6 (15.8%) patients in 1st & 1 patient in the 2nd DNC. Oculovestibular reflex was not done in 2 (5.3%) patients due to traumatic tympanic perforation and otorrhoea.

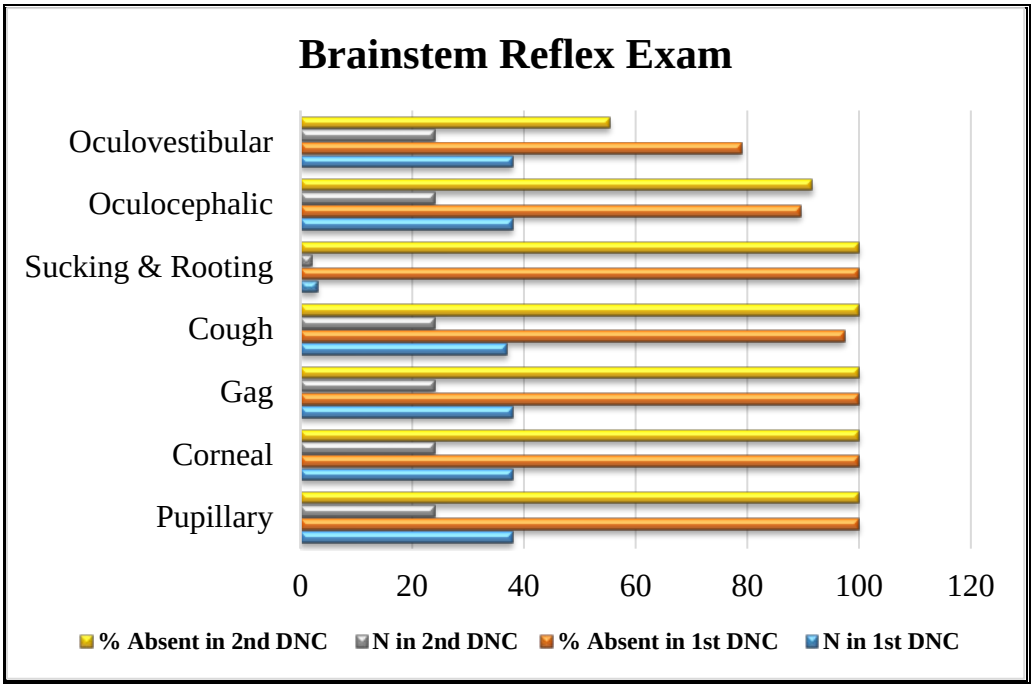


Fig.17: A Clustered Bar Graph Showing Brainstem Reflex Responses in DNC Exam.

4.5.2: Tone and Motor Response

All the patients (100%) evaluated during the initial and 2nd DNC examination, were flaccid and unresponsive on application of a noxious stimuli.

4.5.3: Pupillary Response

As shown in the Table below, the pupillary size ranged from 4-8mm with a mean of about 5.8mm and a median of 6mm both in the initial and initial and final exam.

Summary Statistics	Pupillary Size in 1st DNC (mm)	Pupillary Size in 2nd DNC (mm)
N	38	24
Mean	5.87	5.79
Median	6.00	6.00
Std. Deviation	0.963	1.103
Variance	0.928	1.216
Range	4	4
Minimum	4	4
Maximum	8	8

Table 6: Showing the Summary Statistics on Pupillary Responses in DNC Exam

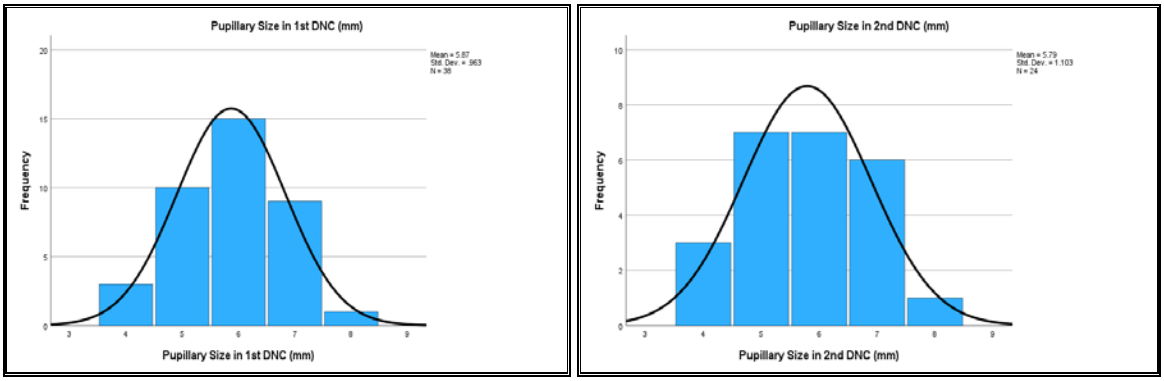


Fig.18: Histograms Showing Pupillary Sizes in DNC Exam

Pupillary light responses, both consensual and direct, were absent in 100% of all DNC examinations done.

4.5.4: Spontaneous Respiratory Efforts

They were absent in 100% of patients evaluated in both both the initial and final DNC exam.

4.5: APNOEA TEST

Apnoea test was done in 3 (7.9%) patients during the initial, and 7 (29.2) patients during the 2nd DNC evaluation (See Fig.19). No documented reason was available for not testing the remainder of the patients.

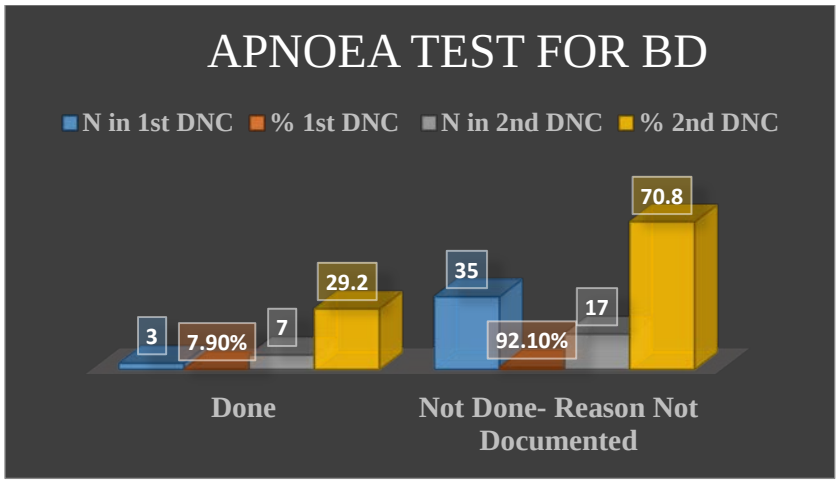


Fig.19: A Clustered Bar Chart Showing Apnoea Test Done in DNC Exam

Below is a summary of apnea test statistics (Table 7). During the 1st DNC evaluation, the pretest PaCO2 ranged from 21.75 mmhg to 37.50 mmhg, with a mean of 32.08 mmhg. Dutaion of Apnoea ranged from 5-10 minutes and post-test PaCO2 ranged between 48 to 65 mmhg. In the 2nd DNC examination, the mean pretest and post-test PaCO2s were 37.57 and 60.71 mmhg respectively, with an apnoea duration ranging from 4-10 minutes.

Summary Statistics	Pretest PaCO2 in 1st DNC (mmHg)	Duration Of Apnoea Test in 1st DNC (Min)	Post-test PaCO2 in 1st DNC (mmHg)	Pretest PaCO2 in 2nd DNC (mmHg)	Duration Of Apnoea Test in 2nd DNC (Min)	Post-test PaCO2 in 2nd DNC (mmHg)
N	3	3	3	7	7	7
Mean	32.08	7.67	59.00	37.57	6.43	60.71
Median	37.00	8.00	64.00	38.00	5.00	58.00
Variance	80.15	6.33	91.00	12.95	6.29	83.57
Range	15.75	5	17.00	11.00	6	24.00
Minimum	21.75	5	48.00	32.00	4	49.00
Maximum	37.50	10	65.00	43.00	10	73.00

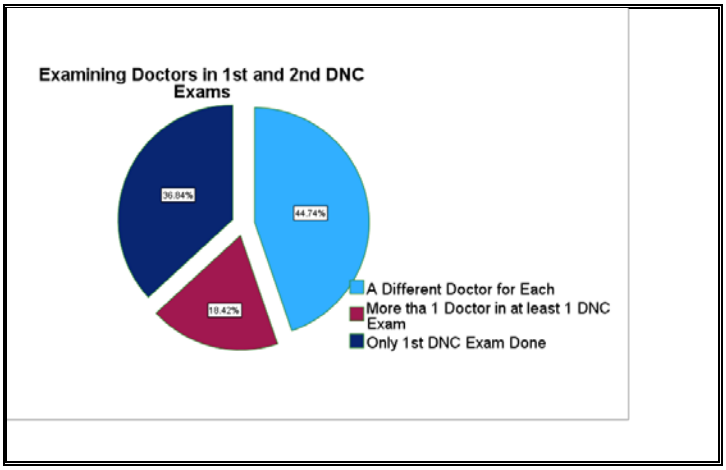
Table 7: Showing Apnoea Test Summary Statistics

In all the apnoea tests, post-test PaCO2 level rose by > 20mmhg or was above 60 mmhg. No spontaneous respiratory effort was recorded for any of these patients. The test was prematurely stopped in 5 (50%) of these tests due to development of bradycardia and desaturations below 85%.

4.6: ANCILLARY TEST

During all the DNC examinations, no ancillary test is reported to have been done, and no reasons were documented for lack of testing.

4.7: DOCTORS PERFOMING BD EXAMINATION



It was found that 17 (44.7%) DNC examinations were carried out by different doctors between initial & final evaluation. More than one doctor participated in a single DNC evaluation in 18.4% of the cases. In 14 (36.8%), only the initial DNC was carried out. (See Fig.20)

Fig.20: A Pie Chart Showing the Doctors who Performed the DNC Exam

The resident doctors perfomed 60 (96.8%) of the examinations, whilst the remaining two were done by a Medical officer (RRA/B) and a Fellow (Pediatrics) each. Neurosurgical residents performed a majority of the BD examination (53.2%), followed by Anaesthesia residents at 24.2%. Some of the BD examination were done by a team composed of residents from different specialties eg Neurosurgery + Anaesthesia (8.1%) and Neurology + Anaesthesia (1.6%). One of ththe evaluation was carried out by a Meidical Officer (Non-Specialist) in Accident & Emergency Unit (See Fig.21).

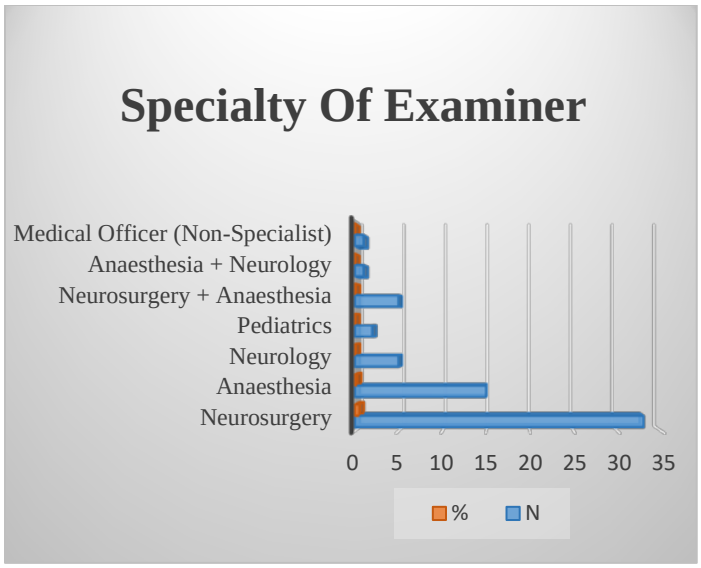
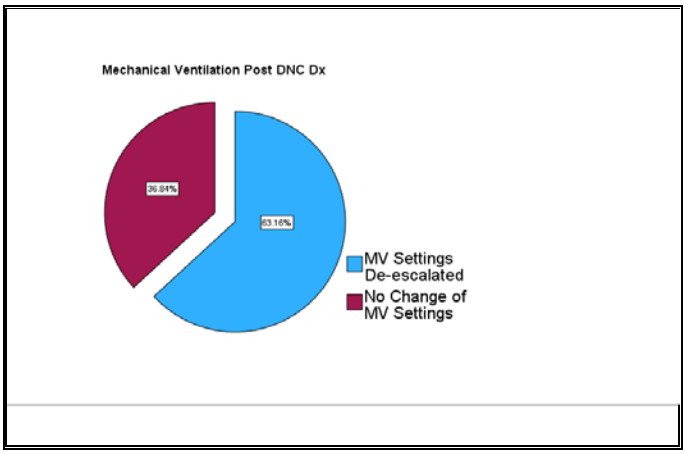


Fig.21: A Bar Chart Showing the Specialty of Examining Doctor

4.8: POST DNC PATIENT MANAGEMENT

4.8.1: Mechanical Ventilation



After a DNC examination, MV settings were de-escalated in 24 (63.2%) of the patient while in 14 (36.8%), they were left unchanged (See Fig…). De-escalation included reduction of FiO2 to ≤ 30%.

Fig.22: A Pie Chart Showing Post-DNC Diagnosis MV Management.

4.8.2: Medical Treatment

Medical treatment was de-escalated in 63.2% and remained unchanged in 36.8% of the patients. Aggressive antibiotic therapy, regular anti-hypertensives etc were withdrawn where de-escalation was adopted. Ionotropic BP support and fluid therapy was generally maintained.

4.8.3: CPR on Asystole

All patients diagnosed with BD (100%), underwent Cardio-Pulmonary Resuscitation upon experiencing asystole. None of these patients was observed to recover from the asystole.

4.8.4: Surgical Intervention

None of the patients underwent any further surgical procedure once a DNC evaluation had been done.

4.8.5: Laboratory Tests and Imaging

For 30 (78.9%) of these patients, further laboratory tests were carried out after a DNC examination. The commonest test was BGA (Table 8). Others included UECs, CBC and LFTs.

List of Labs Done Post DNC Dx

	N	%
BGAs	20	52.6%
BGA + UECs	6	15.8%
BGA + UECs +CBC	2	5.3%
Not Done	8	21.1%
BGA + UECs + CBC + LFTs	2	5.3%

For all (100%) the cases, no further radiological imaging was done

Table 8: Showing Lab Tests Done Post DNC Examination

4.8.6: Supportive Care

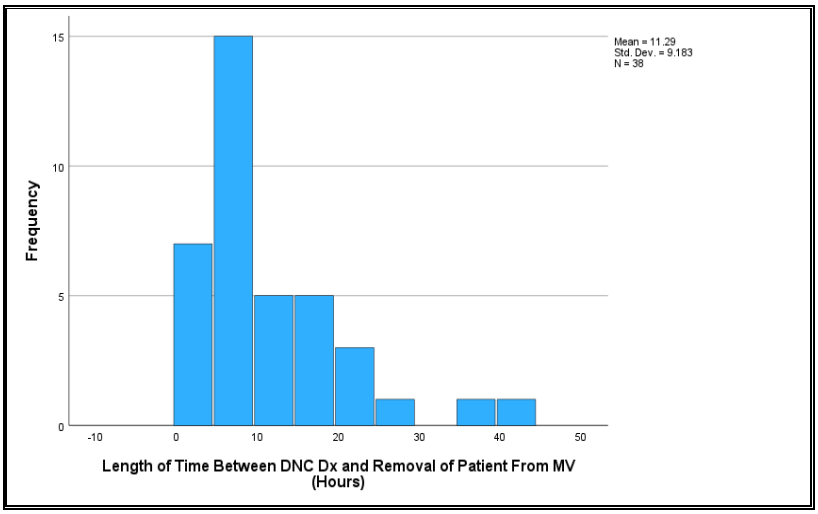
Care was continued unchanged in 36 (94.7%) of these patients. Supportive care included general ICU nursing care eg: Oral and body hygiene, wound care, pressure point care, care of the tubes and IV access points, physiotherapy, among others.

4.8.7: Deceased Organ Donation

None of the patient was a deceased organ donor.

4.8.8: Removal of patient from Mechanical Ventilation

Even after diagnosis of BD all the patients were retained on MV, albeit some on de-escalated vent settings until they went into asystole and for which they did not recover spontaneous cardio-circulatory activity. At this point, the patients were then declared dead were disconnected from the ventilator machines.



Time Interval between BD and Removal from MV (Hours)	
N	38
Mean	11.29
Median	7.50
Std. Deviation	9.183
Range	39
Minimum	2
Maximum	41
Sum	429

Fig.23: A Histogram and Table Showing Time Interval from BD Diagnosis to Removal From MV.

The time interval between the last DNC evaluation and terminal asystole, ranged from 2 to 41 hours, with a mean of 11.29 and median of 7.5 hours. Cumulatively, after BD diagnosis, these patients remained on MV for 429 hours (17.88 days); (see fig.23).

4.8.9: Checklist for BD Evaluation

For all the 62 DNC examinations done, there was no institutional checklist used for documentation of the BD evaluation process. The findings were indicated in the doctors continuation sheets.

CHAPTER 5.0: DISCUSSION

Death is a common and important occurrence with a profound legal, socio-cultural and religious ramifications.[3] Diagnosis of death has evolved over time from relying solely on cessation of cardio-respiratory function, to cessation of brain function, especially with the advent of critical care and mechanical ventilation. [6–8] [9,10] Brain death diagnosis, is dependent largely on clinical evaluation of a critically ill patient. Its important to standardize this process to assure consistency, accuracy and reliability. [3]

This research project sought to review the process of determination of DNC at KNH, identify if a specific protocol is followed, and identify any gaps compared to standard AAN and AAP protocols and determine how patients are managed after DNC diagnosis.

Thirty eight patients were recruited. The age, gender and CCU mix (see figures 4-7), ensured that researcher evaluated practice across different age-groups and critical care centres in KNH. During the study period, no term newborns were recruited. Prematures were not included due to ongoing controversy on earliest age of reliability for BD diagnosis, most protocols preferring not to include them.[1,33,56] Main ICU admits mainly (neuro)-surgical of all ages and gender. Medical ICU admits patients with medical conditions, while PICU and GFB CCU admits children and Obstetrics patients respectively.

All initial DNC evaluation was done >24 hours after severe brain injury or after CPR event. This practice adhered to AAN, AAP and other international BD protocols. [7,10,26,29,32,44–50] Where a 2nd DNC exam was done, age appropriate inter-exam interval was followed ie ≥ 12 hours for children and ≥ 6 hours for adults.[25,28,29] A second DNC evaluation is strongly advocated for in most BD protocols.[25,28,29] Six (15.8%) of the subjects did not undergo a 2nd BD evaluation with no clear documented reason. In countries such as the USA, it's a statutory requirement to conduct 2 BD examination before declaration of DNC.[29,30,33,34] ***Drake et al, 2017***, however noted a lack strong evidence of superiority of 2 over 1 clinical exam in BD diagnosis.[25,28,29]

Establishment of irreversible coma and its likely cause is an important pre-requisite to BD evaluation.[48,59,65] Prior to DNC evaluation of the subjects, GCS was determined to be at 2T and all had neuroimaging in support of a diagnosis consistent with BD. Severe TBI was the

commonest cause of coma (see fig.10), with associated traumatic intracranial bleeds. Hemorrhagic stroke was the commonest cause of coma in GFB CCU patients, mainly in association with Severe Pre-Eclamptic Toxemia (SPET). Sixty-three % of these patients had comorbidies eg AKI, severe anemia, which contributed to worsening of their clinical state. (see fig.11).

Brain death examination findings may be influenced by many factors (confounders) which must be ruled out for the findings to be reliable.[48,59,65] These include: hypotention, hypothermia, severe metabolic anomalies, drug intoxication, upper cervical injury and neurological diseases eg GBS.[1,33,37,38,56]

None of the subjects had hypothermia, with all their pre-exam core temperature > 35^{o}C. Pre-exam BP done showed that 29.8% (1st DNC) and 15.8% (2nd DNC) had their SBP 2 SD below the required for the evaluation (see fig.12). Most of the patients who were hypotensive, were on multiple inotropes, without optimal correction of their BPs. AAP BD guidelines advise that SBP or MAP be within acceptable range based on age.[37,38] Systolic Blood pressure should be > 90mmHg, with a MAP > 60mmHg and can be bolstered by inotropes and fluids.[37,38]

CNS depressants such as NMBAs, opioids, benzodiazepines, sedatives etc, must be ruled out prior to DNC exam.[1,11,66] Eighty four % (1st DNC) and 52.6% (2nd DNC) of the patient were on a CNS depressants. (see fig.14). Phenytoin, an anticonvulsant was the most common drug in use (see Table 5). None of the patient had drug levels measured prior to the exam. Measurement of drug levels is expensive and KNH currently does not have the capacity undertake these tests. Guidelines by AAP and AAN recommend drug levels should be measured and if in a low to mid therapeutic range, then DNC examination can proceed.[37,38]

Severe metabolic disorders must be treated and corrected, because they may interfere with BD examination. These include: electrolyte, pH anomalies, hyper/hypoglycemia, hypothyroidism, hypopituitarism etc.[37,38] About 39.5% (1st DNC) and 17% (2nd DNC) of patients had a severe metabolic disorder prior to the exam (see fig.15). The most prevalent was severe metabolic acidosis. Most of these disorders were corrected fully or partially at the time of the DNC evaluation (see fig 16).

Neurological examination forms the backbone of BD evaluation.[37,38] Coma must be confirmed clinically and demonstrate an absence of brainstem reflexes.[37,38] This was the part of

DNC evaluation where the practice in KNH mirrored closely the internationally acceptable practice. All brainstem reflexes were tested in most of the patients (see fig.17). Cough reflex was not tested in 1 patient in the initial evaluation with no documented reason. Rooting and sucking reflexes were appropriately tested in the infants. They represent primitive brainstem reflexes that develop late in the intrauterine life and persist until 6 months to 2 years of life.[68–72] Oculocephalic reflex was not documented as done in 6 (9.7%) DNC evaluations, while oculovestibular was not documented in 7 (11.3%) examinations. In 2 patients, oculovestibular reflex was not done due to presence of otorrhea and tympanic perforation. Also called caloric test, Oculovestiblar reflex involves instillation of approximately 50cc of ice-cold water in each ear as the movement of the eyes are keenly observed.[1,11,66] Its contraindicated in tympanic perforation and otorrhea. An alternative in these cases is the oculocephalic reflex (Doll's eye), both of which share neural pathways to the brainstem. Oculocephalic reflex on the other hand is contraindicated in cervical spine injury.[1,11,66]

Pupillary reflexes were done in all patients. Pupillary sizes ranged from 4-8mm, and unreactive, which is consistent with BD findings (see table 6 & fig.18). Pupillary size in BD may be in mid to fully dilate.[37,38] It may be influenced by many drugs eg cocaine, amphetamines, phenylephrine etc of which the examiner must be aware. [1,19,49]

Apnoea test is a very important test in the clinical diagnosis of BD. Its mandatory in most BD protocols including AAN and AAP guidelines, unless medically contra-indicated. [1,11,66] The procedure of doing the test must be adhered to for patient's safety and reliability of the test. [37,38] Out of the 62 BD examinations, apnoea test was done in only 10 (3 initial and 7 final), which translated to about 16% of the examination (see fig.19). No documented reason was given for not doing the test. This problem affected all the CCU units. Where the test was done, the procedure was generally adhered to: pretest and post-test PaCO2 were recorded and the duration of apnoea ranged from 4-10 minutes (see table 7). There was no spontaneous respiratory efforts even with PaCO2 above 60 mmhg or $\geq$ 20mmhg above the baseline as is recommended in the guidelines.[1,66] Fifty % of the apnoea tests were prematurely stopped when the patients developed bradycardia and desaturated to below 85%. These are known risks in performance of the test and necessitate stoppage. The patient is reconnected to the MV and allowed about 24 hours before repeat testing, or an ancillary test is done. [37,38]

Ancillary tests are instrumental tests that may be used under certain circumstances to support the diagnosis of BD e.g. where a full neurological exam cannot be done, where apnoea test cannot be done or is aborted.[44,60] Presence of confounders eg use of CNS depressants, may also necessitate use of ancillary tests. [37,38] These studies are either cerebral blood flow-based or aim to demonstrate the brain electrical activity. They include Cerebral angiography, Scintigraphy, EEG etc.[37,38] None of the patients under this study underwent an ancillary test. While catheter angiography and Scintigraphy are currently not available in KNH, EEG, CT Angiography, MR Angiography are available and can be used as alternatives for ancillary testing.[37,38,53]

Regarding the cadres of doctors who can perform BD examination, its still a matter of debate. Most guidelines advocate for doctors who work in the neurocritical care units eg Anaesthetists, neurosurgeons, neurologists.[28,47] AAP guidelines advocate for pediatric intensivists/pediatric neurologists/Neurosurgeons or other physicians participating in the care of the child.[37,38] ***Drake et al, 2017***, advocates for a hospital based training policy for physicians involved in BD determination.[28,47] In KNH, 60 (96.8%) were performed by resident doctors (see fig. 20). Neurosurgical (53.2%), followed by anaesthesia (24.2%) residents, performed the most examinations. Other specialties included neurology (See fig. 21). There was no significant inter-cadre variance in the performance of the DNC evaluation.

After confirmation of BD, in the USA, organ procurement organization is promptly informed. The patient then is managed with the aim of preserving his organs for purposes of organ donation.[7,38,76] In jurisdictions which allow disconnection of patient from the ventilator, its done in a manner that is sensitive to the feelings of the next of kin.[21,47] In KNH, MV settings, and medical treatment were de-escalated for patient after the second DNC evaluation. (see fig. 22). The FiO2 is generally reduced to ≤30% and aggressive therapies eg antibiotics withdrawn. Fluid, ionotropic therapy is generally continued. A number of laboratory tests are continued even after BD diagnosis (see table 8). No further imaging and surgical care was given after BD diagnosis. Supportive care was generally continued after BD determination.

While there transplant surgeries done at KNH, an established organ donor programme is yet to be established both in-hospital and nationally. Deceased donor programme is yet to be supported legally and therefore there was no deceased organ donation from these patients. Brain

dead patient will inevitably deteriorate in cardiorespiratory function to asystole and the period between BD and asystole is numbered in days.[28,58] In KNH, after BD diagnosis because of lack of legal and policy framework allowing for early disconnection of patient from the MV, patient are maintained on the MV until asystole. In this group, time to asystole ranged between 2 and 41 hours, with a mean duration 11.29 hours. Cumulatively, all the patients stayed on MV for 429 hours (17.88 days). Additionally, at the point of asystole, all the patients were resuscitated without ROSC. In all the 62 BD examination, there was no institution based checklist followed by the examiners as a standard guide and for standardized documentation.

5.1: CONCLUSION

In a resource limited country like Kenya, critical care facilities are precious, scarce and expensive. [7] Centers like KNH are becoming important in critical care provision and as transplant centres. It's becoming imperative that cost saving measures be adopted especially around critical care service provision, which are supported by a matching legal and policy framework. Brain Death as a concept has gained acceptance in Kenya especially in the medical community. Religious and socio-cultural sensitization is important in widening understanding and acceptance among the wider lay public.

A clear policy on Brain Death both nationally and intra-hospital would be important in clarifying to health care workers on when to declare death upon BD evaluation, how to de-escalate care in the event of BD, communicate more effectively with next of kin, when to disconnect MV and therefore save on the limited ICU space.

In this study, as articulated in the broad objective, the practice of determination of death by neurological criteria (DNC) at KNH was reviewed. This was done against the internationally accepted AAP and AAN BD protocols. Pre-examination, requirements, Examination Processes and post-BD management of these patients were evaluated. Variuos CCUs in the institution and patients in all age-groups were included, in-order to tease out variation in BD diagnostic processes across units and ages in the Hospital.

As is evident in this study, diagnosis of BD at KNH has notable gaps. Some parts of the examination are skipped without documented rationale. An important aspect of the exam such an

apnoea test is often not done, without documented rationale. Where ancillary tests are warranted, there is no evidence of being done. There is lack of a standardized protocol and checklist on DNC, which would ensure important steps in the process of BD evaluation are not skipped and are duly documented. The hospital would benefit greatly from such a protocol which would form a template for adoption by other critical care providers in the region.

Whilst certain aspects of DNC are expensive and may not be easily achievable in the setting of LMICs, for instance use of SPECT and Catheter Angiography routinely as ancillary tests, there are affordable alternatives EEG, which can fill the gap without compromising the quality of BD diagnosis.

Finally an organized, reliable, consistent and standardized local system of BD diagnosis will spur discussion regarding deceased-organ and tissue donation and transplantation which is an emerging but very vital field in Kenya and the region. Where, like in the Western Countries (HICs), Post-DNC, the patient is either disconnected from the MV or entered into an organ donation programme, its incumbent upon the Health Care providers (Doctors), the Hospitals eg KNH, the MOH and the country, to have a fool-proof system of BD diagnosis which is above reproach in ordered to gain a buy-in of the general public for whom these programmes are designed to benefit.

5.2: RECOMMENDATIONS

5.2.1: TO DOCTORS MANAGING CCU PATIENTS

1. It’s important to be familiar with BD death diagnostic protocols prior to carrying out BD diagnosis in your Unit.

2. Where local institutional protocols are lacking, AAP and AAN DNC protocols can be employed, for children and adult patients respectively.

3. Completeness of BD evaluation, including detailed documentation is vital in ensuring standardization and reliability of BD diagnosis.

4. Local advocacy for local protocols, BD policies including more proactive post BD management e.g. removal of patients from MV, Deceased organ donation & No CPR for BD patients.

5.2.2: KNH and other HOSPITALS

1. Form a task-force headed by the Directorate of Clinical Services with relevant Hospital Stakeholders including CCUs, Hospital legal division to develop a local (Intra-Hospital) Brain Death protocol and can easily be adopted from Brain Death guidelines developed by AAN for adults and AAP for children, which are the most recognizable BD guidelines worldwide.

2. Standard checklists (See Appendix III and IV), be co-opted as part of KNH documentation for mandatory use when doing BD evaluation.

3. Ensure Formal training of all doctors, but especially those managing neurocritical patients, on BD examination. This will enhance a standardized practice around BD evaluation and care.

4. Advocacy to the MOH and government (both County and Central) on refining legal and policy framework on Brain Death, Deceased organ donation and transplant services.

5. Conduct Further research on the cumulative cost of sustaining BD patients in ICU from the time death is declared to asystole.

5.2.3: THE COUNTY & CENTRAL GOVERNMENT (MoHs, LEGISLATURES & EXECUTIVE)

1. Kenya, like many LMICs requires a clear policy framework regarding BD, including: a clear Definition of BD and what happens to the BD patient after diagnosis.

2. Formulate in concert with the Hospitals and County/Country-Wide standard BD diagnosis protocol and therefore standardize this BD diagnosis.

3. Formulate mechanisms for the above standards (in 5.2.1.2), are followed strictly eg periodic audits of BD diagnoses.

4. Bolster deceased-organ Donor programmes in order to utilize the potential salvageable organs from BD patients and therefore serve a greater good to the general public.

5. Fund further local research on BD diagnosis, deceased-Organ and Tissue transplantation through the Local Hospitals.

APPENDIX I: CONSENT FORM

KNH-UoN/ERC/FORM/IC02

UNIVERSITY OF NAIROBI (UoN)
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH-UoN ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: ttps://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC ttps://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL (KNH)
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE:

DEATH BY NEUROLOGICAL CRITERIA: A REVIEW OF DIAGNOSTIC PRACTISE, AIMED AT PROPOSAL OF A STANDADISED PROTOCOL AT KNH

PRINCIPLE INVESTIGATOR

DR SOITA WYCLIFFE CHITIAVI

NEUROSURGERY RESIDENT, UNIVERSITY OF NAIROBI

CONTACT: 0726-269757

EMAIL: wsoita@yahoo.com

Introduction

Dr Soita W. Chitiavi is a senior Neurosurgery Resident at the UON. He is conducting research for his Masters of Medicine in Neurosurgery thesis. The purpose of this consent form is to give you the information you will need to help you decide whether or not to allow your critically ill next of kin in ICU (here in referred to as the ***"Indisposed Kin"***), be a participant in the research. Feel free to ask any questions about the purpose of the research, what happens if your Indisposed kin participates in the study, the possible risks and benefits, his/her rights as a subject, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide to allow participation in the study or not. This process is called ***'informed consent'***. Once you understand and agree that your Indisposed kin can be in the study, I will request you to sign your name on this form. Your decision for participation is entirely voluntary. You may request for withdrawal from the study at any time without necessarily giving a reason for your withdrawal. Refusal to participate in the research will not affect

the services you or your Indisposed kin are entitled to in this health facility or other facilities. We will give you a copy of this form for your records.

May I continue? YES _____ NO _____

This study has approval by The **Kenyatta National Hospital-University of Nairobi Ethics and Research Committee**: Protocol No.....

WHAT IS THIS STUDY ABOUT?

This Research will **review how the diagnosis of patients with Brain Death is made in KNH, and how they are managed subsequently**. Patients admitted to ICU are usually critically ill and most of them are put on ventilators to support their breathing. Those who develop irreversible brain dysfunction and are diagnosed as Brain dead, will form the subjects of this study. There will be approximately 38 patients in this study, of all age groups, who meet the inclusion criteria. We are asking for your consent as the next of kin of such an ICU patient to consider that he/she be enrolled in this study.

WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH STUDY?

If you agree to participate in the study. The following will happen.

1. One of our researchers will assign your indisposed Kin a unique identification number that will be used to track his/her records. The researcher will then use the predesigned data collection tool to collect relevant information on how the Brain Death diagnosis was arrived at. The researcher will study the patient's scans and medical records and enter the findings in the data collection form.
2. The researcher will clarify any information with the Diagnosing Doctor (s), as necessary, regarding the process of Determination of Death.

ARE THERE ANY RISKS, HARMS DISCOMFORTS ASSOCIATED WITH THIS STUDY?

Medical research has the potential to introduce psychological, social, emotional and physical risks. A potential risk of being in the study is loss of privacy. We will keep all the information from you and the medical records for your loved one, confidential. Only a code number will identify your Indisposed kin, in a password-protected computer database. All paper records used in the research will be under lock and key, accessible only to the researchers. However, no system of protecting your confidentiality can be absolutely secure, there is a small chance of inadvertent exposure of the data to unwanted persons.

The subject matter of this study is sensitive, psychologically and emotionally draining. Answering some questions in the interview may be uncomfortable for you. If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview. No additional risk to you or your patient, shall be introduced.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

You and your indisposed kin will potentially play a major role in the development a standardized protocol on Brain Death, not only in KNH, but also nationally and regionally. This may form a building block to improving Kenyan laws around ICU care. This information is a contribution to science and helps improve patient outcomes.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

Being in this study will not cost you anything beyond what you would have spent were you not part of the study.

WILL YOU GET REFUND FOR ANY MONEY SPENT AS PART OF THIS STUDY?

You will not spend anything beyond what you would have spent were you not a part of the study.

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page. For more information about your rights as a research participant you may contact the

Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.

The study staff will pay you back for your charges to these numbers if the call is for study related communication.

WHAT ARE YOUR OTHER CHOICES?

Your decision to have your Indisposed Kin participate in this research is voluntary. You are free to decline or withdraw participation of your Indisposed Kin in the study at any time without injustice or loss of benefits. Just inform the study staff and the participation of your Indisposed Kin in the study will be stopped. You do not have to give reasons for withdrawing your child/Kin if you do not wish to do so. Withdrawal of your Indisposed Kin from the study will not affect the services your Indisposed Kin is otherwise entitled to in this health facility or other health facilities.

CONSENT FORM (STATEMENT OF CONSENT)

The person being considered for this study (Indisposed Kin) is unable to consent for him/herself because he or she is a minor (a person less than 18 years of age)/ critically ill. You are being asked to give your permission to include your Indisposed Kin in this study.

Parent/guardian statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered by him or her in a language that I understand. The risks and benefits have been explained to me. I understand that I will be given a copy of this consent form after signing it. I understand that my participation and that of my Indisposed Kin in this study is voluntary and that I may choose to withdraw it any time. I understand that all efforts will be made to keep information regarding me and my Indisposed Kin's personal identity confidential. By signing this consent form, I have not given up my Indisposed Kin's legal rights as a participant in this research study.

I voluntarily agree to my Indisposed Kin's participation in this research study:
Yes_____ No_____

I agree to provide contact information for follow-up: Yes_____ No_____
Parent/Guardian signature /Thumb stamp: _____ Date _____
Parent/Guardian printed name: _____

Researcher's statement
I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given his/her consent.
Printed Name: _____ **Date**: _____
Signature: _____
Role in the study: _____
For more information contact DR Soita W. Chitiavi on 0726-269757 or email @ wsoita@yahoo.com, from 8:00am to 5:00 PM Monday to Friday

Witness Printed Name (*If witness is necessary*) _____

Signature: _____ Date; _____

APPENDIX II: DATA COLLECTION TOOL FOR DNC

S/No: **CCU Unit:**

PATIENT DEMOGRAPHICS

1. **Age** of the patient: ☐ years/Months

   ☐ Term Newborn ☐ Child ☐ Adult

2. **Sex** of the patient:

   ☐ Male ☐ Female

3. Date and time of:

   a) First DNC Examination: _____

   b) Second DNC Examination: _____

4. Timing of first DNC Exam:

   Term Newborn: Post-Delivery ☐ <24 hrs ☐ >24 hrs

   Post CPR/Severe BI ☐ <24 hrs ☐ >24 hrs ☐ N/A

   Child: Post CPR/Severe BI ☐ <24 hrs ☐ >24 hrs ☐ N/A

   Adult: Post CPR/Severe BI ☐ <24 hrs ☐ >24 hrs ☐ N/A

5. Inter-examination interval

   Term Newborn: ☐ <24 hrs ☐ ≥24hrs ☐ N/A

   Child: ☐ <12 hrs ☐ ≥12hrs ☐ N/A

   Adult: ☐ <6 hrs ☐ ≥6 hrs ☐ N/A

PREREQUISITES FOR BRAIN DEATH EXAMINATION AND APNEA TEST

6. Pre-examination **GCS** of the patient (**x/15**): ☐ ☐ Not Indicated.

7. Neuro-Imaging done

   a) Type of Study:

   ☐ CT ☐ MRI ☐ CTA ☐ Cranial US

   ☐ Other (Specify) _____

   b) Main Radiologic Diagnosis: _____

8. Irreversible and Identifiable Cause of Coma

   ☐ TBI ☐ Brain SOL

   ☐ Anoxic Brain Injury ☐ Metabolic Disorder

   ☐ Other (Specify) _____

CONFOUNDERS TO BRAIN DEATH NEUROLOGIC EXAMINATION

	1st Exam	2nd Exam
9. Pre-Examination **Core temperature**:	☐ ≤ 35^0C	☐ ≤ 35^0C
	☐ > 35^0C	☐ > 35^0C

10. Pre-Examination **Blood Pressure** readings:

a) Absolute values: **SBP**_____mmhg **SBP**_____mmhg

MAP_____ mmhg **MAP**_____ mmhg

a) Was the **SBP** within **2 SD** of **normal SBP for age**? ☐ Yes ☐ Yes

☐ No ☐ No

11. Was the patient on any of these **medications** 24 hours prior DNC?

a) Opioids ☐ Yes ☐ Yes

b) Muscle Relaxants ☐ No ☐ No

c) Barbiturates

d) Benzodiazepines

e) Other CNS Depressants

If yes, list specific drugs given_____

12. If **Yes** (in **No. 11** above), were **drug levels** measured prior to DNC?

☐ Yes ☐ Yes

☐ No ☐ No

13. Where drug levels were measured, was the level **allowable** for DNC exam to be carried out?

☐ Yes ☐ Yes

☐ No ☐ No

14. Did the patient have any **severe metabolic derangements** prior to DNC?

☐ Yes ☐ Yes

☐ No ☐ No

If Yes, Specify_____

15. Were the metabolic derangements noted (in **14** above), **corrected** prior to DNC exam?

☐ Yes ☐ Yes

☐ No ☐ No

NEUROLOGIC EXAMINATION TO DNC

	1st Exam	2nd Exam
16. Was the **tone** and **motor response** to noxious stimuli, **flaccid** and **unresponsive?**		
	☐ Yes	☐ Yes
	☐ No	☐ No
17. **Pupillary light reaction**:		
a) What was the **size** of pupils?	_____mm	_____mm
b) Light **reflexes**	☐ Present	☐ Present
	☐ Absent	☐ Absent
18. Were **Corneal Reflexes** Absent?		
	☐ Yes	☐ Yes
	☐ No	☐ No
19. Was **gag reflex** absent?		
	☐ Yes	☐ Yes
	☐ No	☐ No
20. Was **Cough reflex** absent?		
	☐ Yes	☐ Yes
	☐ No	☐ No
21. Were **Sucking** and **rooting reflexes** are absent (in **neonates** and **infants**)?		
	☐ Yes	☐ Yes
	☐ No	☐ No
22. Were **Oculocephalic reflexes** are absent?		
	☐ Yes	☐ Yes
	☐ No	☐ No
23. Were **Oculovestibular reflexes** are absent?		
	☐ Yes	☐ Yes
	☐ No	☐ No
24. Was **Spontaneous respiratory effor**t while on mechanical ventilation absent?		
	☐ Yes	☐ Yes
	☐ No	☐ No

APNEA TEST

	1st Exam	2nd Exam
25. Was the **apnoea test** done?		
	☐ Yes	☐ Yes
	☐ No	☐ No
26. **If No** in **25** above, specify reason_____		
27. What was the **Pretest $PaCO_2$** ?:	_____mmHg	_____mmHg
28. What was the **apnoea duration** in minutes?	_____	_____
29. What was the **Post-test $PaCO_2$** ?:	_____mmHg	_____mmHg
30. Were there any **spontaneous respiratory efforts** observed with a final $PaCO_2$ of **≥60mmHg** and a **≥20mmHg** increase above baseline?		
	☐ Yes	☐ Yes
	☐ No	☐ No
31. Was the test **prematurely abandoned**?		
	☐ Yes	☐ Yes
	☐ No	☐ No
32. **If Yes** in **31** above, state the reason_____		

ANCILLARY TESTING

33. Was **ancillary testing** done in this patient?		
	☐ Yes	☐ Yes
	☐ No	☐ No
34. **If yes** in **33**, **why** was ancillary testing done?		
a) To **shorten** the inter-Examination period:	☐ Yes	☐ Yes
	☐ No	☐ No
b) Presence of a **confounding variable**:		
	☐ Yes	☐ Yes
(If yes, specify) _____	☐ No	☐ No

	1st Exam	2nd Exam
c) Parts of the **Neurological Exam** could not be done: (If Yes, Specify which & why) _____	☐ Yes	☐ Yes
	☐ No	☐ No
d) **Apnea Exam** could not be completed (If yes, why?)_____	☐ Yes	☐ Yes
	☐ No	☐ No

35. If Yes in 33, **which ancillary test** was used?

☐ EEG ☐ CBF Study

36. What were the **results** of the ancillary test?

a) **EEG** study showed **electro-cerebral silence**?	☐ Yes	☐ Yes
	☐ No	☐ No
e) **CBF** study documented **no cerebral perfusion**?	☐ Yes	☐ Yes
	☐ No	☐ No

CADRES OF THE EXAMINERS

37. Were **both** examinations done by the **same Doctor**?

☐ Yes ☐ No

38. What was the **qualification** of the Examiner (s)?

☐ MO ☐ Resident ☐ Consultant

40. If the Examiner(s), was a **Resident/Consultant**, state their **specialty**:

_____ _____

POST DNC PATIENT MANAGEMENT

41. After declaration of DNC, how did the **Mechanical ventilation** change?

☐ MV Switched off ☐ Settings De-escalated ☐ No Change

42. After declaration of DNC, how did the **Medical Therapy** (MRx) change?

☐ All MRx stopped ☐ Some MRx stopped ☐ No change

43. After declaration of DNC, was there any **additional surgical intervention** done?

☐ Yes ☐ No

If Yes, specify_____

44. After declaration of DNC, were there further **Laboratory & Imaging Investigations** done?

☐ Yes ☐ No

If Yes, Specify_____

45. After declaration of DNC, how did the **supportive care** of the patient change?

☐ All care stopped ☐ Care Des-escalated ☐ No Change

46. After declaration of DNC, was there **deceased organ donation** by this patient?

☐ Yes ☐ No

If Yes, Specify_____

47. After declaration of DNC at what point was the patient **removed from** the **MV**?

☐ Immediately ☐ Confirmed Asystole ☐ When the Next of Kin decided

48. After declaration of DNC, **how long** did it take until the patient was removed from MV?

_____Hours.

APPENDIX III: Check List for Documentation of Brain Death In Adults by AAN [53,55]

Prerequisites (all must be checked)

- ☐ Coma, irreversible and cause known
- ☐ Neuroimaging explains coma
- ☐ CNS depressant drug effect absent (if indicated toxicology screen; if barbiturates given, serum level 10 g/mL)
- ☐ No evidence of residual paralytics (electrical stimulation if paralytics used).
- ☐ Absence of severe acid-base, electrolyte, endocrine abnormality
- ☐ Normothermia or mild hypothermia (core temperature 36°C)
- ☐ Systolic blood pressure 100 mm Hg
- ☐ No spontaneous respirations

Examination (all must be checked)

- ☐ Pupils nonreactive to bright light
- ☐ Corneal reflex absent
- ☐ Oculocephalic reflex absent (tested only if C-spine integrity ensured)
- ☐ Oculovestibular reflex absent
- ☐ No facial movement to noxious stimuli at supraorbital nerve, temporomandibular joint
- ☐ Gag reflex absent
- ☐ Cough reflex absent to tracheal suctioning
- ☐ Absence of motor response to noxious stimuli in all 4 limbs (spinally mediated reflexes are permissible)

Apnea testing (all must be checked)

- ☐ Patient is hemodynamically stable
- ☐ Ventilator adjusted to provide normocarbia (PaCo2 34 – 45 mm Hg)
- ☐ Patient preoxygenated with 100% FiO2 for 10 minutes to PaO2 200 mm Hg
- ☐ Patient well-oxygenated with a PEEP of 5 cm of water
- ☐ Provide oxygen via a suction catheter to the level of the carina at 6 L/min or attach T-piece with CPAP at 10 cm H2O
- ☐ Disconnect ventilator
- ☐ Spontaneous respirations absent
- ☐ Arterial blood gas drawn at 8 –10 minutes, patient reconnected to ventilator
- ☐ PCO2 60 mm Hg, or 20 mm Hg rise from normal baseline value OR:
- ☐ Apnea test aborted

Ancillary testing (only 1 needs to be performed; to be ordered only if clinical examination cannot be fully performed due to patient factors, or if apnea testing inconclusive or aborted)

- ▫ Cerebral angiogram
- ▫ HMPAO SPECT
- ▫ EEG
- ▫ TCD

Time of death (DD/MM/YY) _____

Name of physician and signature _____

APPENDIX IV: Check List for Documentation of Brain Death in Children by AAP[37]

Brain Death Examination for Infants and Children

Two physicians must perform independent examinations separated by specified intervals.

Age of Patient	Timing of first exam	Inter-exam. interval
Term newborn 37 weeks gestational age and up to 30 days old	☐ First exam may be performed 24 hours after birth OR following cardiopulmonary resuscitation or other severe brain injury	☐ At least 24 hours ☐ Interval shortened because ancillary study (section 4) is consistent with brain death
31 days to 18 years old	☐ First exam may be performed 24 hours following cardiopulmonary resuscitation or other severe brain injury	☐ At least 12 hours OR ☐ Interval shortened because ancillary study (section 4) is consistent with brain death

Section 1. PREREQUISITES for brain death examination and apnea test

A. IRREVERSIBLE AND IDENTIFIABLE Cause of Coma (Please check)

☐ Traumatic brain injury ☐ Anoxic brain injury ☐ Known metabolic disorder ☐ Other (Specify) _____

B. Correction of contributing factors that can interfere with the neurologic examination	Examination One		Examination Two	
a. Core Body Temp is over 95° F (35° C)	☐ Yes	☐ No	☐ Yes	☐ No
b. Systolic blood pressure or MAP in acceptable range (Systolic BP not less than 2 standard deviations below age appropriate norm) based on age	☐ Yes	☐ No	☐ Yes	☐ No
c. Sedative/analgesic drug effect excluded as a contributing factor	☐ Yes	☐ No	☐ Yes	☐ No
d. Metabolic intoxication excluded as a contributing factor	☐ Yes	☐ No	☐ Yes	☐ No
e. Neuromuscular blockade excluded as a contributing factor	☐ Yes	☐ No	☐ Yes	☐ No

☐If ALL prerequisites are marked YES, then proceed to section 2, OR
☐ _____confounding variable was present. Ancillary study was therefore performed to document brain death. (Section 4).

Section 2. Physical Examination (Please check) NOTE: SPINAL CORD REFLEXES ARE ACCEPTABLE	Examination One Date/ time: _____		Examination Two Date/ Time: _____	
a. Flaccid tone, patient unresponsive to deep painful stimuli	☐ Yes	☐ No	☐ Yes	☐ No
b. Pupils are midposition or fully dilated and light reflexes are absent	☐ Yes	☐ No	☐ Yes	☐ No
c. Corneal, cough, gag reflexes are absent	☐ Yes	☐ No	☐ Yes	☐ No
Sucking and rooting reflexes are absent (in neonates and infants)	☐ Yes	☐ No	☐ Yes	☐ No
d. Oculovestibular reflexes are absent	☐ Yes	☐ No	☐ Yes	☐ No
e. Spontaneous respiratory effort while on mechanical ventilation is absent	☐ Yes	☐ No	☐ Yes	☐ No

☐The _____ (specify) element of the exam could not be performed because_____.
Ancillary study (EEG or radionuclide CBF) was therefore performed to document brain death. (Section 4).

Section 3. APNEA Test	Examination One Date/ Time_____	Examination Two Date/ Time_____
No spontaneous respiratory efforts were observed despite final $PaCO_2 \geq 60$ mm Hg and a ≥ 20 mm Hg increase above baseline. (Examination One) No spontaneous respiratory efforts were observed despite final $PaCO_2 \geq 60$ mm Hg and a ≥ 20 mm Hg increase above baseline. (Examination Two)	Pretest $PaCO_2$: _____ Apnea duration: _____min Posttest $PaCO_2$: _____	Pretest $PaCO_2$: _____ Apnea duration: _____min Posttest $PaCO_2$: _____

Apnea test is contraindicated or could not be performed to completion because_____.
Ancillary study (EEG or radionuclide CBF) was therefore performed to document brain death. (Section 4).

Section 4. ANCILLARY testing is required when (1) any components of the examination or apnea testing cannot be completed; (2) if there is uncertainty about the results of the neurologic examination; or (3) if a medication effect may be present. **Ancillary testing can be performed to reduce the inter-examination period however a second neurologic examination is required. Components of the neurologic examination that can be performed safely should be completed in close proximity to the ancillary test**	**Date/Time:** _____
☐ Electroencephalogram (EEG) report documents electrocerebral silence OR	☐ Yes ☐ No
☐ Cerebral Blood Flow(CBF) study report documents no cerebral perfusion	☐ Yes ☐ No

Section 5. Signatures

Examiner One

I certify that my examination is consistent with cessation of function of the brain and brainstem. Confirmatory exam to follow.

_____ _____
(Printed Name) (Signature)

_____ _____ _____ _____
(Specialty) (Pager #/License #) (Date mm/dd/yyyy) (Time)

Examiner Two

☐I certify that my examination☐ and/or ancillary test report ☐confirms unchanged and irreversible cessation of function of the brain and brainstem. The patient is declared brain dead at this time.
Date/Time of death: _____

_____ _____
(Printed Name) (Signature)

_____ _____ _____ _____
(Specialty) (Pager #/License #) (Date mm/dd/yyyy) (Time)

APPENDIX V: GLASGOW COMA SCALES- ADULT & PEADIATRIC[31,59,63,106]

Glasgow Coma Scale (Adult): 15 Points (Teasdale and Jennett[14])		Paediatric Glasgow Coma Scale: 14 Points (Simpson and Reilly[16])	
Response	**Score**	**Response**	**Score**
Eye Opening		**Eye Opening**	
Spontaneous	4	Spontaneous	4
To sound	3	To sound	3
To pain	2	To pain	2
Nil	1	Nil	1
Best Verbal Response		**Best Verbal Response**	
Oriented	5	Oriented	5
Confused conversation	4	Words	4
Inappropriate words	3	Vocal sounds	3
Incomprehensible sounds	2	Cries	2
Nil	1	Nil	1
Best Motor Response*		**Best Motor Response**	
Obeys commands	6	Obeys commands	5
Localizes pain	5	Localizes pain	4
Flexion-withdrawal	4	Flexion	3
Flexion-abnormal	3	Extension	2
Extension	2	Nil	1
None	1		
Maximum Score	**15**	**Maximum Score**	**14**

*Teasdale and Jennett's 14-point scale, which was described in 1974,[11] has a total of 5 points for the best motor score because there is only one tier for flexion, rather than two tiers, as in the 15-point scale, which is currently used in most centers.

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