

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.

A clarifying point on the diagnostic models to be compared: the NIRUDAK model is to be used for patients five-years-old and over; the DHAKA model is to be used for patients under five years of age. The cost-effectiveness comparisons will be (1) between the NIRUDAK model and the WHO algorithm for patients five-and-over and (2) between the DHAKA model and the WHO algorithm for patients under-five. Therefore, the under-five and five-and-over populations will be analyzed separately under the assumption that patients would be treated exactly as dictated by the recommendations of a given diagnostic method. This point of clarification is responsive to Reviewer Comments 6 and 7.

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.

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: I will use two short-term measures of effectiveness:

- (1) the proportion of patients with severe dehydration detected by a given diagnostic method. For example, for the cut-points used in Levine et al. 2021 (a paper the reviewer mentions), in the over-five population, the NIRUDAK model had a sensitivity of 80% 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%.
- (2) the proportion of patients treated correctly i.e., not overtreated or undertreated. Each patient has both a predicted dehydration level (No, Some, or Severe) from each diagnostic method and an observed (ground truth) dehydration level derived from evidence-based clinical guidelines using post-treatment weight change (Levine et al. 2021). Because there are guidelines for how a patient should be treated based on their dehydration level, each patient can be classified as undertreated, appropriately treated, or overtreated for each diagnostic method. 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 mean that the patient would have been overtreated with a given diagnostic method.

We will also use evidence from the literature to translate short-term effectiveness into Disability Adjusted Life Years (DALYs). 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 diagnostic method 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.

Disability Adjusted Life Year (DALY)

$$= \text{Years Lost due to Disability (YLD)} + \text{Years of Life Lost (YLL)}$$

- (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.

$$YLL = N \times L$$

N = number of deaths

L = life expectancy at age of death (in years)

For example, a simple assumption would be 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.

- (2) YLD: However, we also consider the harms of undertreatment that doesn't cause death, and overtreatment. For example, the NIRUDAK/DHAKA models may prevent over- and under-administration of fluids and sequelae like urinary bladder distension, ureter dilation, hydronephrosis, water intoxication, thrombophlebitis, encephalopathy, and electrolyte imbalances ([Fonseca et al. 2004](#), [Hew-Butler et al. 2019](#), and [Srivastava et al. 1985](#)). We will seek to estimate from the literature the risk of these types of sequelae as well as disability weights and durations for the conditions (Troeger et al. 2018 and Karambizi et al. 2021 — as the reviewer mentions, plus [Salomon et al. 2015](#), and [Haagsma et al. 2015](#)).

$$YLD = I \times DW \times L$$

I = number of incident cases

DW = disability weight

L = average duration of the case until remission or death (in years)

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 ($\Delta C/\Delta E$) 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 estimate the cost-effectiveness of using the DHAKA and NIRUDAK models (relative to the WHO algorithm) from both the healthcare system perspective and the social perspective which may be important for publication in a journal. For the latter, we will seek to include patient time and transportation costs as well as downstream productivity costs associated with mortality and serious morbidity.

- **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 diagnostic method (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).

In other words, the table below will be used to arrange the competing diagnostic methods in increasing order of cost, exclude strongly dominated options (those that are more expensive and less effective), calculate ICER for remaining options, exclude weakly dominated options (with higher ICERs), and recalculate ICER for remaining options.

We will calculate the ICER using both short-term measures of effectiveness and DALYs.

incremental cost effectiveness ratio (ICER)

$$= \frac{\Delta \text{Cost}}{\Delta \text{Effectiveness}}$$

$$= \frac{\text{Cost}_{\text{intervention (NIRUDAK/DHAKA)}} - \text{Cost}_{\text{WHO}}}{\text{Effectiveness}_{\text{intervention (NIRUDAK/DHAKA)}} - \text{Effectiveness}_{\text{WHO}}}$$

DIAGNOSTIC METHOD	COST	EFFECTIVE-NESS MEASURE (see Reviewer Comment 1)	ΔC (cost of NIRUDAK full/NIRUDAK simplified/ DHAKA minus cost of WHO)	ΔE (effectiveness of NIRUDAK full/NIRUDAK simplified/ DHAKA minus effectiveness of WHO)	ICER (ΔC/ ΔE)
WHO algorithm					
NIRUDAK model (full or simplified) or DHAKA model					
NIRUDAK model (full or simplified)					

A brief note: there are actually two NIRUDAK models, as outlined in [Levine et al. 2021](#). The simplified NIRUDAK model requires only nine basic clinical

inputs; the full NIRUDAK model requires 16 clinical inputs plus age and sex. I would be interested in comparing the cost-effectiveness of each.

- **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-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-and-over)

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.

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. All figures presented here for the NIRUDAK model refer to the full NIRUDAK model (see Reviewer Comment 3, Cost-effectiveness measure for a discussion on the full vs. simplified NIRDUAK models).

Table 1. Total cost of initial recommended resuscitation — NIRUDAK model

	ACTUAL MEDIAN	WHO MEDIAN	NIRUDAK MEDIAN	ACTUAL IQR	WHO IQR	NIRUDAK IQR	ACTUAL TOTAL	WHO TOTAL	NIRUDAK TOTAL	ACTUAL OBSER- VATIONS	WHO OBSER- VATIONS	NIRUDAK OBSER- VATIONS
ALL PATIENTS	37.75 (3222)	5.23 (449)	5.18 (445)	15.69 - 45.00 (1332 - 3841)	5.09 - 22.17 (437 - 1883)	0 - 25.46 (0 - 2166)	68684 (5854650)	28458 (2425359)	30515 (2602843)	2168	2168	2136
NO DEHYD- RATION	37.39 (3200)	0 (0)	0 (0)	12.26 - 44.99 (1052 - 3842)	0 - 0 (0 - 0)	0 - 0 (0 - 0)	13122 (1120904)	0 (0)	0 (0)	430	491	606
SOME DEHYD- RATION	37.77 (3231)	5.21 (448)	5.16 (443)	16.17 - 44.93 (1369 - 3836)	5.18 - 5.24 (445 - 451)	5.14 - 5.18 (441 - 446)	45746 (3897372)	4861 (417865)	3208 (275687)	1435	933	622
SEVERE DEHYD- RATION	39.14 (3331)	30.31 (2579)	28.22 (2405)	18.99 - 45.48 (1611 - 3860)	21.45 - 38.27 (1820 - 3259)	20.01 - 36.50 (1704 - 3109)	9298 (791346)	23598 (2007496)	27306 (2327156)	278	744	908

Actual costs are the sum of the costs of the actual amount of fluid administered plus the actual cost of hospital stay in the NIRUDAK study. Costs are set to zero for patients classified as having No Dehydration by the WHO or models, as both models recommend that these patients be managed expectantly. For patients classified as experiencing Some Dehydration by either model, costs equal four hours of hospital stay (for observation) plus the amount of fluid needed for resuscitation as predicted by the model. For patients with a Severe Dehydration classification, costs equal the actual length of hospital stay in the NIRUDAK prospective cohort study, plus the amount of fluid needed for resuscitation as predicted by either model, plus the actual amount of fluid in the given in the NIRUDAK prospective cohort study after 6 hours of admission to the hospital. Observations missing diagnostic labels for a particular model were omitted in analysis for that model. Costs outside parentheses are in USD; costs within parentheses are in BDT.

Table 2. Cost of fluid needed for initial recommended resuscitation — NIRUDAK model

	ACTUAL MEDIAN	WHO MEDIAN	NIRUDAK MEDIAN	ACTUAL IQR	WHO IQR	NIRUDAK IQR	ACTUAL TOTAL	WHO TOTAL	NIRUDAK TOTAL	ACTUAL OBSER- VATIONS	WHO OBSER- VATIONS	NIRUDAK OBSER- VATIONS
ALL PATIENTS	5.43 (449)	4.55 (375)	3.27 (3217)	4.16 - 5.43 (345 - 553)	0 - 5.76 (0 - 476)	0 - 4.27 (0 - 354)	10625 (880330)	8574 (708647)	5850 (483949)	2173	2172	2139
NO DEHYD- RATION	2.96 (245)	0 (0)	0 (0)	1.06 - 4.80 (89 - 398)	0 - 0 (0 - 0)	0 - 0 (0 - 0)	1397 (115975)	0 (0)	0 (0)	431	491	607
SOME DEHYD- RATION	5.44 (451)	4.45 (367)	3.34 (276)	4.18 - 6.68 (347 - 553)	3.81 - 5.12 (314 - 423)	2.84 - 3.85 (235 - 318)	7492 (620577)	4125 (340489)	2072 (171002)	1437	937	624
SEVERE DEHYD- RATION	5.64 (468)	6.04 (500)	4.30 (356)	5.42 - 6.75 (449 - 559)	5.16 - 6.81 (427 - 563)	3.54 - 4.92 (293 - 407)	1668 (138098)	4449 (368158)	3778 (312946)	278	744	908

Actual costs are the sum of the costs of ORS administered in the first six hours after admission (if applicable), plus IVF administered in the first six hours after admission and associated intravenous (IV) equipment (if applicable). For patients classified as having No Dehydration by the WHO or NIRUDAK model, costs were set to zero as both models recommend that these patients be managed expectantly. For patients with a classification of Some Dehydration, costs equal the cost of ORS needed for initial resuscitation as predicted by either model. Patients classified as having Severe Dehydration were assigned costs equal to the amount of IVF needed for resuscitation (as predicted by the model), plus associated IV equipment. Observations missing diagnostic labels for a particular model were omitted in analysis for that model. Costs outside parentheses are in USD; costs within parentheses are in BDT.

Table 3. Total cost of fluid — DHAKA model

	ACTUAL MEDIAN	WHO MEDIAN	DHAKA MEDIAN	ACTUAL IQR	WHO IQR	DHAKA IQR	ACTUAL TOTAL	WHO TOTAL	DHAKA TOTAL	ACTUAL OBSER- VATIONS	WHO OBSER- VATIONS	DHAKA OBSER- VATIONS
ALL PATIENTS	0.51 (44)	0.04 (4)	0.02 (2)	0.45 - 1.71 (39 - 146)	0.03 - 1.24 (3 - 105)	0 - 0.97 (0 - 83)	885 (74499)	421 (35669)	432 (36912)	820	849	847
NO DEHYD- RATION	0.46 (39)	0 (0)	0 (0)	0.45 - 0.50 (39 - 43)	0 - 0 (0 - 0)	0 - 0 (0 - 0)	226 (19339)	0 (0)	0 (0)	349	91	267
SOME DEHYD- RATION	1.10 (93)	0.03 (3)	0.01 (1)	0.47 - 1.73 (41 - 145)	0.03 - 0.04 (3 - 4)	0.01 - 0.02 (1 - 2)	447 (37551)	18.08 (1627)	2.67 (240)	341	496	176
SEVERE DEHYD- RATION	1.73 (145)	1.55 (131)	0.98 (84)	1.10 - 2.37 (93 - 198)	1.30 - 1.73 (110 - 146)	0.80 - 1.24 (69 - 106)	162 (13536)	403 (34042)	429 (36672)	83	262	404

Actual costs are the sum of the costs of all ORS administered during the hospital stay (if applicable), plus all IVF administered during the hospital stay and associated IV equipment (if applicable). For patients classified as having No Dehydration by the WHO or DHAKA model, costs were set to zero as both models recommend that these patients be managed expectantly. For patients with a classification of Some Dehydration, costs equal the cost of ORS needed for initial resuscitation as predicted by either model. Patients classified as having Severe Dehydration were assigned costs equal to the amount of IVF needed for resuscitation (as predicted by the model), plus associated IV equipment. Observations missing diagnostic labels for a particular model were omitted in analysis for that model. Costs outside parentheses are in USD; costs within parentheses are in BDT.

REVIEWER COMMENT 5: The hsim package in 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: See Reviewer Comment 1 for a discussion of model selection. 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.

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.

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-and-over. The DHAKA model is to be used for patients under-five. 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 icddr (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