Pilot Implementation of a Nighttime Telemedicine and Medication Delivery Service to Increase Access to Pre-emergency Pediatric Care in Ghana

NCT05506683

April 4, 2023

University of Florida IRB-01
Protocol:

1. Project Title: Pilot Implementation of a Nighttime Telemedicine and Medication Delivery Service to Increase Access to Pre-emergency Pediatric Care in Ghana

Subtitle: Improving Nighttime Access to Care and Treatment (INACT2-G)

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3. Abstract

Globally, leading causes of death among children one month to 5 years old are pneumonia, diarrheal disease and malaria which are treatable early in the disease-course with low-cost medications. However, these diseases can progress to emergencies when access to care is delayed, especially in low- and middle- income countries (LMICs). In response, our team has designed a telemedicine and medication delivery service (TMDS) called MotoMeds to overcome barriers to seeking care. We target the nighttime period when barriers to accessing care are highest. Our strategic plan is to design, deploy and evaluate MotoMeds through the improving nighttime access to care and treatment (INACT) studies. The TMDS was initially deployed in Haiti and now will be evaluated for generalizability and portability in Ghana. In Ghana, we have initiated a formative needs assessment (INACT1-G) to inform the design and approach of the pilot implementation of the TMDS (INACT2-G). The study objectives are to assess clinical safety and logistical feasibility. The study population is an urban slum within Accra and the enrollment period is nine months. The workflow consists of parents/guardians calling the TMDS on their child's behalf, Emergency Medical Technicians (EMTs) referring severe cases to emergency services, EMTs performing a phone assessment for non-severe cases, and EMTs travelling to the household to perform an exam and deliver protocoled medications for cases within the delivery zone. Eligibility criteria includes patient participants aged 0-10 years old with medical problem, parent/guardian participants calling on behalf of a patient participant, and TMDS staff aged 18 years and older. Written consent/assent will be obtained from patient and parent/guardian participants receiving a household visit. Parent/guardian participants who do not receive a household visit and TMDS staff will be

offered a waiver of documentation of consent. Estimated enrollment is up to 1,365 child and parent/guardian participant pairs, 15 call center EMTs, 10 delivery drivers, and 3 on-call physicians. Clinical safety will be evaluated through guideline adherence, congruence analysis between call center and in-person assessments, and clinical status at 10 days. Feasibility will be evaluated in terms of logistical data, parent/guardian feedback, and TMDS staff feedback.

4. Background

4.1 Pediatric health and healthcare. Pneumonia, diarrheal disease, and malaria are the first, second, and third leading causes of mortality for children between one month and 5 years of age globally[1]. Oral amoxicillin for bacterial pneumonia, oral rehydration solution for dehydration from diarrheal disease, and artesunate-amodiaquine for malaria can reduce mortality rates by 32%, 93% and 99.7%, respectively[2, 3, 4]. However, these treatments are most effective when administered early after symptoms start [5, 6], which is difficult when healthcare access is limited, especially at night. Delayed treatment, especially in children, can result in rapid progression to an emergent state[5, 6]. In LMICs emergency care is considerably more difficult to access and more expensive than pre-emergency care[7]; thus emergencies must be prevented in order to decrease pediatric mortality. The WHO/UNICEF action plan for Ending Preventable Child Deaths calls for innovation within the domains of "delivery strategies, overcoming barriers to interventions and better ways for implementation"[8].

Since the COVID-19 pandemic, telemedicine has gained accelerated interest as an innovative approach to improve access to care[9, 10]. By improving clinician efficiency and accessibility, telemedicine has the potential to overcome workforce as well as distance barriers[11, 12]. Successful pediatric use cases in LMICs include a virtual clinic for pediatric ambulatory surgical patients in Egypt[13] and a telemedicine service for pediatric cancer and blood disorders in the Caribbean[14]. However, the need for physical assessments limits what can be accomplished via telemedicine alone[15]. A systematic review of interventions for improving access to healthcare for children under 5 in LMICs found "delivery of services close to home" was one of two interventions that was consistently associated with increased healthcare utilization[16]. Accordingly, community health worker programs (CHWPs) continue to gain prevalence[17, 18, 19]. CHWPs train community leaders to deliver healthcare resources directly to households in their neighborhood. These programs have been found to decrease both disease prevalence and mortality in LMICs [20, 21]. However, such programs are largely limited to the daytime[22].

The rise and success of community paramedicine programs exemplifies the potential of 24-7 telemedicine and medication delivery services. Community paramedicine is an evolving healthcare model in which EMTs operate in expanded roles to provide primary care to low-resource communities. The scope of community paramedicine practice varies by settings but often includes education, vaccination, and basic medication/fluid administration. Community paramedicine programs have been shown to effectively decrease emergency department visits through the provision of preventative and chronic care services in high income countries[23, 24]. The potential for telemedicine and medication delivery services to avert emergencies through the provision of acute care services in LMICs remains to be realized.

4.2 Health and healthcare in Ghana. The Ghanaian pediatric population could benefit from improved acute cares services. The Ghanaian National Ambulance Service (NAS), a nationwide Emergency Medical Services (EMS) agency, works to provide timely emergency care [25, 26]. The NAS has prioritized EMS through the development of a Paramedic & Emergency Care Training School, operation of 297 EMS stations, and purchase of 307 new ambulances[25].However, the endeavor has exposed unanticipated costs that limit sustainability and scalability[27, 28]. Both NAS personnel and the Ghanaian public express concern over NAS resources and response[28, 29]. Currently a major challenge is how to prevent and manage pre-emergency cases that consume resources intended for emergencies[30].

To meet this need, Ghana Health Services manages a robust network of CHWPs[31]. CHWPs have worked under the National Expanded Programme on Immunisation (EPI) to increase complete vaccination coverage for children 12-23 months from 85% in 1998 to 95% in 2014[32]. Further, CHWPs have been found to be instrumental in treating pediatric acute illnesses such as pneumonia, diarrhea, and malaria in Accra and Northern Ghana[33]; however, progress is insufficient.

Ghana‘s U5M rate is 48 per 1,000 live births[34] with malaria, acute respiratory illness, and diarrheal disease accounting for 20%, 13%, and 8% of the U5M rate, respectively[35]. Pediatric care in Ghana is compromised by a low level of general health education, shortage of healthcare personnel, and limited pediatric health facilities[36]. The ratio of medical doctors to population is 1: 9,434[37]. The 2014 Demographic and Health Survey found 43% of adult women–many mothers–were dissatisfied with primary care services[38].

4.3 Clinical considerations in Ghana. The high burden of malaria poses unique challenges to assessing and treating pediatric patients with fever. Conventional and point of care diagnostics play an important role. With respect to malaria, diagnostic modalities include polymerase chain reaction, smear microscopy, and rapid diagnostic testing. While polymerase chain reaction and smear microscopy are more sensitive than rapid diagnostic testing the need for conventional laboratory capabilities limits their use in point-of-care testing in low-resource settings. Performance metrics for rapid diagnostic testing vary widely up to 98% sensitivity and 92% specificity[39]. With respect to acute respiratory infection, diagnostic modalities include imaging, lung function tests, culture, and polymerase chain reaction. Rates of coinfection among outpatient febrile children under 10 in Tanzania were found to be frequent, with viral and bacterial co-infection being most common, but also co-infection of parasitic and bacterial and/or viral origin[40]. However, rates of single agent as well as dual agent infections in our study population are unknown.

4.4 Feasibility Studies. Interventions must be assessed for feasibility to determine whether scaling and comprehensive evaluations are justified[41]. Feasibility studies focus on development of implementation strategies and refinement of research methods[42, 43]. Feasibility studies may be fixed–rigid in design–or flexible–allowing for changes during the course of the study[44]. Conventional feasibility metrics for healthcare interventions include demand[45], implementation[46], integration[41], adherence[47], cost-effectiveness[48], clinical safety[49], and acceptability[50]. However, there exists little guidance pertaining to feasibility thresholds. Rather, the theory and application of feasibility thresholds is widely questioned with the only

consensus being that feasibility thresholds must be determined realistically with attention to circumstance[44, 51].

5. Specific Aims:

Aim I: Assess the clinical safety of a nighttime TMDS in a prospective cohort pilot study of pediatric patients 10 years and younger. Paired exams will be performed at the call center (virtual) and at the household (in-person).

- The primary objectives are to determine the rate of guideline adherence at the call center (primary outcome measure) and household as well as evaluate congruence between call center and in-person assessment and determine clinical status at follow-up at 8-12 days.

Aim II: Evaluate the feasibility of the TMDS model with respect to patients.

- Logistical data on patient workflow will be collected (duration of call, time to delivery). Data will be analyzed against benchmarks set in formative research (call duration < 25 minutes and time to delivery < 2 hours).
- Parent/guardian feedback will be collected on the clinical, cost and quality aspects of the TMDS. Both quantitative and qualitative data will be analyzed to identify strengths and weaknesses of the TMDS design.

Aim III: Evaluate the feasibility of the TMDS model from the perspective of the staff.

- Data will be obtained from EMTs, drivers and on-call physician participants by questionnaires and focus groups. Domains of inquiry are clinical decision making, formulation of medications, communication with team members and households, and opportunities for improvement.
- Data will be transcribed, evaluated for themes using an inductive code, and summarized for strengths and weaknesses of the TMDS design.

6. Research Plan:

6.1 Definitions

ARI: Acute respiratory infection defined as the presence of fever and cough.

EMT: Emergency medical technician trained to provide emergency medical services.

Household (HH): A group of two or more individuals living in the same structure and share at least one daily meal

INACT: Improving Nighttime Access to Care and Treatment.

INACT1-H: Survey assessment in Haiti

INACT2-H: Initial TMDS implementation in Haiti

INACT1-G: Survey assessment in Ghana

INACT2-G: TMDS implementation in Ghana

RDT: Rapid diagnostic test.

Telemedicine and Medication Delivery Service (TMDS): A service offering phone-based assessments and treatment plans as well as household medication delivery.

6.2 Study design: Prospective cohort study (pilot).

6.3 Population The population of this study will include residents in or approximate to the adjacent communities of Jamestown and Usshertown within Greater Accra (Figure 1). Jamestown and Usshertown are urban communities together known as Ga Mashie or Old Accra. Due to word of mouth, participants residing outside the study area may contact the TMDS; they will receive advice without corresponding delivery/household visits.

Accra Metropolitan, the District in which Jamestown and Usshertown are located, has a youthful population; approximately 20% of the population is under the age of 10. Ghana's under-5 mortality rate is 48 per 1,000 live births[34], with 57.1% of the population having access to satisfactory primary care[38]. Ghana ranks 133 out of 180 on the Flourishing Index[52].

6.4 Recruitment The TMDS (e.g. 'MotoMeds nighttime healthcare for children') will be advertised to targeted communities within the study area. It will be promoted through flyers in an incremental manner at health facilities, schools, religious institutions, etc. as a service for families needing access to non-emergent healthcare for children 10 years and younger during the night. Messaging will clarify that the TMDS is a pilot initiative with a 9-month trial

Figure 1. Approximate study area comprised of Jamestown and Usshertown

period. In addition, audio messaging (radio and public announcements) may occur; content will be similar to that in the written advertisements. Ghana Health Services and local health promoters may assist with advertising efforts. Participants from INACT1-G (survey assessment, ongoing) will be actively notified of the service by phone; INACT1-G participants are consented to a 1-year follow-up period and/or follow-up until the post-study analysis has finished.

6.5 Inclusion criteria and enrollment estimates

6.5.1 Patient participant

Inclusion criteria:

1. Patient must be 10 years of age or younger
2. Has a medical problem
3. Provides written assent (10 years and household visit).

Exclusion Criteria:

1. Patient older than 10 years
2. Does not have a medical problem.
3. Medical problem involves physical trauma or mental health.
4. Refusal of assent (10 years and household visit).

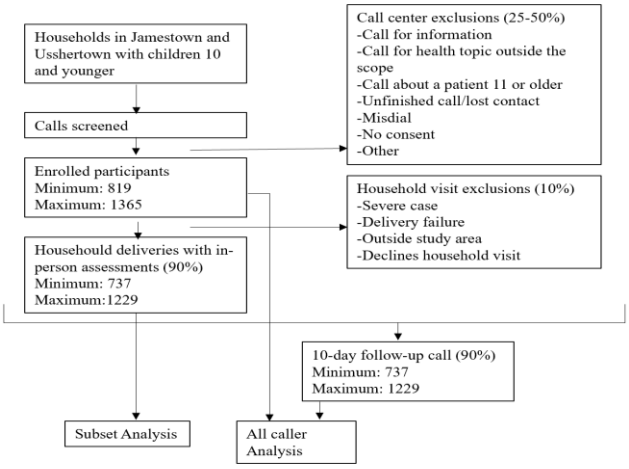

Figure 2. CONSORT recruitment, enrollment, and analysis figure for patient participants.

6.5.2 Parent/guardian participants

Inclusion criteria:

1. Calls MotoMeds during operating hours
2. Parent/guardian of a patient participant meeting inclusion criteria
3. Provides written consent (household visit) or waiver of consent of documentation (no household visit).

Exclusion Criteria:

5. No consent/waiver of documentation of consent
6. Corresponding child participant does not meet inclusion criteria

Enrollment estimates: Enrollment will be determined by the number of eligible patient and parent/guardian participants that contact MotoMeds call center. Based on staff capacity, advertising will be controlled to target 3-5 patients per night. As such, a minimum of 819 and a maximum of 1365 patient and parent/guardian participant pairs will be enrolled. We estimate that loss of follow up at 8-12 days will be 10% (Figure 2). Repeat patients within

30 days will be excluded from analysis; other repeat patients will be considered unique participants.

6.5.3 TMDS staff participants.

Inclusion criteria:

1. Age 18 years and older.
2. TMDS staff member.

Enrollment estimates: Call center EMT enrollment is estimated to be 5 to 15. Driver enrollment is estimated to be 5 to 10. On-call physician enrollment is estimated to be 1 to 3.

6.6 Consent/Assent

6.6.1 Patient participants receiving a household visit

Written assent will be obtained from patient participants aged 10 years. Participants unable to sign may assent via fingerprint. Explanation of informed assent procedures may be obtained in English (official language of Ghana) or another locally spoken language (ex: Ga) in which the EMT obtaining consent and the participant providing consent are fluent as is common research practice in Ghana given that the Ga language is seldom written (see Gamada Letter of Support).

6.6.2 Parent/guardian participants receiving a household visit

Written consent to participate will be obtained in English from the parent/guardian of each patient who receives a household visit; all genders, including pregnant mothers will be included. Participants unable to sign may consent via fingerprint. Explanation of informed consent procedures may be obtained in English (official language of Ghana) or another locally spoken language (ex: Ga) in which the EMT obtaining consent and the participant providing consent are fluent as is common research practice in Ghana (see Gamada Letter of Support).

6.6.3 Parent/guardian participants not receiving a household visit

For parent/guardian participants that are not receiving a household visit due to danger signs present, met capacity, or failed/declined delivery, a waiver of documentation of consent will be presented at the time of the initial call or at the time of the follow-up call (either 24-hour or at the 8-12-day follow-up call). The rationale for the waiver of documentation of consent is that the survey questions pose no more than minimal risk and written consent is not logistically feasible. Explanation of informed consent procedures may be obtained in English (official language of Ghana) or another locally spoken language (ex: Ga) in which the EMT obtaining consent and the participant providing consent are fluent as is common research practice in Ghana (see Gamada Letter of Support).

6.6.4 TMDS staff participating in questionnaire/focus group

A waiver of documentation of consent to participate will be obtained in English from MotoMeds staff members. The rational is that staff focus groups are likely to be performed over Zoom or a similar video-conferencing software.

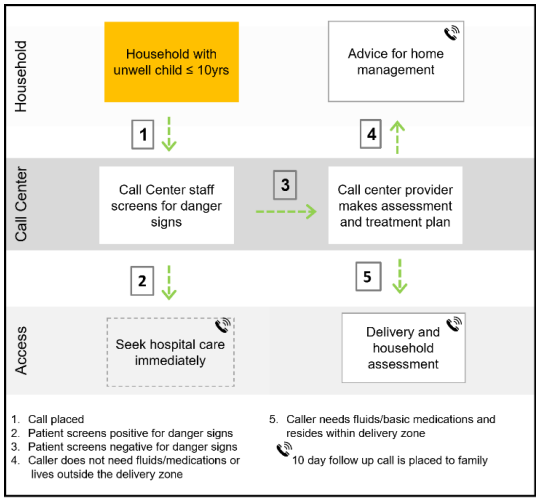

Figure 3. MotoMeds Workflow. Follow-up calls will be placed within a range of 8-12 days.

6.7 Workflow. The call center will operate during the nighttime (exact hours will be determined from INACT1-G). Staffing will be elastic to the needs of the call center case volume. If there are multiple calls at one time, the call center will be staffed to field 1-2 calls at a time. If the call volume is greater than expected, the calls will be placed on hold until a call center EMT is available. If the delivery/household visit volume is greater than the capacity to respond, the contingency plan is as follows: A restriction ('cap') will be activated such that no more than 3 participants can be waiting for a delivery at one time. If there are more than 3 participants waiting, the participants will receive advice by phone and will not receive a delivery/household visit. These cases will be recorded as study data. If volume consistently exceeds the planned capacity, the number of staff (EMTs and drivers) will be increased as funding allows.

Call intake will be managed by the HIPAA-compliant call center software Twilio and case dispatch will be managed by the Beacon Crisis Response. Dispatch alerts via Beacon will include the caller's name, phone number, location, as well as patient complaints; Beacon is also HIPAA-compliant.

Severe cases, certain fever cases and cases with unsuccessful deliveries will be contacted by phone within 24 hours (maximum of 2 attempts over the course of another 24 hours) and all participants will be contacted (maximum of 3 attempts) at 8-12 days to ascertain disposition, if additional care was sought, and qualitative feedback about the service. Responses will be recorded on paper forms and/or directly into REDCap.

Focus groups with TMDS staff will be performed to determine service usability and acceptability from an operational perspective.

6.8 Clinical procedures. The clinical guidelines will adhere to Ghanaian and WHO standards of care and have been developed in collaboration with Ghanaian and US government experts in malaria. During each call it will be disclosed that the call center objectives are to provide pre-emergency health support and conduct research to improve nighttime access to standard of care. To identify emergency cases, triage will occur at the level of the call center EMT (mild, moderate, and severe, see clinical guideline appendix) and leverage WHO derived danger signs for life-threatening illness. If the EMT identifies a

danger sign at the call center or household and thus triages the case as severe, the EMT will advise the patient to seek care at a medical facility and will offer to refer the patient to NAS emergency dispatch (for an ambulance to be dispatched if so desired by the caller).

The clinical guidelines define the clinical scope of the TMDS (also discussed above in the inclusion criteria section). This study is being conducted in an area with high pediatric morbidity and mortality from malaria. Our approach is to follow WHO standards of 'test and treat'. Febrile patients will all be tested with a commercial RDT for malaria. RDT positive patients will be treated with antimalarials. Caregivers of RDT negative patients who do not have another source of their fever will receive a next-day follow-up phone call.

A follow-up call will be placed within 24 hours for severe cases and for those mild/moderate cases with a fever without source and a negative RDT as described above. If a case is triaged as mild or moderate (no danger signs identified), local EMTs will conduct a phone-based assessment. If the patient household is outside the delivery zone, consult alone will be provided as a clinical case; the data from these encounters will not be recorded as study data, given that these patients represent a different patient population. Therefore, they will not receive a waiver of informed consent or follow-up call. If the household is inside the delivery zone (Jamestown/Usshertown), the EMT will generate a treatment plan and medications/fluids will be delivered to the household. A follow-up call will be placed at 8-12 days, ideally at 10 days. In the INACT2-G pilot study, all patient participants will receive a paired in-person exam at a household visit.

The clinical approach will be standardized across EMTs at the call center and at the household. Standardization will occur through paper and/or digital guideline generation for the common chief complaints identified in INACT1-G. Each call center assessment will produce a treatment plan that may include direction to seek emergency care, clinic follow-up, fluids, and/or basic medications (see clinical guideline appendix). The clinical guidelines and workflow (Figure 3) were localized to standards of practice (e.g. selection of guideline-recommended antimalarial medications) and epidemiology (high malaria burden).

Neither the ability to receive care nor the type of care will be affected by the decision to participate in the study. If a family declines to consent to inclusion in the research study, evaluation/care will be provided as outlined in the clinical guidelines. The data from this encounter will not be recorded as study data.

All household medication/fluid deliveries will be accompanied by an EMT with the intent that the medication handoff will happen after the EMT examines the patient and any necessary adjustments to the treatment plan are made. If patients are excluded from participation in the study, standard of care information will be conveyed and/or indications for seeking emergency care. The data from this interaction will not be recorded as study data.

6.9 Testing.

Malaria: Rapid diagnostic tests will be used to evaluate malaria as a source of fever in all febrile patients; febrile is defined as parent/guardian report of fever at the call center or household or objectively measured fever at the household visit. EMTs trained in rapid

diagnostic testing will perform the test at the household. A positive malarial RDT will be used to initiate anti-malarial treatment. A finger prick will be performed with a retractable safety lancet, up to 0.5 ml of blood will be collected in a capillary/collection tube and spotted onto the RDT.

6.10 Outcome Measures.

6.10.1 Aim I (clinical safety). Establish rate of guideline adherence at the call center (primary outcome measure) and household. Determine sensitivity and specificity of each clinical variable using the in-person exam at the household as the reference standard. Establish congruence between call center and in-person assessment in terms of severity categorization, danger signs, disease type, and treatment. Determine clinical status at 8-12 days. Since evaluation of guideline adherence and congruence between the call center and household are part of the research question itself, and because clinical equipoise can exist beyond what can be reflected in written guidelines, small deviations from guidelines based on the clinical facts of the case are not considered protocol violations. Violations that led to an adverse or severe adverse effect will be reported as further specified in this study protocol.

6.10.2 Aim II (feasibility from patient perspective). Logistical data on patient workflow will be collected (duration of call, time to delivery). Parent/guardian feedback will be collected on the clinical, cost and quality aspects of the TMDS.

6.10.3 Aim III (feasibility from staff perspective). Domains of inquiry are clinical decision making, formulation of medications, communication with team members and households, and unanticipated opportunities for improvement.

6.11 Data collection. During the initial call, study staff will capture household contact information, details of the illness assessment and treatment recommendations from all callers meeting inclusion criteria. During the home visit the EMT will capture details of the in-person illness assessment and physical exam that includes anthropometric measurements (MUAC), vital signs, and/or RDT results. During the follow-up call, study staff will capture information on illness progression, outcome, and service feedback. During staff focus groups, a third party will capture staff opinions relating to service operations.

Data collection instruments will include paper screening forms and paper case report forms, digital data collection forms (e.g. REDCap; see data collection instruments) and zoom recordings. Data collected on participants that refuse consent (e.g. initial call center data) will be kept to enumerate rates of study exclusion and reasons for refusal of consent; the data will be excluded from analysis and will be maintained confidentially. Data may be collected up to 12 days after the initial call. Participants may be contacted by phone for clarifications up to 365 days after the initial call. Paper documents will only be accessed by trained clinical and study personnel and will be secured in a locked cabinet in Ghana. These documents will be scanned and uploaded onto a UF secure server.

6.12 Sample size calculation. The enrollment is based on TMDS census over the study period which is estimated to be 819 patient participants. Determination of the effect size of guideline adherence at the call center is the primary outcome. If the call center treatment

plan adheres to the clinical guidelines for 86% of cases (data from INACT2-H), then a sample size of 819 (1.5 patients per night) will estimate guideline adherence to within a 95% confidence interval of +/- 2.4%.

6.13 Staffing and Training. The TMDS will be staffed by Ghanaian medical professionals including physicians and Advanced EMTs. On-call physicians with experience in pediatrics will provide supervision of guidelines and care. Consults will be flexible to mode of communication as to local standards of care; this may involve modes of communication beyond voice (e.g. images, video). If these modes are used, they will always occur with direct end-to-end encryption and they will not be saved nor used as research data. This flexibility prioritizes safety and yet respects protected health information. The staff will be trained on this distinction. All EMTs will have completed a minimum of 2 years of medical education at the NAS Paramedic and Emergency Care Training School or an equivalent institution. They will receive incoming calls, conduct phone assessments following standard of care guidelines, and make treatment recommendations. They will also perform consent and in-person assessments during home visits and will complete follow-up calls. Advanced EMTs will not make independent decisions but rather act within the scope of pre-defined clinical guidelines and/or consult on-call physicians. Trained local motorcycle taxi drivers will be contracted to deliver any needed medications, drive study EMTs to and from home visits. All staff members will be trained in occupational safety measures and human research protections. Staff members will receive training specific to this study, the clinical guidelines and study procedures by the PI and CIs and will undergo an assessment by the PI/CIs prior to being cleared for participation at the TMDS. They will receive on-going supervision by the PI/CIs and a NAS paramedic supervisor who completed paramedic-level training in the United States.

6.14 Incentives. No monetary benefits will be offered for participation in this study.

6.15 Costs. There is no cost for families to participate in this study and/or receive care.

6.16 Study endpoint and timeline Advertisement of the call center and outreach will begin in the month prior to starting the service. Enrollment will take place over 9 months (estimated November 2022 to July 2023). If the minimum enrollment of 819 patients is reached before 9 months, enrollment will continue for the full 9 months to assess sustainability. No more than 2000 patients will be screened/enrolled without subsequent IRB approval. If the minimum enrollment is not reached by 9 months, the enrollment period will be extended to a maximum of 15 months. IRB approval will be requested for further extension beyond 15 months. Primary analysis may continue up to 5 years after study conclusion. See data collection section for duration of enrollment per participant.

6.17 Data Security Paper-based survey forms will be handled by staff trained in the protections of personal health information; forms will be stored in a locked cabinet in Ghana. Data collected electronically will use a HIPAA compliant survey tool (e.g. REDCap and server). All devices will be password protected and encrypted. The de-identification plan for data publication is as follows: Names and phone numbers will be removed. Each case will be given a de-identified number that will be used to link the data sources. Upon publication, these ID numbers will be removed and replaced with a random generated

number and there will be no key to link the files. De-identified data will be shared with the USAID.

6.18 Data Analysis

Data will be aggregated with REDCap and analyzed in R. Statistical support will be provided by the UF Clinical and Translational Science Institute.

Quantitative data will be analyzed using frequentist statistics, which will include using proportions for categorical variables, median and interquartile ranges for quantitative variables, effect size, sensitivity/specificity calculations, interrater agreement (e.g. Cohen's kappa). Qualitative data will be transcribed, coded to evaluate themes, and summarized to identify opportunities for improvement.

6.19 Limitations

Low sample size. Household visits at nighttime are logistically challenging, therefore the study area must be limited in size to ensure safety and efficiency. The size of the study area dictates the population eligible for enrollment. Prior to commencing the intervention, it is difficult to assess whether the designated study area will provide adequate call volume to reach enrollment. We will address this limitation through active advertisement.

Enrollment biases. The intervention is intended to provide pre-emergency care to children who are experiencing a health problem during nighttime hours. Due to the lack of affordable, qualified healthcare options in the study area, households who could potentially visit a health center during the day may wait until nighttime to take advantage of the call center service. This could bias our understanding of the nighttime healthcare needs and call center functionality.

Geographic bias. The call center will be advertised as a service for households in a specific geographic area. In Ghana, boundaries at the community level (US equivalent to neighborhoods) are not officially defined and the address system is based on proximity to landmarks. As a result, it is possible that some callers outside of the study area could be enrolled or some callers inside the study area could be excluded, although the former is more likely to occur. While a 'fuzzy radius' impacts logistics, we do not anticipate this to impact the primary outcomes.

Limited scope. The study is designed to evaluate congruence of phone vs in-person assessments for non-emergent patients. Emergent patients will be advised to seek care immediately. The exclusion of emergency patients limits the scope and generalizability of the study to the full spectrum of EMS services. In-person data on emergent patients will not be obtained in this study.

Limited diagnostic ability. The study is designed to provide acute care at the community level; thus, it is not possible for gold standard diagnostics such as microscopy and PCR to directly inform individual treatment plans. For malaria, in lieu of microscopy, point-of-care rapid diagnostic testing may be used for diagnosis.

7. Data Safety Monitoring Committee

Similar to the iteration of this study that was conducted in Haiti, this study is considered minimal risk and a DSMC is not required, unless instructed by the IRB.

A Medical Advisory Committee consisting of Ghanian and University of Florida physicians specializing in emergency medicine, prehospital medicine, infectious disease, and pediatrics will be convened. The Medical Advisory Committee will receive biweekly email updates including case summaries and relevant medical questions for discussion.

Severe adverse events will be reported per protocols of the Ghana Health Service Ethics Review Committee and the UF IRB. SAE will be defined as: Any event that results in death, significant disability, incapacity, and/or life-threatening situation that developed after enrollment of any patient within the enrollment period (enrollment to the 8-12 day follow-up call). In the event of an SAE, the paramedic supervisor, on-call physicians (primary and secondary), and study director will be notified immediately. NAS leadership and UF leadership (PIs) will be notified the following morning. The leadership will review the situation, dispatch a team to conduct an on-site review/verbal autopsy of the case, and notify the clinical advisory committee. A verbal report will be made to the Ghana IRB within 3 days per their requirements. A preliminary written report will be submitted to both the Ghana IRB and the USA (UF) IRB within five days, as well as the clinical advisory committee. After IRB review and recommendations, a final report will be submitted. The study will continue, be amended, suspended or terminated based on this review process. Given high rates of morbidity and mortality among the participant population[34] and prior research that found the mortality rate in an INACT2 TMDS model in Haiti to be one in 391 participants (0.2%)[53], we anticipate in a population of 891 enrollment participants there will be two mortalities. The threshold for suspending the study for review will be 2 mortalities per two hundred patients enrolled (1%).

8. Possible Discomforts and Risks

Discomforts and risks.

1. Breach of confidentiality.
2. Caller may understate severity of symptoms. A caller may understate the severity of a patient's symptoms, either intentionally or unintentionally, leading to an enrollment that does not meet inclusion criteria. This may result in a delay of seeking immediate care for a true emergency.
3. Financial cost. Seeking care at night at established health facilities is expensive. If we conservatively recommend seeking emergency care but the patient does not have an emergency, this will create unnecessary financial burden for the family.

Efforts to minimize risk.

1. To address risk of breach of confidentiality, paper-based data collection will be minimized and when possible, secure electronic-based data collection tools will be used (REDCap). All staff will be trained in the protections of personal information as well as protections of human subjects research. All paper-based documents will

be maintained in a locked cabinet in a secure building with keyed-access limited to study leadership.

2. To minimize understating disease severity, the guidelines for diverting callers directly to a healthcare facility will adhere to established guidelines (e.g. WHO IMCI). The approach will draw on best practices to interrogate callers and have scripts that ask clear dichotomous questions. The study data will be monitored to determine the concordance between phone and household assessments.
3. When directing callers to seek immediate care at a medical facility, study staff will be clear that they are providing qualified recommendations based on the relayed information, but the final decision is the responsibility of the family. Given the conservative approach, we acknowledge that a small percentage of families may experience unnecessary cost exposure which is weighed against the benefit of likely reducing overall morbidity and mortality.

9. Possible Benefits

Direct:

The primary direct benefit to study participants is access to qualified healthcare during nighttime hours, when alternative healthcare options are scarce.

Indirect:

The service may decompress high morning caseloads at area hospital and clinics by addressing urgent care needs overnight.

The study has potential to benefit the larger regional, national, and international communities, as it could lead to a sustainable option for nighttime pre-emergent healthcare.

10. Conflict of Interest

None. The study investigators and affiliates hold no patents or stock in related technologies.

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