Greetings,

We thank the reviewer for their thoughtful comments and critical assessment of the proposal. We believe the comments will strengthen the analysis and eventual manuscript. In the following, we address the concerns point by point.

**MAJOR COMMENTS**

**REVIEWER COMMENT 1:** 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.

I will use two short-term measures of effectiveness: (1) the proportion of patients with severe dehydration detected by a given triage strategy and (2) the proportion of patients treated correctly, i.e., not overtreated or undertreated. However, we will also use evidence from the literature to translate short-term effectiveness into Disability Adjusted Life Years (DALYs). In particular, each patient has both a predicted dehydration level – no, some, or severe – for each triage strategy (e.g., prediction model or actual care) and an observed dehydration level – derived from established (gold standard) methods based on post-treatment weight change. Because there are guidelines for how a patient should be treated based on their dehydration level, each patient can then be classified as undertreated, appropriately treated, or overtreated for each triage strategy. For example, if a patient would have been given intravenous fluid treatment based on the predicted dehydration level but actually had little to no dehydration, this would entail the patient would have been overtreated with a given strategy. We will use previous modeling results from the literature, or, if necessary, develop a simple decision model (decision tree or Markov model), to assign each of the 9 possible outcomes from a 3x3 table a DALY. The DALY is defined below. The proportion of patients in each outcome category for a given triage strategy will then determine the DALYs associated with that strategy. For both short term effectiveness and DALYs, we will calculate incremental effectiveness by taking the difference (in proportions or DALYs) between strategies after arranging the considered strategies from least effective to most effective.

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.

**REPLY:**

1. YLL: As the reviewer suggests, we could measure effectiveness as the number of patients with severe dehydration who were detected by each model — in other words, the sensitivity of each model. Levine et al. 2021 (a paper the reviewer mentions), in the over-five population, the NIRUDAK model had a sensitivity of 80% for versus the WHO adult algorithm’s 53%. In Levine et al. 2016, for children under-five, the DHAKA model had a sensitivity of 86% for severe dehydration compared to the WHO pediatric algorithm’s 77%.

For example, a simple assumption would bee that any patients with true severe dehydration who would have been treated as though they only had no or some dehydration would have died. We can then use the YLL formula above.

1. YLD: However, we also much consider the harms of overtreatment. For example, he NIRUDAK/DHAKA models may prevent over-administration of fluids and subsequent sequalae like urinary bladder distension, ureter dilation, hydronephrosis, water intoxication, thrombophlebitis, and electrolyte imbalances. ([Fonseca et al. 2004](https://pubmed.ncbi.nlm.nih.gov/15123483/), [Hew-Butler et al. 2019](https://doi.org/10.3390/nu11071539), and [Srivastava et al. 1985](https://pubmed.ncbi.nlm.nih.gov/4067224/)). We will seek to estimate from the literature the risk of these types of sequalae as well as disability weights(, [Salomon et al. 2015](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X%2815%2900069-8/fulltext), and [Haagsma et al. 2015](chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https:/d-nb.info/1117920453/34" \l ":~:text=This%20is%20illustrated%20by%20increasing,diarrhea%20(disability%20weight%200.239).)) and durations for the conditionsrted to YLDs.

**Error! Hyperlink reference not valid.Error! Hyperlink reference not valid.REVIEWER COMMENT 2:** 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

**REPLY:** Diarrheal outcomes will be converted to DALYs using established methods.

See Reviewer Comment 1.

**REVIEWER COMMENT 3:** 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

**REPLY:**

* + **Perspective:** We will need the societal perspective for the eventual manuscript, based on my discussions with the reviewer and Dr. Popp. To accomplish this, I will work with Dr. Adam Levine’s clinical research team to ascertain the hourly salaries for nurses and doctors and model costs such as transportation fees for patients and missed days of work.
  + **Cost-effectiveness measure:** To estimate the cost-effectiveness of using the different prediction models relative to care as usual, we will calculate the incremental cost-effectiveness ratio (ICER), defined below. Specifically, we will compare each triage strategy (excluding the least effective strategy) with the next most effective strategy, e.g., strategy B with the somewhat less effective strategy A, by taking the difference in effectiveness between the two strategies. We will then calculate the difference in mean costs between the same two strategies and take the ratio of the differences (cost to effectiveness). We will calculate the ICER using both short-term measures of effectiveness and DALYs.

Please note that NIRUDAK model is for patients over-five and the DHAKA model is for patients five-and-under (see Reviewer Comment 7), so these models will be assessed separately.

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| TREATMENT | COST | EFFECTIVE-  NESS MEASURE  (see Reviewer Comment 1) | ΔC (cost of WHO/  NIRUDAK/  DHAKA minus cost of actual care) | ΔE (effectiveness of WHO/  NIRUDAK/  DHAKA minus effectiveness of actual care) | ICER  (ΔC/  ΔE) |
| Actual care |  |  |  |  |  |
| WHO algorithm |  |  |  |  |  |
| NIRUDAK or DHAKA model |  |  |  |  |  |

* + **Willingness to pay thresholds: To determine whether an intervention is cost-effective, we will assign a value to a (lost) DALY.** We will select the exact willingness to pay threshold after further review of the literature, but we will consider using the WHO-recommended threshold of 1-3x a country’s gross domestic product per capita.

**REVIEWER COMMENT 4:** 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.

**REPLY:** Below is the micro-costing. Due to incomplete data (missing discharge/admit times) in the under-five population (DHAKA model), only fluid costs could be calculated. Hence, in the preliminary data presented, hospital fees are accounted for in the five-years-old-and-over population (NIRUDAK model) but not in the under-five (DHAKA) population. Moreover, the preliminary results do not include costs associated with provider labor though we will incorporate these into the proposed analyses. (see Reviewer Comment 3, Perspective).

Items included in total cost for NIRUDAK model (patients five-years-old-and-over)

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| **FIXED COST: IV EQUIPMENT** | IV tubing/solution set + 1 pair of gloves + 1 22G butterfly needle  0.17 + 0.08 + 0.13 = $0.38 (32.59 Bangladeshi taka, BDT) |
| **VARIABLE COST: ORAL RESUSCITATION SOLUTION (ORS)**  given to moderately dehydrated patients | $0.00006 (0.0054 BDT) per mL |
| **VARIABLE COST: INTRAVENOUS FLUID (IVF)**  given to severely dehydrated patients | $0.00126 (0.104 BDT) per mL |
| **VARIABLE COST: HOSPITAL STAY**  all patients admitted to short stay unit | $30 (2573.1 BDT) per 24 hours (1 day)  $1.25 (107 BDT) per hour  additional $30 for each day |

Items included in total cost for DHAKA model (patients under-five). The same fluids (oral resuscitation solution and intravenous fluid) are used in both the under-five and five-and-over populations, so the per-unit cost of fluid is the same.

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| **FIXED COST: IV EQUIPMENT** | IV tubing/solution set + 1 pair of gloves + 1 24G butterfly needle  0.17 + 0.08 + 0.15 = $0.40 (34.31 BDT) |
| **VARIABLE COST: ORAL RESUSCITATION SOLUTION (ORS)**  given to moderately dehydrated patients | $0.00006 (0.0054 BDT) per mL |
| **VARIABLE COST: INTRAVENOUS FLUID (IVF)**  given to severely dehydrated patients | $0.00126 (0.104 BDT) per mL |

In response to the query on what’s driving the differences in costs between models — there are two mechanisms for high costs in actual clinical care:

1. overtreating patients by assigning them to an inappropriate dehydration category (e.g., “Severe Dehydration” when the patient only has “Some Dehydration” causing them to be inappropriately admitted to the hospital and given IVF when they only need outpatient monitoring and ORS) — demonstrated by the blue boxes on the tables
2. overtreating patients within the same dehydration category (e.g., monitoring patients in the hospital for too long, administering too much fluid, etc.) — demonstrated by the red boxes on the tables

Note that the DHAKA model preliminary costing results only incorporate fluid cost, while the NIRUDAK model costing includes hospital costs.

Table

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**REVIEWER COMMENT 5:** 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.

**REPLY:** Given the revised and clarified analysis plan, To the second point on statistical packages — one of the goals of this project is to help me gain a deeper understanding of the methods of cost-effectiveness research and learn practical skills related to conducting one.

Because patients are only evaluated at a single point in time (arrival at health care facility) and only one decision is being made (which model to use — this dictates total cost), we will be using a decision tree, not a Markov cohort model. Below is a draft of what our decision tree might look like.

Chart, diagram

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**MINOR COMMENTS**

**REVIEWER COMMENT 6:** 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?

**REPLY:** No — the two models are used in different patient populations (see Reviewer Comment 7).

**REVIEWER COMMENT 7:** Page 2 – Background and significance – The author should specify the target population for this research – is it pediatric patients under 5 years of age?

**REPLY:** The NIRUDAK model is to be used for patients five years and over. The DHAKA model is to be used for patients five years and under. The under-five and five-and-over populations will both be analyzed separately.

**REVIEWER COMMENT 8:** 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.

**REPLY:** We are happy to publish a single manuscript.

***OTHER ISSUES (not considered in the score)***

**REVIEWER COMMENT 9:** 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.

**REPLY:** For the NIRUDAK study, the Lifespan protocol number is 1244580 and for icddrb (the hospital in Bangladesh) it is PR-18077. Additionally, all data being used is retrospective, freely available (on Open Science Framework), and de-identified.

**REVIEWER COMMENT 10:** 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”

**REPLY:** Fixed in our internal version of the analysis plan.

**REVIEWER COMMENT 11:** Could include manuscript publication fees in the budget along with target journal(s)

**REPLY:** We agree; this is another reason funding would be enormously helpful. We may be too early in the process to be able to provide specific estimates based on costs for target journals, but this would especially aid in publishing the paper open source.

Many thanks again to the reviewer and to the Global Health Initiative for the opportunity.

Best regards,

Anagha Lokhande