Peer Review File

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Comment 1: Page 2 line 29 and page 5 line 98. The authors refer to the 1987 American Academy of Pediatrics Task Force on Brain Death in Children. This Taskforce was not an AAP Taskforce and the Guideline did not represent an Academy policy as is commonly cited in the literature. The Taskforce was composed of experts from the medical and legal communities. The Guidelines were published in Pediatrics but never "endorsed" as an official policy by the AAP. (Narkewicz RM. Guidelines for the Determination of Brain Death in Children. Pediatrics. 1989;83:629). This should be corrected.

Reply 1: Thank you for noting this. We agree and have amended in accord with this suggestion. On **Page 3, Paragraph 1**, we now state: "In spite of early trepidation, criteria for pediatric brain death certification were first proposed in 1987 ***by a multidisciplinary committee comprised of experts in the medical and legal communities.***" Similarly, on **Page 6, Paragraph 2**, we have amended the sentence, "Medical criteria for the diagnosis of brain death in children were developed in 1987 by the American Academy of Pediatrics Task Force on Brain Death in Children…" to now read, "Medical criteria for the diagnosis of brain death in children were developed in 1987 ***by a multidisciplinary panel of medical and legal experts.***"

Comment 2: The abstract clearly states the author's position on the endorsement of the joint guidelines. I would consider including something to this effect in the introduction as well, though it's not absolutely necessary.

Reply 2: Thank you for this feedback. We have amended our introduction to make our viewpoints more explicit, and have added the following sentence on **Page 4, Paragraph 2**: "Our views are in alignment with the current published guidelines for pediatric brain death determination and other brain death guidance statements written by our professional societies. We advocate that it is important that providers familiarize themselves with these documents to prevent perpetuation of controversy and confusion surrounding brain death in children."

Comment 3: Page 5 line 102. In review of the current 2011 Guidelines, status epilepticus is not mentioned as a confounding issue or a condition that mimics neurologic death. Other variables such as drug intoxication, toxins, and hypothermia more precisely reflect conditions that can mimic neurologic death.

Reply 3: Thank you for noting this. We agree. We have amended the sentence on **Page 6, Paragraph 2** as follows: "The guidelines recommend that to diagnose brain death in children, a mechanism of irreversible brain injury must be identified with confounders and mimicking conditions excluded, such as electrolyte derangements, ***drug intoxication, and hypothermia.***"

Comment 4: Page 5 paragraph on medical criteria. It might be helpful to readers to include other unique issues such as age specificity and determination of neurologic death in neonates that were specific areas expanded upon in the revised Pediatric Guideline. The large age range of pediatric patients can make determination of death challenging based on changes in physiology and mechanism of disease based on age of the patient.

Reply 4: Thank you for this feedback. We agree and have added additional detail **on Page 6, Paragraph 6** regarding age-specific recommendations in brain death determination as follows: "Age-specific recommendations address the challenge of diagnosing brain death in the pediatric patient, as physiology and disease processes manifest differently depending on age. For term neonates up to 30 days of age, the observation period between examinations should be 24 hours, but only 12 hours is required for infants and children from 30 days to 18 years of age. Ancillary studies in neonates may have limited sensitivity, and thus providers should rely on repeated examinations to make the diagnosis when possible. The guidelines state that it is not appropriate to diagnose brain death in preterm infants, as brainstem reflexes may be incompletely developed in this patient population."

Comment 5: Page 6 line 119 refers to the concept of brain death. This is something that ethicists have debated. Many of the high profile cases really focus on the belief of the family that brain death is not death.

Reply 5: Thank you and we agree. We have amended the sentence on **Page 7, Paragraph 2** to now read: "Controversy surrounding brain death has centered largely around these ethical and

philosophical questions and has resurfaced in the wake of several highly-publicized cases in which a ***belief was expressed that brain death is not equivalent to biological death.***"

Comment 6: P 7, line 138. Agree that western cultures in general more accepting, but would provide a reference.
Reply 6: Thank you; we agree and have added the following reference on **Page 8, Paragraph 2**: Bowman KW. Culture, Brain Death, and Transplantation. *Progress in Transplantation*. 2003;13(3):7.

Comment 7: P8, line 174: "The dead donor rule underscores…" – I think I get your point but I think a different choice of words could make this statement more clear and therefore more poignant.
Reply 7: Thank you for the feedback and we agree. We have deleted and re-worded the sentence on **Page 10, Paragraph 2,** which now reads as follows: "Brain death determination should be standardized and objective, denoting a sharp boundary between life and death that upholds the dead donor rule and precludes significant ethical quandaries related to identifying suitable organ donors."

Comment 8: Page 9 line 186 should clarify that the 2011 pediatric guidelines were a revision of the 1987 pediatric guidelines. Perhaps rephrasing: first standardized by the American Academy of Neurology in 1995 with a revision in 2010, and for children in 1987 with revision in 2011. It is also important to note that the guidelines provide the minimum criteria that must be met to make a determination of neurologic death.
Reply 8: Thank you for the feedback. We agree that more clarity could be provided and the sentence on **Page 10, Paragraph 3** has been edited as follows: "The procedures by which this diagnosis is made in adults were first standardized by the American Academy of Neurology in the 1990s and revised in 2010, and in children in 1987 with revisions in 2011."

Comment 9: Page 9 line 189: The determination of brain death is well documented in the literature. Although there is variation that can lead to controversy, many times it is the definition

of brain death the leads to the controversy not the determination of neurologic death. Additional references to support this statement might be helpful.

Reply 9: Thank you for this comment and we agree. We have amended the sentence on **Page 11, Paragraph 1** as follows: "Current controversies center on whether brain death can be equated with biological death, as well as whether its means of determination accurately measure irreversible loss of function of the entire brain." We have added several references in support of this statement.

Comment 10: Page 9 Whole brain versus brainstem death: If this is a discussion about the ethical issues, then one should expand on biologic versus legal determination of death. The pediatric and adult brain death guidelines provide the minimum clinical criteria to make a legal determination of death. The guidelines do not challenge the definition of death and this is clearly stated in the 2011 revised pediatric guidelines. A more in depth discussion about function is in order for the reader. Function is what the organ is supposed to do, not just what a collection of cells do physiologically which is the action of ie hypothalamus. Because a collection of cells exhibits physiologic activity does not mean the organ is functioning.

Reply 10: Thank you. We agree that the discussion should be augmented and clarified. We have made significant edits to the section, *"Whole Brain versus Brainstem Death"* on **Pages 11-12**. The concepts of *whole brain* and *brainstem* death have been further explained and clarified. We additionally discuss the distinction between *organ function* and *cellular activity* as related to concerns about persistent neuroendocrine functions in brain dead patients.

Comment 11: Page 9 200: The apnea test in particular *has* been scrutinized

Reply 11: Thank you for noting this. We have corrected the grammar on **Page 11, Paragraph 2** consistent with the above feedback.

Comment 12: Page 10 line 212: The close of this paragraph should specifically mention that: The pediatric guidelines state that apnea testing should not be performed until the patient has met criteria for brain death testing. Most would agree that allowing CO2 to rise would worsen ICP. The pediatric guidelines are specific in when apnea testing should be performed. The critics seem to imply that apnea testing is haphazard and done in random fashion when in fact the

guidelines provide specific recommendations when apnea testing should be performed which only occurs after prerequisite criteria for brain death have been met.

Reply 12: Thank you for this feedback. On **Page 14, Paragraph 2,** we have added the following sentence to provide more clarity: "Guidelines for pediatric determination of brain death provide clear recommendations for conducting this test, including prerequisites that must be met to reduce the risk of cardiopulmonary instability."

Comment 13: P 10, line 213: Agree that it is likely not current standard of practice to provide informed consent for apnea testing, but would include a reference if possible.

Reply 13: Thank you for this feedback. We have added 2 references to support the statement on **Page 13, Paragraph 3:** Lewis A, Greer D. Current controversies in brain death determination. *Nat Rev Neurol*. 2017;13(8):505-509. doi:10.1038/nrneurol.2017.72; and Lewis A, Greer D. POINT: Should Informed Consent Be Required for Apnea Testing in Patients With Suspected Brain Death? No. *Chest*. 2017;152(4):700-702. doi:10.1016/j.chest.2017.05.030.

Comment 14: Page 10 line 224-227 should also include other confounding variables such as pharmacologic coma.

Reply 14: Thank you for the feedback. We have expanded the statement on **Page 14, Paragraph 1** as follows: "Patients may have severe cardiopulmonary dysfunction that precludes tolerance of the apnea test, injuries that affect feasibility of the exam (such as ocular trauma, facial fractures, or cervical spine injury), or other conditions that are unable to be corrected (such as electrolyte abnormalities) that can confound the clinical evaluation."

Comment 15: P 11, line 228: could cut the "offering additional data…" part of the sentence to be more succinct

Reply 15: Thank you for the feedback. We have edited the sentence on **Page 14, Paragraph 1** as stated above to be more succinct.

Comment 16: Page 10 line 232-233 discusses EEG and that it is no longer recommended for routine use in diagnosing brain death due to its inadequate sensitivity and specificity. This should be clarified that this applies to adults. EEG remains an accepted ancillary study in

children. The following discussion should also specify adults in that ancillary studies available for adults have expanded and include…

Reply 16: Thank you and we agree that the sentence could use more clarity. We have amended the section on **Page 14, Paragraph 2** to more clearly delineate ancillary studies recommended in children as compared with adults and have added references to support the statements.

Comment 17: Line 241 discusses controversial use of ancillary studies. Is this pertaining to adults or children? Please clarify this point. One of the major factors that can alter perfusion studies is regional perfusion that can occur with the open fontanelle in infants or decompression craniotomy, both which affect intracranial pressure dynamics. This should be mentioned for completeness. Additionally, there are limitations to our testing abilities as image resolution may not be able to detect extremely low flow states. Consistent with evolving technology, newer imaging studies may more precisely delineate low or no flow.

Reply 17: Thank you and we agree that this point needs to be clarified. We have edited the section on **Page 15, Paragraph 2** to clarify challenges in the use of ancillary studies in both children and adults. We have included the point about the open fontanelle in infants as well as limitations to the resolution of existing imaging studies.

Comment 18: P 12, line 265: "her story was widely reported…" was already stated in line 259-260 so this could be cut.

Reply 18: Thank you for this feedback. We have edited out this sentence as suggested on **Page 16, Paragraph 2** to make the section more succinct.

Comment 19: Page 13 paragraph 1, 277-282. A more recent study from Jones and October reflects where the public receives their information and that much of the information that comes from YouTube and Google is incorrect. The study revealed a significant amount of inaccurate information about brain death, affecting the public's understanding of the concept of brain death and resulting in negative emotions specifically toward physicians, and the link between brain death and organ donation. This is a more recent and good article to reference. Chest. 2018 Aug;154(2):286-292. Investigation of Public Perception of Brain Death Using the Internet. **Amy**

H Jones, Zoelle B Dizon, Tessie W October. doi: 10.1016/j.chest.2018.01.021. Epub 2018 Jan 31. This article also supports the conclusions of the next paragraph on page 13.

Reply 19: Thank you for noting this. We have added the following sentence on **Page 17, Paragraph 2** citing the reference above as another analysis of newspaper articles mentioning brain death (Daoust et al): "One recent study by Jones et al. evaluated public perception of brain death by analyzing the most commonly accessed online resources. The authors found a significant amount of misinformation as well as negative emotions toward brain death and the medical community. Another study found that only 3% of newspaper articles that mentioned brain death in the United States and Canada provided an accurate definition of brain death, and many insinuated in specific cases that death occurred twice: once by neurologic criteria, and again at the time of organ procurement."

Comment 20: P 14, line 297: suggest cut the "which is why the mcmath family move their daughter there", same thing for the "Like in the mcmath case" portion of line 306

Reply 20: Thank you for this suggestion. We have cut the sentence mentioned above on **Page 18, Paragraph 2** to make the section more succinct.

Comment 21: Page 14, line 307: suggest editing to continuation of organ or somatic support such as…

Reply 21: Thank you for this suggestion. We have adjusted the terminology and the sentence on **Page 19, Paragraph 1** now reads as follows: "Varied perceptions about brain death due to personal, religious and/or cultural beliefs have led surrogates of some patients declared dead to request continuation of organ or somatic support such as ventilators."

Comment 22: Page 15 section title: The future of brain death. This might be better titled evolving technologies that may impact brain death testing.

Reply 22: Thank you for this feedback. We have edited the section title on **Page 19, Paragraph 2** accordingly: "Brain Death and Evolving Technologies."

Comment 23: Page 15 paragraph 2 discusses new technologies. This paragraph seems to speak more to adults than children and this should be clarified. It should be noted that further

investigation and validation will be needed in children. Like many technologies, the pupillometer has limitations for use with younger children and this should be so noted. There are very limited studies with children < 1 year of age and the accuracy of the pupillometer in children < 6 months of age is less reliable than adults. One publication cited only 17 pediatric patients with the youngest being 3 months of age.

Reply 23: Thank you for this feedback. We have expanded on this section on **Page 20, Paragraph 2** to better differentiate pediatric from adult data with regard to fMRI and pupillometry and have cited additional references in support of our statements.

Comment 24: Page 15 and 16 discusses the use of the pupillometer. This should be qualified that these are adult studies and do not necessarily pertain to children. Perhaps the authors should state that use in children needs to be studied in more detail to determine if these technologies will be useful in assisting in the determination of neurologic death.

Reply 24: Thank you for the feedback. We have qualified our statements on **Page 20, Paragraph 2** that some of the referenced studies pertain to adults and have noted that more data is needed to determine the technologies' utility in pediatric patients.

Comment 25: Page 16 line 344. This might be better phrased, modifications to certain aspects of the brain death evaluation process.

Reply 25: Thank you. We have rephrased the sentence on **Page 20, Paragraph 3** according to the above recommendation.

Comment 26: The conclusion should be more specific and consistent with the abstract by stating that providers should endorse the criteria for brain death diagnosis in children as proposed by SCCM, AAP, CNS to prevent controversy and subjectivity about brain death in children.

Reply 26: Thank you for this feedback. We have addended our conclusion on Page 21 to be more consistent with our introduction and abstract as follows: "Additionally, providers who perform brain death evaluations must be familiar with the published criteria for brain death determination in children, as well as state laws and institutional protocols."