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| **Name:** Anagha Lokhande  **Faculty Mentor:**  Adam Levine | **Proposal Title:**Cost-effectiveness analysis of the DHAKA and NIRUDAK clinical diagnostic models for volume deficit in patients with acute diarrhea |  |
| **Reviewer Comments:**  This is a very thought-provoking proposal that aims to estimate the cost-effectiveness of two new modelling tools compared to the WHO model (standard care) for accurately assessing dehydration status of patients with diarrheal disease in Bangladesh. This proposal is timely given then recent 2021 publication of the effectiveness of NIRUDAK model. Successful execution of the proposed scope of work would add to the literature surrounding cost-effectiveness diagnostic tools for diarrheal disease. However, there are concerns that the applicant does not have a clear enough understanding of cost-effectiveness methods; several important pieces are missing from the analysis plan. If the applicant is able to more clearly lay out the analysis plan then this project would likely be successful in achieving the objectives. The applicant would greatly benefit from reviewing the cost-effectiveness literature and structuring the tables and figures similarly. Please see major and minor comments on the scientific merit of the proposal below.  Major comments   * The author is proposing to measure the cost-effectiveness of (1) the NIRUDAK model compared to the standard WHO algorithm, and (2) the DHAKA model compared to the standard WHO algorithm. It is not clear how incremental effectiveness will be measured for either of these comparisons.   A realistic measure of effectiveness could be the number of patients with severe dehydration who were detected by each model (and started on treatment), based on the performance measure in the Levin AC et al. 2021 paper for the NIRUDAK model and in the Leven AC et al, 2016 paper for the DHAKA model. The number of severe dehydration cases detected (and deaths prevented) could then be converted to DALYs following established methods.   * Relatedly, on page 4 of the proposal, the applicant states that disability-adjusted life years are not applicable to diarrhea. This is incorrect given the extensive body of literature quantifying the DALYs attributable to diarrheal disease (DD)-associated mortality and diarrheal disease (DD)-associated morbidity. See for example:   • Karambizi NU, McMahan CS, Blue CN, Temesvari LA (2021) Global estimated Disability-Adjusted Life-Years (DALYs) of diarrheal diseases: A systematic analysis of data from 28 years of the global burden of disease study. PLoS ONE 16(10): e0259077. https://doi.org/10.1371/journal.pone.0259077  • Troeger, Christopher et al. “Global disability-adjusted life-year estimates of long-term health burden and undernutrition attributable to diarrhoeal diseases in children younger than 5 years.” The Lancet. Global health vol. 6,3 (2018): e255-e269. doi:10.1016/S2214-109X(18)30045-7   * There are several key steps of a cost-effectiveness analysis that are missing from this proposal.   + **Perspective:** The author says they are not able to use a societal perspective due to limitations of the available data. However, they do not state from which perspective they will conduct the CEA. Who is paying for the fluid resuscitation treatment? Are patients paying out of pocket? If so, then costing is from a patient perspective. Are the health facilities paying? If so, then this is a provider perspective. Are national health insurance funds or NGOs paying for this? If so, then a health systems perspective might be more appropriate. This needs to be clear before starting any CEA.   + **Cost-effectiveness measure:** Once the effectiveness measure is clear, how will cost-effectiveness be measured? Generally, this is measured via the incremental cost-effectiveness ratio (ICER). I would like to see the most basic formula for constructing an incremental cost-effectiveness ratio (ΔC/ΔE) included in the proposal to know that the applicant understands what is needed.   + **Willingness to pay thresholds:** Once we have the ICERs for each comparison, how will we know that a given model is cost-effective compared to the WHO algorithm? Each ICER will need to be compared against a willingness-to-pay threshold. A commonly used threshold (though by no means the only one) is the WHO threshold of 1x, 2x, or 3x a country’s gross domestic product per capita corresponding to cost-effective, moderately cost-effective, and highly cost-effective. See for example:     - Marseille, Elliot et al. “Thresholds for the cost-effectiveness of interventions: alternative approaches.” Bulletin of the World Health Organization vol. 93,2 (2015): 118-24. doi:10.2471/BLT.14.138206 * Page 3 – Analysis plan – Good to see that the applicant has already started reviewing the costs of both models and is able to provide some descriptive statistics; this signifies that there is clearly scientific interest here. However, if the applicant is going to present preliminary data in the proposal (which I support) then the methods used to ascertain and the assumptions underlying these data need to be clear. The applicant should present the specific items that were included in the total cost for each model (e.g., micro costing) and for actual care. This would greatly help the reader understand what is causing the huge difference between the total cost of all 3 models and the actual amount spent (figures 1 & 2). It is not clear why there is this big difference in total costs, and a reviewer might initially think that the 3 models are not accurate in terms of predicting actual expenditures. * The hsim package is R is a cohort discrete time state transitions model based on probabilities of participants moving between each health state and the costs associated with each state. Is this the most appropriate model for this type of analysis given that the cost of the NIRUDAK, DHAKA, and WHO models will be the same regardless of which diarrheal state a patient is in? Also, and most importantly, we should be interested in the applicant’s understanding of the core components and methods of a cost-effectiveness analysis rather than devoting substantial time to learning a new statistical package. If the applicant is able to achieve both simultaneously, then we would fully support them using the hsim package or another appropriate program.   Minor comments   * Page 2 – Objective/specific aims – For the proposed second aim, is the author also interested in looking at cost-effectiveness between the NIRUDAK model and DHAKA model? * Page 2 – Background and significance – The author should specify the target population for this research – is it pediatric patients under 5 years of age? * Timeline - two manuscripts seems too ambitious. Perhaps focus on just one robust manuscript of the cost-effectiveness analysis given that the effectiveness data for both of the models have already been published.   *Other issues that the Committee may want to consider (e.g., other support, independence, budgetary issues, etc.) Do NOT take these into account in your score.*   * Page 1 – Applicant says IRB review has already been completed but then lists “pending” for the IRB approval date. An IRB protocol number should be included if one is currently available. * Applicant should edit their proposal for grammatical and other formatting errors   + E.g., Background – “Episodes of acute diarrhea led to dehydration” should be “lead to dehydration”   + E.g., Timeline – “I will submit a covering the DHAKA” should be “I will submit an abstract covering the DHAKA”   Could include manuscript publication fees in the budget along with target journal(s) | | |