VESIKARI CLINICAL SEVERITY SCORING SYSTEM MANUAL

Kristen Lewis | 2 May 2011

TABLE OF CONTENTS

Introduction

Objective

In combination with laboratory assays, the Vesikari Clinical Severity Scoring System is currently considered the best measurement tool for identifying the endpoint (i.e., severe rotavirus gastroenteritis) in rotavirus vaccine trials. Due to the complexity of the Vesikari Clinical Severity Scoring System and multiple organizations/companies/institutions using the scoring system in clinical trials and surveillance studies, it is important to standardize the use of this measurement tool across studies. This will help to ensure that study implementation methods are as similar as possible between studies. This manual provides a suggested standardized methodology for implementing the Vesikari Clinical Severity Scoring System across studies. This manual also provides rationale for using the Vesikari Clinical Severity Scoring System, details on scoring system parameters, identifies implementation challenges, and presents instructions for using the template Case Report Form (CRFs), diary card, and collecting symptom information.

Burden of Rotavirus Gastroenteritis in Developing Countries

United Nations Millennium Development Goal Four is to reduce the mortality rate of children under 5 years of age by 2/3 between 1990 and 2015 (United Nations, 2005). Since diarrheal diseases continue to be a major cause of morbidity and mortality among children living in low-resource settings, including countries in Africa and Asia (Bresee et al., 2004; Cunliffe & Nakagomi, 2007; World Health Organization, 2008; World Health Organization, UNICEF, & World Bank, 2009), this development goal will only be reached by preventing diarrheal diseases (Bryce, Boschi-Pinto, Shibuya, & Black, 2005). While there are numerous bacterial, viral, and parasitic pathogens that cause diarrhea, a single viral pathogen (rotavirus) is responsible for more acute diarrhea hospitalizations among children under 5 years of age than any other illness (Glass et al., 2006; Kosek, Bern, & Guerrant, 2003; World Health Organization, 2008). This watery diarrhea leads to dehydration and, if not treated quickly, may lead to death.

The majority of morbidity and mortality caused by rotavirus gastroenteritis is experienced by children under 5 years of age in developing countries. Of the 527,000 rotavirus gastroenteritis deaths occurring annually among children under 5 years of age worldwide, over 80% occur in developing countries in Africa and South Asia (Parashar et al., 2009; Parashar, Alexander, & Glass, 2006; Parashar & Glass, 2009; Parashar, Hummelman, Bresee, Miller, & Glass, 2003; World Health Organization, 2006; World Health Organization, 2007) and approximately 40% of hospitalizations for diarrheal illness that occur among children under 5 years of age in developing countries are due to rotavirus (Parashar et al., 2006; World Health Organization, 2008). The contribution of rotavirus gastroenteritis to diarrheal morbidity and mortality in developing countries is due to the epidemiologic profile of the disease and the severe dehydration resulting from clinical infection.

Rotavirus Epidemiology

Rotavirus gastroenteritis is transmitted primarily via fecal-oral contamination through person-to-person contact or contact with rotavirus contaminated items such as respiratory secretions and generally occurs in children under 5 years of age (Centers for Disease Control and Prevention, 2007; Fontaine, 2004). In developing countries 75% of children are infected prior to 12 months of age and attack rates peak at 6 months of age, but in developed countries, the first episode usually does not occur until

between 2 and 5 years of age (Maldonado & Yolken, 1990; World Health Organization, 2007). Once infection has occurred there is an approximate 24 to 72 hour incubation period followed by between 3 and 8 days of vomiting and diarrhea that may be accompanied by fever and abdominal pain and may last for as long as 3 weeks (Centers for Disease Control and Prevention, 2007; Fontaine, 2004). Rotaviruses are shed in stools and vomitus in high concentrations over many days following infection allowing for a high infection rate (World Health Organization, 2007). It is this high rate of infection that allows rotavirus gastroenteritis to propagate efficiently between people and is the reason that rotavirus gastroenteritis is considered non-discriminating; all children are infected by 5 years of age worldwide, regardless of regional location or socioeconomic status (Black & Lanata, 2007; Parashar et al., 2003).

Rotavirus infection is endemic worldwide, but outbreaks can coincide with specific situations (e.g., daycare settings) or seasons (Fontaine, 2004). A full understanding of seasonality in developing countries is hindered by a lack of surveillance data. In countries where surveillance has been implemented, seasonality can be better assessed. In some countries, the rotavirus season coincides with the dry season, while in others rotavirus occurs year-round with seasonal peaks occurring during the dry season (Cunliffe et al., 1998). Immunity does not occur after one infection and reinfection is common, though the severity of subsequent infections is reduced (Centers for Disease Control and Prevention, 2007; World Health Organization, 2007). The first episode usually protects about 40% of children from another infection, 75% from more diarrhea caused by rotavirus, and 88% from an additional round of severe disease (Grimwood & Buttery, 2007). Repeat episodes are likely caused by a different serotype than that which caused the first (Grimwood & Buttery, 2007). Protection against severe diarrhea and heterotypic rotaviruses is boosted with such repeat infections (Grimwood & Buttery, 2007). Due to the high-rate of infection causing severe disease in infants and young children and the subsequent immune response developed following an initial infection, prevention of rotavirus prior to the initial infection is of paramount importance.

Methods for treating rotavirus gastroenteritis focus on treating the effects of dehydration using supportive measures like Oral Rehydration Therapy (ORT) and intravenous rehydration (IV) for rehydration (UNICEF & World Health Organization, 2009). However, these treatment methods do not save children ubiquitously world-wide. The vomiting episodes characteristic of rotavirus gastroenteritis episodes, combined with explosive diarrhea, are responsible for causing rapid dehydration. For this reason, children with rotavirus are more likely to require care in an emergency room or to be hospitalized and require IV therapy (Mast et al., 2009; Senecal et al., 2008). It is these same characteristics that make the dehydration caused by rotavirus difficult to treat using ORT (UNICEF & World Health Organization, 2009; World Health Organization, 2007). In addition, parents must understand when a child is dehydrated and actively seek care for rehydration. In developing countries, recognizing that a young child requires care and then translating this recognition into health care seeking behavior is hampered by practical economic, social, and cultural considerations. Since rotavirus causes a significant amount of the morbidity and mortality in children younger 5 years of age with diarrhea and treating rotavirus is complicated by disease epidemiology and access to care issues, a critical path in preventing diarrheal deaths includes prevention of rotavirus gastroenteritis (Parashar, Holman, Clarke, Bresee, & Glass, 1998; Parashar et al., 2003). Rotavirus vaccines hold particular promise for preventing rotavirus gastroenteritis among developing country populations in Africa and Asia (Parashar et al., 2003).

Vaccine Development

Models suggest that rotavirus vaccines could prevent 5% of all-cause child mortality and up to 40% of gastroenteritis hospitalizations worldwide (Glass et al., 2006; UNICEF & World Health Organization, 2009; World Health Organization, 2008). Recent developing country efficacy and effectiveness studies have shown that a substantial proportion of clinical rotavirus gastroenteritis disease can be prevented by rotavirus vaccines. In Latin America, the introduction of rotavirus vaccines was associated with a reduction in rotavirus morbidity and mortality. In Nicaragua, the introduction of Pentavalent Rotavirus Vaccine (PRV) provided a 45% to 49% risk reduction for children less than 2 years of age admitted to a hospital or requiring IV therapy (Patel et al., 2009). In El Salvador, the introduction of Human Rotavirus Vaccine (HRV) provided a 69% to 84% reduction in cases among children less than 5 years of age admitted to a hospital (de Palma et al., 2010). Finally, in Mexico, the introduction of rotavirus vaccines has been attributed with a 41% reduction in diarrhea related mortality among children 11 months of age and younger and a 29% reduction in children between 12 and 23 months of age (Richardson et al., 2010).

In Africa and Asia, results from clinical efficacy trials also demonstrate that rotavirus vaccines prevent a substantial proportion of disease. While vaccine efficacy is clearly lower than in developed country settings, 49.4% in Malawi and 76.9% in South Africa through the first year of follow-up and 48.3% in Asia (Vietnam, Bangladesh) and 39.3% in Africa (Ghana, Kenya, Mali) through the second year of follow-up, the number of cases prevented is substantial and is influenced more by the burden of disease in each country than by absolute efficacy (Armah et al., 2010; Madhi et al., 2010; Zaman et al., 2010). For example, when comparing results within trials, although vaccine efficacy was higher in South Africa as compared to Malawi, more cases per 100 infants vaccinated per year were prevented in Malawi; 4.2 and 6.7 cases respectively (Madhi et al., 2010). In the PRV developing country trial, approximately 2.0 and 3.0 cases per 100 person-years were prevented respectively (Armah et al., 2010; Zaman et al., 2010). Together the results from Africa, Asia, and Latin America demonstrate the important role that rotavirus vaccines play in preventing the morbidity and mortality caused by rotavirus gastroenteritis.

Based on the overall public health impact that could be achieved, two rotavirus vaccines, (RotaTeq™ (PRV), Merck & Co, Inc.; Rotarix™ (HRV), GlaxoSmithKline) were recently recommended for use by the WHO in developing country settings (World Health Organization, 2009). However, these vaccines have a lower efficacy (approximately 50%) as compared to the efficacy of rotavirus vaccines in developed country settings (approximately 90 to 100%) and are not able to realize their full public health impact in developing country settings. In addition, while these vaccines are cost effective (Atherly et al., 2009), their expense is beyond the reach of many developing country settings. In order to address the outstanding cost and efficacy challenges, it is important for other manufacturers to develop additional rotavirus vaccines that may provide a greater benefit at a lower cost in developing countries.

History of Clinical Severity Scoring Systems in Rotavirus Vaccine Trials

During early vaccine studies conducted in the 1980's, researchers quickly realized that rotavirus vaccines did not protect equally well against all severities of rotavirus gastroenteritis and that a vaccine should protect against the most severe clinical outcome. For this reason, rotavirus vaccine development aimed to prevent the most severe cases, those most likely to require hospitalization or result in mortality. In these early trials conducted in a developed country, different definitions of *clinically significant rotavirus diarrhea* were used for measuring vaccine efficacy against severe disease. One definition included only diarrheal episodes requiring rehydration therapy using ORT according to a pediatrician (Clark et al., 1988). However, this definition was only applicable in trials where subjects would be seen by a clinician

for all episodes of diarrhea (Clark et al., 1988; Vesikari et al., 1985). Another definition of *clinically significant diarrhea* included watery stools lasting for 24 hours or more (Clark et al., 1988; Vesikari et al., 1984). Table 1 demonstrates the rise in efficacy realized in early rotavirus RIT-4237 vaccine efficacy trials when endpoints of severe or moderately severe rotavirus gastroenteritis are used as compared to disease of all severities.

Table 1*: Vaccine Efficacy by Endpoint in RIT-4237 Rotavirus Vaccine Trials-Finland

Pub. Year	Age at Vacc (mo.)	No. Doses	Season	Score	Efficacy Any Severity (%)	Efficacy Moderately Severe to Severe (%)
1984	8-11	1	1	RV diarrhea lasting >24 hrs	55	89
1985	6-12	2	1	Clinically significant diarrhea (diarrhea lasting >24 hours+ requiring rehydration)	62	80
1987	0 & 7	2	2	Numerical Composite Score (0-20, ≥11 severe)	43	89

*Table adapted from Vesikari, Giaquinto, & Huppertz, 2006.

Following the initial 1984 and 1985 RIT-4237 vaccine trials and the 1988 WC3 study (results not included in Table 1), researchers subsequently began refining the definition of *clinically significant diarrhea* based on the clinical presentation profile of the disease. Clinical severity scoring systems soon became a standard for defining severe rotavirus gastroenteritis endpoints based on subsequent vaccine efficacy trials (Clark et al., 1988; Duffy et al., 1986; Flores et al., 1987; Gothefors et al., 1989; Hjelt et al., 1986; Iturriza et al., 2008; Riepenhoff-Talty et al., 1981; Vesikari et al., 1984; Vesikari et al., 1985).

Vesikari Clinical Severity Scoring System

The full history of rotavirus gastroenteritis clinical severity scoring system development is not presented in this manual. However, it is important to recognize that while two clinical severity scoring systems, the Clark and Vesikari Clinical Severity Scoring Systems, were eventually developed and used routinely in rotavirus vaccine clinical trials the Clark and Vesikari Clinical Severity Scoring Systems <u>do not</u> uniformly score severe disease and discrepant results are common when these two clinical severity scoring systems are compared within the same trial (Givon-Lavi, Greenberg, & Dagan, 2008; Lewis et al., 2012). For this reason, it is important to identify a single clinical severity scoring system that can be used consistently within and between trials in order to standardize endpoint measurement. In addition to not including a dehydration assessment, the Clark Clinical Severity Scoring System is less likely to identify an episode of disease as severe as compared to the Vesikari Clinical Severity Scoring System (Givon-Lavi et al., 2008; Lewis et al., 2012). As very few cases of severe disease could be identified using the Clark Clinical Severity scoring system, it is assumed to be a non-sensitive measure of severe disease. For this reason, the Vesikari Clinical Severity Scoring System is currently recognized as the most accurate system for use in developing country vaccine trials (Armah et al., 2010; Madhi et al., 2010; World Health Organization, 2008; Zaman et al., 2010).

The Vesikari Clinical Severity Scoring System is a composite measure initially utilized in the 1987 RIT-4237 vaccine trial (Table 1). It is the clinical severity scoring system described in detail here due to trial location (i.e., developing countries), PATH's past practical experience implementing the two clinical severity scoring systems, published methodological information regarding scoring system development (Ruuska & Vesikari, 1990), and WHO recognition (World Health Organization, 2008). In addition, the Vesikari Clinical Severity Scoring System is a composite measure which relies on the clinical presentation profile of rotavirus to identify severe rotavirus gastroenteritis episodes. Unlike the Clark Clinical Severity Scoring System, it includes dehydration status as one of the parameters rather than relying on a surrogate measurement, behavior.

Rotavirus Clinical Presentation Profile

Rotavirus gastroenteritis episodes have a unique clinical presentation profile that remains consistent across regions and economic settings. Disease burden and etiology studies worldwide concur that it is common for diarrhea, vomiting, fever, and some combination of these symptoms, to all occur in a single rotavirus episode (Aloun et al., 2009; Binka et al., 2003; Coffin et al., 2006; de Villiers, Sawyerr, & de Villiers, 2009; Georges et al., 1984; Huilan et al., 1991; Jenney et al., 2009; Mast, DeMuro-Mercon, Kelly, Floyd, & Walter, 2009; Naficy et al., 1999; Nguyen, Le, Le, & Weintraub, 2004; Nokes et al., 2008; Nyambat et al., 2009; Qazi et al., 2009; Reither et al., 2007; Rodrigues et al., 2007; Senecal et al., 2008; Staat et al., 2002; Suwatano, 1997; Wildi-Runge, Allemann, Schaad, & Heininger, 2009; Wilopo et al., 2009). These studies conclude that, while exact rates of vomiting and fever accompanying diarrhea differ across studies possibly based on the age of children included in the studies and settings (inpatient vs. outpatient), vomiting and diarrhea are common (>50%) in patients with rotavirus. Notably, it is not uncommon for vomiting to precede diarrhea. Children under 5 years of age with rotavirus requiring an inpatient admission more commonly present with vomiting than children with other diarrheal illnesses (Rivest, Proulx, Lonergan, Lebel, & Bedard, 2004). In addition to vomiting, fever, and diarrhea, the majority of studies indicate that dehydration is also common in rotavirus episodes due to the explosive watery diarrhea and vomiting. In numerous studies, dehydration occurred more often among rotavirus-positive study participants as compared to rotavirus-negative participants (Aloun et al., 2009; Black,

Merson, Huq, Alim, & Yunus, 1981; de Villiers et al., 2009; Georges et al., 1984; Kim et al., 2005; Nguyen et al., 2004; Nokes et al., 2008; Nyambat et al., 2009; Zaman et al., 2009). In addition, results from numerous studies do not indicate that there is a specific, tightly defined duration of illness characterizing rotavirus gastroenteritis in either inpatients, outpatients, or by age (Binka et al., 2003; Duffy et al., 1986; Suwatano, 1997; Vesikari, Sarkkinen, & Maki, 1981), but rotavirus-positive participants generally do have a shorter duration from disease onset to clinic/hospital visit and have a shorter episode duration (Kim et al., 2005; Senecal et al., 2008; Uhnoo, Olding-Stenkvist, & Kreuger, 1986). Because the symptoms and duration of diarrhea, vomiting, fever, and dehydration are also commonly experienced with diarrheal illnesses caused by other etiologies, researchers have concluded that there is no combination of symptoms or specific duration which easily confirm that a person has rotavirus (Vesikari, Maki, Sarkkinen, Arstila, & Halonen, 1981). For these reasons, the Vesikari Clinical Severity Scoring System <u>must</u> be used in combination with laboratory assays in identifying the primary endpoint in rotavirus vaccine efficacy trials, severe rotavirus gastroenteritis.

Parameters and Scoring

More details on how to score an episode are included in the accompanying episode scoring manual. The following is a brief overview to prepare the reader for the following in-depth discussion regarding symptom collection methods.

There are seven scoring parameters included in the Vesikari Clinical Severity Scoring System. These parameters take into account each of the symptoms identified as important in the clinical presentation profile: diarrhea, vomiting, fever, dehydration, and the duration of diarrhea and vomiting. An additional parameter considered is treatment status. Each of the seven parameters is broken into thirds according to an equally divided severity distribution (i.e., bottom third=1, middle third=2, top third=3) as initially identified by Ruuska and Vesikari (1990). The scores for each parameter within the clinical severity scoring system are added allowing for a severity score between 0 and 20 points. The seven parameters and the corresponding scores provided for each categorical level of severity are outlined in Table 2. Severity scores above 10 points (i.e., ≥11 points) are considered severe, scores between 7 and 10 moderate, and scores less than 7 mild (Table 3). If the scoring system is being implemented correctly, approximately 50% of rotavirus positive participants should have a "severe" classification (score ≥11). Any participant in a clinical efficacy trial with a score ≥11 points is included in the primary analysis of efficacy.

Table 2*: Vesikari Clinical Severity Scoring System Parameters and Scores

	Score		
Parameter	**1**	**2**	**3**
Diarrhea			
Maximum Number Stools per Day	1-3	4-5	≥6
Diarrhea Duration (Days)	1-4	5	≥6
Vomiting			
Maximum Number Vomiting Episodes per Day	1	2-4	≥5
Vomiting Duration (Days)	1	2	≥3
Temperature	37.1-38.4	38.5-38.9	≥39.0
Dehydration	N/A	1-5%	≥6%
Treatment	Rehydration	Hospitalization	N/A

*Table adapted from rotavirus clinical trials utilizing the Vesikari clinical severity scoring system (Clark et al., 2004; Ruuska & Vesikari, 1990).

Table 3*: Vesikari Clinical Severity Scoring System Severity Rating Scale

Severity Category			
Mild	*Moderate*	*Severe*	*Maximum Score*
<7	7-10	≥11	20

*Table adapted from rotavirus clinical trials utilizing the Vesikari clinical severity scoring system (Clark et al., 2004; Ruuska & Vesikari, 1990).

In order to accurately score each parameter in the analysis phase study staff must understand the symptom definitions and how to capture each symptom. The following parameter descriptions outline how each of the symptoms is collected in order to ensure accuracy. Since the total duration of each episode and the symptom severity from the first day of an episode must be considered, *symptoms must be collected from the day that any single symptom (i.e., diarrhea and/or vomiting) begins* rather than from the day of presentation to a clinic or the day that diarrhea begins (i.e., it is important to capture vomiting episodes that precede diarrhea). In addition, because it is important to capture the full scope of symptoms for participants experiencing diarrhea and/or vomiting from the beginning of an episode, it is important for study clinicians to capture all symptoms, regardless of whether or not the episode eventually is classified as an Acute Gastroenteritis Episode (AGE) episode and deemed eligible for inclusion in the primary efficacy analysis during data cleaning and analysis.

Diarrhea, Vomiting, Temperature

- *Diarrhea*: The <u>maximum number (i.e., highest amount) of diarrheal episodes occurring in a 24 hour period</u> should be captured from the first day that the illness begins. Episodes with maximum of between 1 and 3 stools per day are given a score of 1; 4 or 5 stools per day a score of 2; 6 or more stools per day a score of 3.

- *Vomiting*: The <u>maximum number (i.e., highest amount) of vomiting episodes occurring in a 24 hour period</u> should be captured from the first day that the illness begins. As vomiting commonly precedes diarrhea, it is important for trial staff to be aware that they need to ask participants about the first day of vomiting and not just the first day of diarrhea. This point should also be emphasized when instructing participants how to complete the diary card. Episodes with a maximum of 1 emesis per day are given a score of 1; 2 to 4 emeses per day a score of 2; 5 or more emeses per day a score of 3.

- *Temperature*: The <u>highest temperature in any 24 hour period</u> must be captured. Temperatures in a clinic should be collected using the routine collection method in each setting (i.e., axillary, oral, rectal, otic). Temperatures collected at home should be measured using the axillary method. All non-rectal temperatures are converted to the rectal equivalent*. As fever is a non-specific symptom and is a symptom associated with a number of illnesses, fever should only be captured once either vomiting or diarrhea has started. Episodes with maximum temperature below 37.1°C rectal equivalent are given 0 points; 37.1-38.4°C 1 point; 38.5-38.9°C 2 points; ≥39.0°C 3 points.

  *Rectal Equivalent Conversion:
  1. Convert the temperature to Fahrenheit
     - $T_{fahrenheit} = (9/5 * T_{celcius}) + 32$,
  2. Add 2 degrees for Axillary (1 degree for oral or otic)
  3. Covert back to Celsius
     - $T_{celcius} = (5/9) * (T_{fahrenheit} - 32)$

Duration of Diarrhea and Vomiting Episodes

- *Duration of Diarrhea:* The total number of days that one or more episodes of diarrhea (i.e., looser-than-normal stools) occur from the <u>beginning of an episode</u> must be captured without missing days or counting stools twice (once on one day and then again in the tally for the following day). While this may seem simple, study participants may be visiting multiple facilities for assessments (i.e., referral to a hospital following a primary clinic visit). The methods for implementing the CRFs must be carefully defined (see Appendix 1: Definitions, 24-Hour Period) so that study staff members, who may be located at different health facilities, consistently capture symptoms according to methods used at that specific facility.

- *Duration of Vomiting:* Like with the duration of diarrhea, the total number of days that one or more episodes of vomiting occurs from the <u>beginning of an episode</u> must be captured without missing days or counting them twice. The other caveats specified for duration of diarrheal episodes also apply to this parameter.

Dehydration

This measure is a composite score and includes four different parameters; eye appearance, condition, level of thirst, and skin elasticity (World Health Organization, 2005). This brings the total number of parameters requiring measurement in the Vesikari Clinical Severity Scoring System to ten, increasing the complexity of accurate endpoint measurement. The current WHO IMCI dehydration treatment criteria classify the degree of symptoms experienced into categories of A (treat at home; mild dehydration), B (treat using oral rehydration salts (ORS) in clinic; some dehydration (1-5% loss body weight)), and C (treat using IV therapy in clinic; severe dehydration (≥6% loss body weight)). Table 4 provides an overview of how to determine whether a participant is classified to have no, moderate, or severe dehydration. Dehydration is determined by assessing dehydration from the bottom of the table (Plan C) and moving up.

1. If a participant meets the criteria for severe dehydration, then the participant is classified as "severe" for the purposes of Vesikari scoring.
2. If the participant does not meet the severe dehydration classification, then he/she is assessed for some dehydration and classified as "moderate" if he/she meets the criteria defined.
3. If the participant does not meet the severe or some dehydration classification, then he/she is considered to have no dehydration.

Table 4*: WHO IMCI Dehydration Treatment Criteria

Treatment Plan	Signs	Dehydration Classification	Treatment
Plan A	Does not meet criteria for Plan B or C	No Dehydration	Treat at home by giving fluid and food
Plan B	*Two Signs:* • Restless, Irritable • Sunken eyes • Drinks eagerly, thirsty • Skin pinch goes back slowly	Some Dehydration (Equivalent to 1-5% loss body weight)	Treat using ORS solution in the clinic, as well as food
Plan C	*Two Signs:* • Lethargic or unconscious • Sunken eyes • Not able to drink or drinking poorly • Skin pinch goes back very slowly	Severe Dehydration (Equivalent to ≥6% loss body weight)	Treat using IV therapy administered at a clinic

*Table adapted from WHO's Integrated Management of Childhood Illness Guidelines (World Health Organization, 2005)

Treatment

The treatment parameter combines hospitalization with rehydration. The Vesikari Clinical Severity Scoring System considers an inpatient admission (i.e., hospitalization) as more concerning than rehydration (i.e., IV therapy or ORT); 2 points are provided for hospitalization and 1 point for rehydration. In developed countries, where IV therapy is only provided in an inpatient setting, this classification considers IV therapy and hospitalization as similar signs of "severe" illness . Anyone receiving IV therapy in a developed country study would be hospitalized and participants would always receive a score of 2 for either hospitalization or IV rehydration. However, in developing countries, where IV therapy can be provided in outpatient settings, if the treatment measure considered the literal meaning of "hospitalization" and "rehydration", the intent of the original Vesikari Clinical Severity Scoring System would be modified. For this reason, in developing country trials, participants who are "hospitalized" for at least 24 hours OR who receive IV therapy are considered "hospitalized" and receive a corresponding score of 2 points for this parameter. Participants who are not hospitalized or who are

hospitalized for less than 24 hours AND <u>do not</u> receive IV therapy, but do receive ORT are classified as "rehydrated" and receive a score of 1 point for this parameter.

Measurement Methods and Standardization

Knowing what parameters are included in the Vesikari Clinical Severity Scoring System and how each parameter should be scored is the simple part of trial implementation. Due to the delinking of symptom collection from episode scoring, two necessary steps are required to accurately implement the Vesikari Clinical Severity Scoring System. First, symptoms must be collected in an accurate and uniform manner across episodes and study health facilities in order to accurately score each episode within a trial. Secondly, the data analysis methods for classifying severe rotavirus gastroenteritis episodes must be carefully defined *a priori* and severe cases identified according to these analysis methods. Symptom collection and associated challenges are expanded in the following section. As data analysis methods are specific to the data management staff responsible for coding study data, these methods are outlined in detail in an episode scoring manual.

Methods to Ensure Accurate Collection of Symptoms

Accurate collection of symptoms is highly subjective and based on the ability of parents to accurately recall symptoms. For this reason, frequent home visits by field workers and diary cards are employed to assist in reducing differences attributable to subjectivity between episodes. It is also important to consider how and when participants will be assessed by study clinicians and methods for capturing data so that symptoms are not missed or duplicated.

Definitions

Standardized definitions of each parameter and related terms are included in Appendix 1. These definitions should be used throughout symptom collection and episode assessment.

Local Context and Health Care Seeking Behaviors

Before implementing use of the Vesikari Clinical Severity Scoring System, study leaders and clinical operations experts must reflect on local standards for health care seeking behaviors, ORT use, and the ability of the study population to access care for diarrheal illnesses. This concern is an ethical one, but is also important when considering how and when to measure symptoms resulting from a gastrointestinal illness. In many developing country settings, people are likely to attempt self-treatment and visit traditional healers or other community-based, alternative treatment options, before taking their child to a study clinic or hospital (Adegboyega, Onayade, & Salawu, 2005; Nkwi, 1994; Vaahtera et al., 2000). Care seeking with alternative care providers may be more common in rural areas where access to allopathic care is limited by long distances between homes and government health care facilities (Pillai

et al., 2003). Finally, in some settings, because young children get many illnesses, most of which resolve on their own, parents in some settings may be apprehensive to seek care for young children (Pillai et al., 2003).

In a clinical trial, it is this reluctance to seek care and these visits to alternative healers and treatment providers that can be detrimental to identification of severe rotavirus gastroenteritis. For example, if a parent takes her child to an alternative healer and either never visits a study clinic or visits a study clinic late, it is likely that the study data will be compromised; either the episode is missed, or if ORT was administered outside of a study clinic or before the dehydration assessment, the opportunity to capture the true severity of symptoms has been missed. In addition, the longer a parent waits to take a child to a study health center, the less likely that parent is to accurately recall symptoms as they occurred from the beginning of an episode.

For these reasons, it is important to establish an <u>active surveillance</u> system which includes <u>weekly home follow-up visits</u> by a well-trained staff of field workers (FWs) and <u>parental use of diary cards</u> for recording symptoms as they occur. While active surveillance has the potential to significantly reduce the natural course of an episode and full episode severity, it is important to have a higher standard of care and early treatment interventions, especially in trials utilizing an active comparator. One study conducted in urban and rural Kenya found that parental recall of children's symptoms was reduced when more than 3 days elapsed between the symptoms and the recall session (Feikin et al., 2010). In addition, based on experience with other, more passive surveillance designs, follow-up on less than a weekly basis does not accurately capture the full course of symptoms experienced by participants in developing country rotavirus vaccine trials. For this reason, active surveillance dependent upon weekly home visits is a compromise between shorter visits to optimize parental recall, as well as reduce the chances of experiencing adverse effects, and longer visits allowing participants to experience the full disease severity.

Weekly Home Follow-up Visits

FWs visit each home once per week to determine whether a participant is experiencing or has experienced an episode of gastroenteritis in the past week. During these visits, parents are reminded to complete the Diary Card and visit the nearest study health facility should their child become ill with <u>any</u> gastroenteritis symptoms (i.e., diarrhea and/or vomiting with or without accompanying fever) or should they require health care for any other reason. These weekly home visits serve three purposes. First, they ensure that symptoms can be accurately captured. Second, they help the family to feel connected to the study and remind the parent that study staff care about their child's welfare. Finally, these visits provide a safety net for identifying ill children and capturing adverse and serious adverse events.

An example organogram of field staffing is included in Appendix 2. A Field Coordinator (FC) should be employed to provide oversight and overall coordination for the field team. The FC will be responsible for coordinating FW and Field worker supervisor (FWS) schedules, standardizing follow-up methods across field workers, and ensuring that field activities are being conducted according to protocol. FWSs should be employed to provide direct field worker oversight. FWSs are responsible for tracking FW performance by checking weekly home visit FW logs and accompanying FWs on randomly chosen home

visits in order to ensure procedures are done according to protocol and according to standardized methods. FWSs ensure that every participant is visited once per week, regardless of FW sicknesses or absences and they must identify back-up field workers to fill gaps. In general, there should be 1 FWS per every 10 to 15 FWs and approximately 1 FW per 20 to 25 person study population with field workers visiting between 4 and 5 homes each a day. Of course, this suggested standard may need to be modified depending on the geographical reach and density of the study area (i.e., distance between homes) with more FWs and FWs allocated for less densely packed, rural study areas and fewer field workers allocated for more densely packed, urban study areas. FWSs must report back to a team leader who is responsible for standardizing methods across FWSs.

NOTE: While FWs and FWSs may assist parents in completing the diary card at home, <u>FWs and FWSs are not clinicians and cannot record severity information on the study CRF</u>. Severity information should be recorded on the study CRF only by specially trained study clinicians based on parental completion of the Diary Card (for symptoms occurring prior to admission to a study health facility) and symptoms experienced while in a study health facility (for symptoms occurring while in a study health facility).

Diary Cards

At each weekly home follow-up visits, FWs should ensure that parents have an adequate supply of blank diary cards (Appendix 3) and understand how and when to complete diary cards. Parents should begin filling in a Diary Card at the first sign that their child has a gastrointestinal illness (i.e., vomiting and/or diarrhea) and continue completing the Diary Card until the episode has resolved. FWs must discuss the importance of accurately collecting information in a timely manner on the diary cards. Shorter periods between symptom occurrence and parental recall are more likely to result in accurate capture of symptom information. For this reason, parental recall of symptoms must be completed on the same day as the symptoms occur, preferably within the same hour.

Illiterate parents should be encouraged to contact a field worker for assistance in completing the diary card. Field workers who are contacted by illiterate parents for assistance should visit the home once per day to assist with completion of the diary card on a daily basis. FWs who discover a parent with a completed Diary Card during the weekly home visit should collect the diary card, verify the symptoms and any illegible information included on the Diary Card with the parent, and submit the Diary Card to their FWS. While all entries on the Diary Card should be verified, FWs should pay special attention to verifying that vomiting occurred rather than just spit up. Vomiting is a forceful expulsion of stomach contents, as compared to spit-up which is the easy flow of stomach contents out of the mouth and frequently occurs with a burp. This Diary Card must be given to a clinician and information extracted onto the Gastroenteritis Symptom CRF (Appendix 4) for entry into the study database.

FWs who discover a parent with a partially completed Diary Card or who have a child with any gastroenteritis symptoms (i.e., vomiting and/or diarrhea with or without fever) or other symptoms requiring clinical care (e.g., respiratory symptoms) during a weekly home visit should assist the parent in completing the diary card and then refer that parent to the nearest study clinic for follow-up care. FWs should follow-up on a daily basis to ensure that parents report to the study clinic and the information on the Diary Card is captured by a study clinician.

Clinic Visits and Referral Considerations

Upon presentation at a study clinic, a trained study clinician should review the Diary Card with the parent to verify symptoms that occurred prior to the clinic visit and should complete the Gastroenteritis Symptom CRF (Appendix 4). During the clinic stay, clinicians should continue to collect symptoms by visiting participants every 4 hours and these should be recorded on the Gastroenteritis Symptom CRF (Appendix 4) for the duration of the clinic visit. Symptoms may be collected based on parental recall of symptoms that occurred over the last 4 hours, but temperature must be measured by a clinic staff member at each 4 hour assessment.

Participants requiring overnight hospitalization or care at a referral facility (i.e., study hospital) should be referred for care and their diary cards and CRFs should be transferred with them in order to ensure continuity of symptom collection. If symptoms are ongoing at discharge and the parent is not referred to the hospital, the parent should be sent home with an ample supply of blank diary cards and requested to complete the diary cards or to contact field workers who can assist in completing the diary cards on a daily basis until symptoms resolve.

Hospital Visits

Similar to a clinic visit, participants referred for hospital/inpatient care should continue to have their symptoms collected by a study clinician using the Gastroenteritis Symptom CRF (Appendix 4). Symptoms should be collected based on visits to the participant that occur every 4 hours through discharge. Like with the clinic visit assessments, parental recall of symptoms may be used, but temperature must be taken by a study clinician during each assessment. If symptoms are ongoing at discharge, the parent should be sent home with an ample supply of blank diary cards and requested to complete the diary cards until symptoms resolve.

Transportation

To facilitate accurate clinical care and symptom capture, transportation should be provided to participants who have gastroenteritis symptoms or other symptoms requiring clinician assessment. Study staff should assist in arranging transportation between homes and study clinics, as well as between study clinics and study hospitals for participants who are referred. Transportation by a study car, autorickshaw or motorbike is preferable. While there is no guarantee that participants will arrange their own transportation, a transportation reimbursement may also be provided to participants who arrange their own transportation. This guarantees poor families that household money for food or other living expenses that is used on transportation to the study clinic or hospital will be reimbursed, thereby encouraging study visits according to the protocol. While all attempts to provide direct transportation for clinic visits should be made, in remote areas, it may not be feasible to coordinate transportation and a transportation reimbursement may be the only feasible option. Whether transportation is provided directly or reimbursed, each study should carefully track the transportation methods implemented in each study area and ensure that this does not affect case capture rates disproportionally between study areas.

Pretesting/Validation

While this guidebook provides good information for standardizing information collection between studies, the implementation of the Vesikari Clinical Severity Scoring System is highly subjective. Not all study-specific factors, including study facilities and cultural context, can be accommodated in a guidebook. For this reason, each site must conduct a pretest of the study collection methods and materials (e.g., during a preparatory study), including home visits by FWs and FWSs, during which all health facilities that will be utilized in the study by study clinicians. This pretesting period should include periodic scoring at the data management level and blinded review by scoring experts to ensure that methods are optimized prior to study conduct.

Ongoing Episodes and Gaps in Symptom Collection

Episodes may not all resolve prior to discharge from a clinic/hospital. For this reason, it is important to instruct parents to continue collecting symptoms on the Diary Card for ongoing episodes. FWs should also be contacted and requested to follow-up with parents every 2 days during an ongoing episode. These frequent follow-up visits will serve two purposes. First, FWs should encourage participants with episodes that do not resolve within 2 days to seek additional care. This will ensure that ongoing episodes do not turn into serious illnesses. Second, for participants that do not return to a facility for additional follow-up, these visits will allow the field worker to verify symptoms on the diary cards, ensure that parents have an adequate supply of diary cards, and collect completed diary cards for review and CRF transcription by a qualified study clinician.

In some cases, participants may have symptom free days in the middle of an episode. Symptom free days are defined as days that no gastroenteritis symptoms occur (i.e., no vomiting, diarrhea, with or without fever ≥37.1). If there are ≤3 symptoms free days, the subsequent symptoms are considered part of the current episode. If there are ≥4 symptom free days, the subsequent symptoms are considered part of a new episode. While this information is most relevant for coding during data analysis, clinicians and field workers should be aware of this definition to ensure that forms are completed according to the symptom collection guidance information presented in the following section of this guidebook.

Gastroenteritis Symptom Collection Guidance

Information Collection

This section of the manual describes the procedures to be used in collecting symptom information and completing the CRFs provided in Appendices 3 and 4.

Diary Card

Symptoms of gastroenteritis (vomiting and/or diarrhea) that occur at home at any time during the study should be collected by the parent using the diary card (Appendix 3). Diary cards should be given to parents by field workers at each home visit or by study clinicians following collection of a completed diary card.

Diary Card Completion Instructions

The Diary Card is formatted so that, once printed, it can easily be folded into booklet format. During printing, both sides of the paper should be used. Once the pages are placed together in the order printed, the booklet can be created by folding the stacked papers in half and placing staples on the crease.

Parents of study participants should be provided with thermometers and stool collection materials and taught how to use these supplies by the field worker. The parent temperature and stool collection instructions are meant to be modified depending upon the type of thermometers and stool collection containers purchased for each study. Also, culturally specific photos demonstrating correct axillary temperature collection and stool collection may be added in the space below each of these instruction pages.

The Diary Card should be completed for all participants who have <u>any</u> looser-than-normal stools or vomiting. While this does not meet the primary case definition (i.e., 3 or more looser-than-normal stools and/or forceful vomiting), it is important for parents to collect all symptoms that resemble gastroenteritis. The determination regarding whether the episode meets acute gastroenteritis criteria can be made during data analysis.

<u>**Header Information:**</u>
- Enter study title for each specific study into the template prior to printing.
- The study staff member who gives the Diary Card to the parent should complete the participant identification number, initials, and contact information at the time that the Diary Card is given to the parent.

<u>**Instructions:**</u>
Parent instructions for how to complete the diary card, take a child's temperature, and collect a stool specimen are provided on the diary card. The instructions also include definitions for some of the terms. These instructions and definitions should be reviewed with the parent by the field worker at each

weekly visit and the parent reminded to complete the Diary Card if the child has any looser-than-normal stools or vomiting.

Symptom Collection:
The Diary Card includes eight pages, one for each day that a participant is ill with either diarrhea and/or vomiting. As long as field worker visits occur on time (every 7 days +2 days or -1 day), this should provide adequate space for recording episodes that begin immediately following one home visit and continue to the next weekly home visit. Each study will need to consider whether parents should be provided with a back-up diary card, just in case field worker visits don't occur according to schedule.

Parents should complete one page in the diary card, in order (i.e., day 1, day 2, day 3, etc.) for each calendar day that their child has any looser-than-normal stool and/or vomiting episode. A calendar day is the 24-hour period from midnight of one day to midnight the next. A 24-hour period may be defined by the mother (e.g., sunrise of one day to sunrise the next day, midnight of one day to midnight the next, etc.) for the purpose of recalling maximum severity on the diary card. However, the parent should ensure that symptoms are not counted twice (i.e., counted in the symptom count on days 1 and 2). In data analysis, calendar days should be counted for all "duration" fields.

Parent Instructions:

- **Date:** The "Date" should be recorded for each day that at least one looser-than-normal stool or vomiting episode occurred. The date format should be reported as : Day: |_0_|_2_| Month: |_O_|_C_|_T_| Year: |_1_|_0_|.

- **Highest Temperature:**
    o Parents should always take temperatures <u>using the axillary method</u>.
    o Temperatures should only be recorded here if the child has any looser-than-normal stools or vomiting episodes. Temperatures in the absence of vomiting or looser-than-normal stools are not indicators of gastroenteritis.
    o Parent should record the highest temperature taken at anytime on a specific day here.
    o Check the box "Not Taken" if the parent did not take a temperature using a thermometer.

- **Vomiting:** Parent should circle the number of times the child has vomiting <u>last night and through the day</u>. If more than 6 vomiting episodes occurred, the parent should write the total number in the box provided.

- **Diarrhea:** Parent should circle the number of times the child has looser-than normal or watery stools <u>last night and through the day</u>. If more than 6 stools occurred, the parent should write the total number in the box provided.

- **Medication:** Parent should <u>check one box</u> corresponding to the type of medication that the child received; oral rehydration, IV rehydration, oral & IV rehydration, other.
    o If another medication was given, this should be written in on the line provided.
    o If no medication was given, the "no medication given" box should be checked.

Completed Diary Cards

Once complete, the Diary Card should either be taken with the participant to a study health facility when seeking care and given to a study clinician, or, if care is not sought, should be collected by the field worker and returned to a FWS for delivery to a study clinician. The study clinician should always be responsible for transcribing the information onto the Gastroenteritis Symptom CRF.

- If the Diary Card is collected by a field worker, the field worker should review the Diary Card with the parent and clarify any information that is missing or illegible.
- If the Diary Card is collected by a study clinician, the study clinician should review the Diary Card with the parent and clarify any information that is missing or illegible.
- Every time a Diary Card is collected from a parent, a new, blank Diary Card should be provided for use in collecting subsequent episodes or ongoing symptoms.

Only trained study clinicians should record information from the Diary Card onto the Gastroentertis Symptom CRF. In determining where to place Diary Card information on the Gastroenteritis Symptom CRF, the study clinician must consider whether the episode being reviewed is a new episode or an ongoing episode according the following definitions.

> **Episode Definitions**
>
> Underline New Episodes: Symptoms (i.e., diarrhea and vomiting) that occur more than 3 days (i.e., ≥4 days) following the end of the prior symptoms are considered "new episodes".
>
> Ongoing Episodes: Symptoms (i.e., diarrhea and vomiting) that occur ≤3 days following the end of the prior symptoms are considered part of the same episode.

Recording new episode information on Gastroenteritis Symptom CRF: After receiving the Diary Card from a field worker or parent and reviewing/clarifying illegible or missing information, the study clinician should use the information on the Diary Card to complete section 1 ("Symptoms Occurring Prior to Presentation at Study Health Facility") of the Gastroenteritis Symptom CRF using the instructions provided in the Gastroenteritis Episode CRF Completion Instructions section of this guidebook.

Recording ongoing episode information on Gastroenteritis Symptom CRF: In some cases, participants may be sent home from a study health facility with continuing symptoms or may have symptoms that begin again following discharge from a study health facility. If this occurs, the parent should be instructed to complete a Diary Card and this Diary Card should be returned to the study health facility by the parent (when visiting a study health facility to receive care) or by the field worker (if the parent does not seek care at a study health facility). In these cases, the information on the Diary Card should be reviewed with the parent according to the above outlined procedures. Then, information from the Diary

Card should be recorded as new day(s) in Section 3 of the Gastroenteritis Symptom CRF using the instructions provided in the Gastroenteritis Episode CRF Completion Instructions section of this guidebook.

Home Stool Collection Instructions

Participants who have any looser-than-normal stools should have a stool collected <u>as soon as possible following the onset of the looser-than-normal stools and no later than 7 days after the beginning of the symptoms</u>. Stool collection containers should be provided to participants by field workers at each home visit and field workers should instruct and remind parents to collect stool as soon as possible according to the instructions provided in the Diary Card should the child experience <u>any</u> looser-than-normal stools.

Gastroenteritis Episode Case Report Form Completion Instructions (Appendix 4)

The data on gastroenteritis episodes will be captured using:

(a) recall of symptoms (via parental report)

AND

(b) real-time symptom assessment (performed by medical staff)

The data collection process is a 4-step process. Only study clinicians trained to collect symptoms should be responsible for the following data collection activities.

1. <u>Symptoms occurring prior to presentation at health facility:</u> An interview of the participant's parent will be initiated at presentation to a study health facility to collect gastroenteritis symptom information for symptoms that occurred on calendar day(s) *prior* to the day of presentation to the study health facility. This interview will include review of the Diary Card with the parent. Information should be extracted from the Diary Card and placed onto the Gastroenteritis Symptom CRF.

2. <u>Symptoms at time of presentation to health facility:</u> A study clinician will evaluate the participant and collect clinical data relating to the severity of disease and dehydration for day that the subject presents to the medical facility.

3. <u>Symptoms present during calendar days participant at health facility:</u> A study clinician will evaluate the participant and collect clinical data relating to severity of disease every 2-hours while the participant is admitted to a study health facility.

4. <u>Symptoms present following discharge from a health facility:</u> Participants discharged with continuing symptoms will be sent home with diary cards and asked to continue collecting symptom information until <u>all</u> gastroenteritis symptoms (i.e., diarrhea and vomiting with or without fever) resolve completely. Field Workers will follow-up with participants discharged with continuing symptoms at their homes every 2 days until resolution of the illness. After illness resolution, field workers will collect diary cards, confirm information is legible, and forward to study staff members for information to be extracted onto remaining lines in the study CRF (Section 3).

The Gastroenteritis Symptom CRF should be completed for all participants who present to a study health facility with the following symptoms on the day of the visit or the days prior to the visit:
- Three or more watery or looser-than-normal stools occurring within a 24-hour period; *and/or*

- Forceful vomiting.

Header Information: At a minimum, the participant identification number, the health facility, and the date of initial presentation to the study health facility should all be collected as part of the Gastroenteritis Symptom CRF. Each site may choose to add additional background information to this section. The participant identification number and health facility number should be formatted to meet the specifics of each study.

- Date of initial presentation to a health facility: This information is essential in the data analysis phase for linking episodes and stool results to each episode.

Note: Although the data collection process indicates that rehydration/treatment will not be provided until after collection of symptoms occurring prior to the health facility visit (CRF section 1) and an initial dehydration assessment (CRF Section 2), the primary concern of the study clinicians should always be the safety of the participant. For this reason, for participants who present with serious symptoms should be quickly assessed for dehydration (CRF Section 2, Part A) immediately upon presentation to the health facility and rehydration therapy and other required treatments provided immediately. After the immediate danger to a study participant has passed (i.e., following IV fluid initiation or administration of other required medications), the study clinicians should then proceed with collecting the remaining clinical symptoms as specified in this guidance document beginning with CRF section 1. Dehydration information <u>should not</u> be reassessed later in the episode.

1. Symptoms Prior to Presentation at Health Facility

This section should be completed by a trained study clinician as soon as possible after presentation and while interviewing the parent/guardian about the child's symptoms and reviewing the Diary Card with the parent. *This section should include only symptoms that the parent/guardian recalls the child having on the days <u>prior to, but NOT including,</u> the day of presentation to the medical facility.* [This means that if the GE/Diarrheal Illness began today, the day of presentation to the health care facility, a "0" would be entered in all fields of the table, including temperature.]

<u>Date and Time of Symptom Onset:</u> Record the date (dd-mmm-yy) and time (24 hour clock) that diarrhea and vomiting started based on Diary Card review and parent interview, even if the symptoms just began today.

<u>Maximum Number or Intensity AND Duration:</u> The maximum severity of each symptom in a given 24-hour period should be collected in order to capture the severity of the disease from onset. A 24-hour period <u>may be</u> defined by the mother (e.g., sunrise of one day to sunrise the next day, midnight of one

day to midnight the next, etc.) for the purpose of recalling maximum severity; however, calendar days should be counted for all "duration" fields of the table.

- **Number of looser-than-normal stools:** Enter the maximum number of diarrheal episodes that occurred on the most severe day since the onset of the illness, excluding today.

  Duration: Enter the number of calendar days, excluding today, since the onset of the illness, that the child has had ≥1 looser-than-normal stool(s). Days do not have to be consecutive, but only count the days that the participant experienced ≥1 looser-than-normal stool(s). For example, if a participant has 3 looser-than-normal stools on day 1, no looser-than-normal stools on day 2, and 3 looser-than-normal stools on day 3, this participant would have "2" days entered as the duration.

- **Number of Vomiting Episodes:** Enter the maximum number of vomiting episodes that occurred on the most severe day since the onset of the illness, excluding today.

  Duration: Enter the number of calendar days, excluding today, since the onset of the illness that the child has had ≥1 vomiting episodes. Days do not have to be consecutive, but only count the days that the participant experienced ≥1 vomiting episode. For example, if a participant has 1 vomiting episode on day 1, no episodes on day 2, and 3 episodes on day 3, this participant would have "2" days entered as the duration. If the participant has 1 vomiting episode on day 1, 1 episode on day 2, and 2 episodes on day 3, this participant would have "3" days entered as the duration.

- **Temperature:**
  - Record the highest temperature noted on the Diary Card here.
  - Indicate if the parent took the temperature using axillary, otic, oral or rectal site.
  - Check the box "Not Taken" if the parent did not take a temperature using a thermometer or did not record the temperature on the Diary Card or the box "Not Taken" is checked on the diary card.

- **Home ORS Use:** After reviewing the Diary Card and talking with the parent, determine whether ORS was given to the participant 24 hours prior to presentation to a health facility and record the volume of ORS intake (in mL).

2. Symptoms at time of presentation to Health Facility

This section should be completed by trained study staff as soon as possible after presentation to the study health facility.

Section A: Dehydration Assessment

As dehydration quickly resolves following the initiation of rehydration therapies (i.e., ORT or IV fluids), **it is important to assess the following four signs of dehydration before administering rehydration.** If any of the four signs of dehydration are not assessed prior to administration of rehydration, the degree of dehydration will be underestimated and gastroenteritis severity underscored.

For each of the four dehydration assessment questions, use the IMCI WHO Dehydration criteria (World Health Organization, 2005). Check the box that best reflects the worst symptoms at the time of the

current assessment by a study clinician. Assessment of the degree of dehydration (no, moderate, severe) will occur in data analysis and is not included on the CRF.

- **General Condition:** The hierarchical values from most to least serious are as follows: a) lethargic/unconscious, b) restless/irritable, c) well/alert, d) unknown. Check only the value that best reflects the participant's current most serious condition. For example, if a child is both lethargic and irritable, the box "lethargic" should be checked because it is the most serious symptom identified at that point in time.

- **Eyes:** The hierarchical values from most to least serious are as follows: a) grossly sunken, b) sunken, c) normal, d) unknown. Check only the value that best reflects the current most serious eye condition of the participant at that point in time.

- **Thirst:** The hierarchical values from most to least serious are as follows: a) drinks poorly/not able to drink, b) thirty/drinks eagerly, c) drinks normally/not thirsty, d) unknown. Check only the value that best reflects the current most serious thirst condition of the participant at that point in time.

- **Skin Pinch:** The hierarchical values from most to least serious are as follows: a) goes back very slowly (>2 seconds), b) goes back slowly (1-2 seconds), c) goes back quickly (instantly), d) unknown. Check only the value that best reflects the current most serious skin pinch condition of the participant at that point in time.

Section B: Assess Other Symptoms and Stool Collection

- **Stool Collection:** Stool collection should occur as soon as possible following presentation to the health facility AND within 7 days following the onset of gastroenteritis symptoms. Although stool may not be collected immediately upon admission to a study health facility, the date (dd-mm-yy) and time (24 hour clock) of stool collection should be entered here when the stool is collected. Only one stool should be collected. The date of initial presentation should be entered on the stool collection label so that the stool results can easily be linked with each participant episode.

- **Assess Other Symptoms:** The first row of Section 3 (Symptoms present during Calendar Days Subject is at health facility), should be completed during the initial assessment by a study clinician. For participants who do not require admission to a health facility, this may be the only row of Section 3 that is completed. For participants who are admitted to a health facility, the remainder of Section 3 will be completed according to the below instructions.

Section C: Referral Information
Participants seen at primary care study clinics may require referral to the study hospital for additional care and follow-up. The checkboxes indicating whether the participant is referred should be completed accordingly and the referral facility noted. Participants who are referred should have the Gastroenteritis Symptom CRF transferred with them so that symptoms are not missed or double counted.

3. Symptoms Present during the Calendar Days Participant is at Health Facility

Overview:

Regardless of whether a participant is referred or admitted, assessments by study clinicians should occur approximately every 4 hours (excluding the night hours) from the day that the participant first comes to the clinic until the participant is discharged from the study health facility. The table in this section should be completed:

1. For the day of presentation to the medical facility, recording symptoms that occurred for that entire calendar day (i.e., midnight of one day to midnight of the next). Here, symptom data noted by the parent to have occurred at any time on this calendar day should be included in the summary on the first line of the table.

2. For each subsequent calendar day that a child remains in the medical facility.

3. By study clinicians, but recorded information may include both parent-reported and clinician-observed/assessed symptoms.

4. At discharge, to capture symptoms that occurred for the entire calendar day on which the subject was last at the medical facility.

For symptoms collected during (i.e., from the time of the clinic visit forward) a clinic or hospital visit, study staff clinician should collect symptoms on a routine basis (i.e., every 4 hours) throughout the day. Ideally, this would occur based on direct study clinician observation. However, since it is not realistic to assume that a study clinician will be available to view all symptoms, this can be based on reports from other clinicians responsible for routine care OR based on parental observation and recall. At the end of each 24 hour period (i.e., the following morning), the total number of diarrheal episodes for that day should be totaled and the total for that day entered on the CRF.

Assessments Every 4-Hours

It is assumed that study staff will not be available 24 hours a day. The table includes rows to assess each participant up to 7 times in a single day (i.e., every 4 hours from 8:00 to 20:00 OR 6:00 to 18:00, etc.). There is space to record up to 8 days of symptoms. In the case that a participant is admitted for longer than 8 days, an additional CRF should be used to record these symptoms.

The following symptoms will be assessed during each 4 hour interval. It will be important that symptom collection is not duplicated during each 4-hour collection interval; symptoms from one 4-hour interval should not be captured in the subsequent 4 hour intervals recorded each day. The last row of each day should be completed by the study clinician the following morning based on review of overnight symptoms (i.e., symptoms occurring since the last study clinician assessment on the prior day (e.g., 16:00 or 18:00, depending on site practices, through 12 midnight). Symptoms occurring from midnight to the time of the morning assessment should be input on the first row of the next day. For example, symptoms occurring from midnight of day 1 to 8:00 of day 2 are placed on row 1 for day 2.

- **Date:** The "Date" field should be each consecutive calendar date on which symptoms occurred and not the date on which the symptoms may have been later recorded in the table. The date format should be reported as: Day: |_0_|_2_| Month: |_O_|_C_|_T_| Year: |_1_|_0_|.

- **Number of looser-than-normal Stools:** Enter the number of diarrheal episodes that occurred in each calendar day that the participant has been present at the study facility.

- **Number of Vomiting Episodes:** Enter the number of vomiting episodes that occurred in each calendar day that the participant has been present at the study facility.

- **Temperature:** Enter the highest measured temperature that occurred in each calendar day that the participant has been present at the medical facility. Indicate if the site used axillary, otic, oral or rectal (rectal temperature is preferred, but axillary and oral are acceptable).

Daily Summary:

Immediately following the morning assessment, a summary of symptoms for each day is recorded in the rows titled "Day x Summary". It is these daily summary rows that will be entered into the study database for consideration in determining the highest score.

- **Date:** Enter the date (dd-mm-yy) that the symptoms occurred, not the date of the morning that the summary is completed.

- **Number of Looser-Than-Normal Stools:** Sum the total number of stools that occurred on a single day and enter the total here.

- **Number of Vomiting Emesis:** Sum the total number of vomiting emesis that occurred on a single day and enter the total here.

- **Volume of ORS Rehydration:** Sum the total number of mL of ORS taken by the participant and enter the total here.

- **Volume of IV Rehydration:** Sum the total number of mL of IV fluids put in the participant's body and enters the total here.

- **Temperature:** Determine the highest temperature that occurred over the course of a day and enter the highest value her.

4. Discharge Summary and Continuing Symptoms

On the last day of admission at a health facility, the date (dd-mmm-yy) and time (24 hour clock) of discharge should be recorded. The final outcome of the participant; fully recovered, not recovered, or death; should also be checked.

Participants discharged with continuing symptoms should be provided with an adequate supply of blank diary cards and instructed to continue completing the Diary Card until the symptoms resolve completely.

FWs should be notified to check on these participants every 2 days following discharge and should refer participants back to a study health facility if their symptoms become worse at any time OR do not resolve within 7 days following discharge. After symptoms have fully resolved, FWs should collect the Diary Card and bring them to the study health facility so that daily symptoms can be captured by transferring them onto subsequent days in Section 3 of the same CRF used for the initial assessment/inpatient admission.

5. Examples

Example for a typical hospital visit with overnight stays:

A participant is assessed at a medical facility on Monday. Symptoms occurring anytime on Monday through when the subject is discharged from the facility should be collected in Section 3 of the CRF. Symptom data that occurred during the initial study clinician assessment on Monday should be entered on row 1 of the table immediately following the initial assessment. The participant should then be assessed every 4 hours until the end of the day (i.e., 18:00) and symptoms recorded at the time of each assessment. Symptoms noted by parents or other health facility staff from 18:00 to 24:00 should then be collected at the time of the initial study clinician assessment the following morning (i.e., 6:00 or 8:00, etc.) and entered on the last line of the Monday symptom assessment section. Symptom data then collected from 00:01 Tuesday until 24:00 Tuesday should be entered following every 4 hour assessment period on separate rows in the "day 2" section of the table and the process repeated for subsequent nights spent in the study health facility. If the child is discharged at 13:00 Wednesday, then symptom data from 00:01 Wednesday until 13:00 Wednesday should still collected and entered at 4 hour intervals, with the final assessment occurring just prior to discharge.

Example for a typical visit with no overnight stay:

A subject is assessed at a facility on Wednesday. Symptoms occurring anytime on Wednesday through when the subject is discharged from the facility should be collected in the table and recorded in 4 hour intervals. For example if a subject presents to the health facility on Wednesday at 11 AM and is discharged at 16:00 all symptoms that occurred on Wednesday through 16:00 should be captured four lines of the table (i.e., 11 AM, 13:00, 15:00, 16:00 (discharge assessment).

Conclusion

This manual provides a standardized methodology for implementing the Vesikari Clinical Severity Scoring System across studies. The manual provides rationale for using the Vesikari Clinical Severity Scoring System, details scoring system parameters, identifies implementation challenges, and includes implementation instructions for collecting symptom information. To ensure that site-specific implementation challenges are discussed and methods tailored to each site and study prior to use of these methods, this manual is best implemented with site staff along with an accompanying in-person training.

Technical Assistance

If you have questions regarding the use and implementation of this manual, please contact Kristen Lewis at PATH (klewis@path.org).

Appendix 1: Definitions

Gastroenteritis (GE): Any looser-than-normal stools and/or forceful vomiting occurring over a 24 hour period.

Acute Rotavirus Gastroenteritis (AGE): Any episode with 3 or more looser- than- normal stools in a 24 hour period and/or at least one episode of forceful vomiting.

Rotavirus Gastroenteritis: Gastroenteritis episodes meeting the above definition for AGE and which meet the laboratory criterion for rotavirus by ELISA are considered rotavirus positive.

Severe Rotavirus Gastroenteritis: Rotavirus gastroenteritis meeting the above definition and having a score of ≥11 according to the Vesikari Clinical Severity Scoring System.

Gastroenteritis Episode: Gastroenteritis episodes begin on the first day that gastroenteritis symptoms are reported (day 1; vomiting and/or diarrhea with or without fever) and continue through the last day of symptoms (i.e., vomiting and/or diarrhea with or without fever) are reported.

Gastroenteritis Episode Resolution: An episode is considered resolved when a study participant is symptom-free for ≥4 days. Episodes which stop and have additional symptoms occur less than 4 days following the last symptom are considered to be a continuation of the original episode.

Diarrhea: Any watery or looser-than-normal stools.

Vomiting: One or more episodes of forceful emptying of partially digested stomach contents more than 1 hour after feeding (i.e., is not spit-up).

Dehydration: Dehydration is assessed for all episodes occurring throughout the study period according to the WHO dehydration criteria (World Health Organization, 2005). Some dehydration is defined as 1-5% dehydration and severe dehydration as ≥6% dehydration as measured by clinical symptoms, not weight loss.

Rehydration: An attempt to replace bodily fluids lost from expulsion during diarrhea and/or vomiting episodes using either (ORS/ORT) or intravenous therapy (IV).

Hospitalization: An overnight stay in any health facility or a patient who should have been admitted, but due to cultural factors or clinical practices, did not remain in a health facility overnight (i.e., inpatient or outpatient with IV therapy).

Temperature: Axillary, otic, oral, or rectal temperature obtained by a study clinician during a clinic or hospital visit using a thermometer.

Fever: The rectal equivalent of a higher than normal temperature (i.e., ≥37.1° C) as recorded upon assessment of temperature using a thermometer by a study clinician during a clinic or hospital visit or as recorded by a parent on the diary card when collecting the temperature at home. Fever during a gastroenteritis episode should only be captured if it occurs on the same day or after the onset of diarrhea and vomiting.

24-Hour Period: A calendar day is the 24-hour period from midnight of one day to midnight the next. A 24-hour period may be defined by the mother (e.g., sunrise of one day to sunrise the next day, midnight of one day to midnight the next, etc.) for the purpose of recalling maximum severity; however, calendar days should be counted for all "duration" fields.

Appendix 2: Example Field Worker Organogram

| Study Leadership | PI/CO-PI |

| Study Management | CLINICAL RESEARCH COORDINATOR (n=1) |

CLINICAL RESEARCH ASSISTANT (n=1)

| Field Research Staff | FIELD COORDINATORS (n=1) | Drivers (n=1 per 700 population) |

FIELD SUPERVISORS (1 per 10 to 15 Field Workers pending study area)

FIELD WORKERS (1 per 20 to 25 study participants)

30
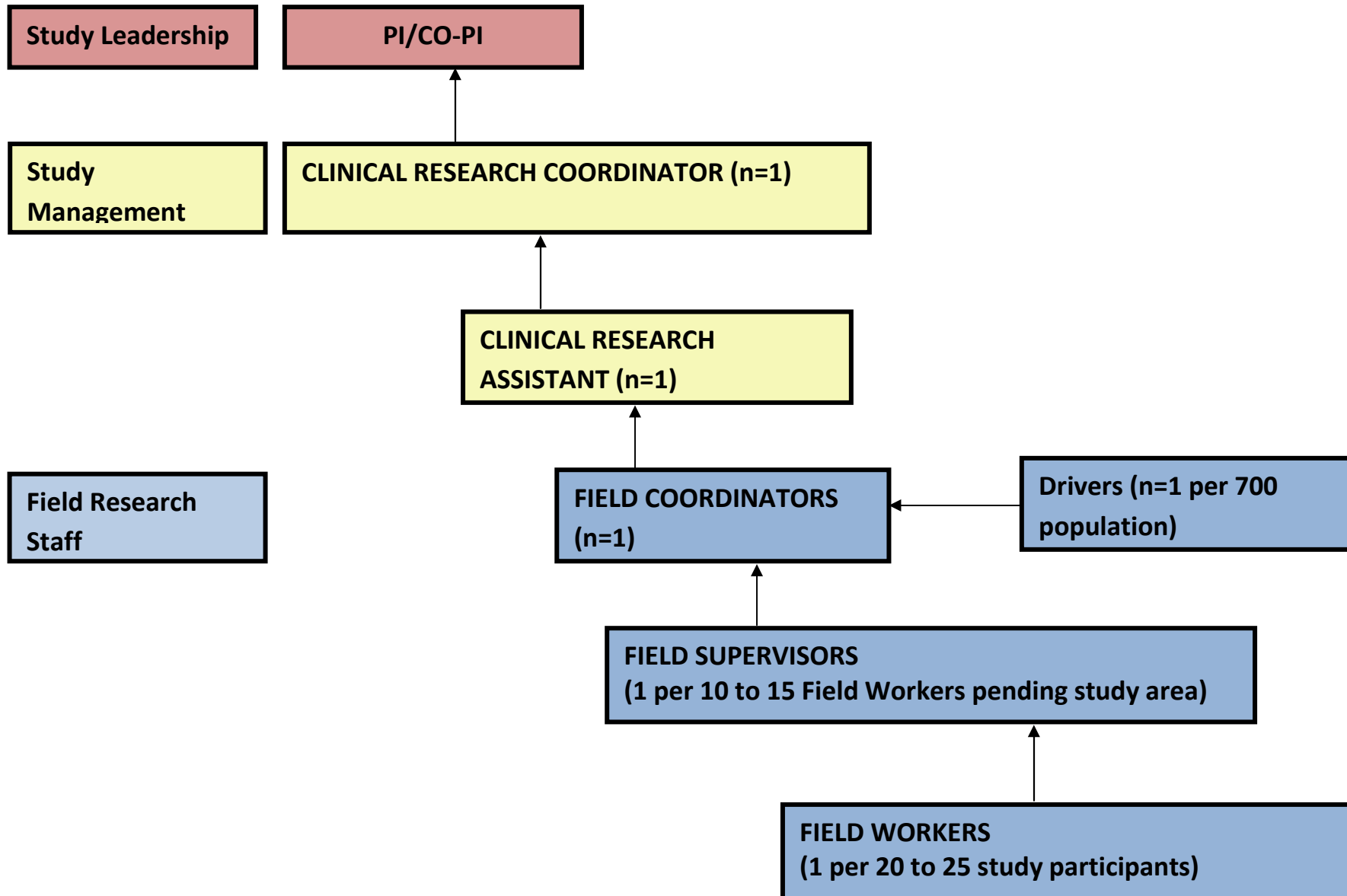
Appendix 3: Diary Card

Day 8 of Diarrhea and/or Vomiting

Date: |____|____| |____|____|____| |____|____|
            dd   mmm   yy

Highest Temperature Morning: |____|____|.|____|°C Not Taken: ☐
Highest Temperature Night: |____|____|.|____|°C   Not Taken: ☐

Vomiting: Circle the number of times your child vomited last night and today.

None   One   Two   Three   Four   Five

Six

0

More than 6? How many? |____|

Diarrhea: Circle the number of times your child had looser-than-normal or watery stools last night and today (if one or more occurred, take a stool sample).

None   One   Two   Three   Four   Five   Six

0

More than 6? How many? |____|

Medication (check one):
No Medication Given   ☐
Oral Rehydration (by mouth: home or sachet)   ☐
IV Rehydration   (by drip)   ☐
Oral & IV Rehydration (by mouth and drip)
Other, please specify: ☐

_____

Gastroenteritis Diary Card

<ENTER STUDY TITLE HERE>

Participant Identification Number: |__|__|__|__|

Participant Initials: |__|__|

If a stool is collected, please call or inform _____ within 24 hours of stool collection OR bring the stool with you to a study health facility.

If child is hospitalized or has a serious illness, please inform: _____

To the parent:

- Complete this card when your child has any looser-than-normal stools or forceful vomiting (see definitions below).
- This card should be completed every day until both the looser-than-normal stools and vomiting have both stopped.
- Bring this diary card with you to the study health facility or give it to the field worker at each weekly visit.
- Use the below definitions and guidelines to complete the card.

Day 7 of Diarrhea and/or Vomiting

Date: |____|____| |____|____|____| |____|____|
                dd   mmm   yy

Highest Temperature Morning: |____|____|.|____|°C   Not Taken: ☐
Highest Temperature Night: |____|____|.|____|°C   Not Taken: ☐

Day: A 24-hour period may be defined by the parent (e.g., sunrise of one day to sunrise the next day, midnight of one day to midnight the next, etc.) for the purpose of recalling symptoms. However, the parent should ensure that symptoms are not counted twice (i.e., counted in the symptom count on days 1 and 2) AND, in data analysis, calendar days should be counted for all "duration" fields.

- **Vomiting**: One or more episodes of forceful emptying of partially digested stomach contents more than 1 hour after feeding.

- **Diarrhea**: Looser-than-normal or watery stools.

- **Temperature**: Record the infant's temperature once every day that the child has either diarrhea or vomiting using the Temperature Measurement Guidelines.

- **Stool Sample**: A stool sample should always be collected as soon as possible and within 7 days following the onset of diarrhea.

- **Medication**: Report any medication that is given for diarrhea or vomiting.

- **Date Format:** The date format should be reported as
    Day: |_0_|_2_| Month: |_O_|_C_|_T_| Year: |_1_|_0_|

Vomiting: Circle the number of times your child vomited last night and today.

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐ ☐☐	☐☐☐ ☐☐	☐☐☐ ☐☐☐

More than 6? How many? |____|

Diarrhea: Circle the number of times your child had looser-than-normal or watery stools last night and today (if one or more occurred, take a stool sample).

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐ ☐☐	☐☐☐ ☐☐	☐☐☐ ☐☐☐

More than 6? How many? |____|

Medication (check one):
No Medication Given   ☐
Oral Rehydration (by mouth: home or sachet)   ☐
IV Rehydration   (by drip)   ☐
Oral & IV Rehydration (by mouth and drip)   ☐
Other, please specify: ☐

_____

Day 6 of Diarrhea and/or Vomiting

Date: |____|____| |____|____|____| |____|____|
             dd   mmm   yy

Highest Temperature Morning: |____|____|.|____|°C   Not Taken: ☐
Highest Temperature Night: |____|____|.|____|°C   Not Taken: ☐

Vomiting: Circle the number of times your child vomited last night and today.

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐☐

More than 6? How many? |____|

Diarrhea: Circle the number of times your child had looser-than-normal or watery stools last night and today (if one or more occurred, take a stool sample).

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐☐

More than 6? How many? |____|

Medication (check one):
No Medication Given   ☐
Oral Rehydration (by mouth: home or sachet)   ☐
IV Rehydration   (by drip)   ☐
Oral & IV Rehydration (by mouth and drip)   ☐
Other, please specify: ☐
_____

Temperature Measurement Guidelines

Temperature should be taken under the arm using the temperature guidelines on the next page. If the temperature is taken more than once each day, report the highest temperature on this card. Temperature should be taken using the thermometer given to you by the field worker.

1. Press the button to switch the thermometer "on" and wait until the display begins to flash.
   *When the display flashes, this shows that the thermometer is ready.
2. Raise your child's arm.
3. Place the thermometer directly on the skin with the metal point in the center of the child's armpit.
4. Fold the child's arm down and squeeze the arm gently against his/her body.
5. The thermometer should be held tightly. You will need to be careful to make sure it stays in place.
6. Hold the thermometer under the child's arm until it beeps or the display stops flashing.
7. Read and record temperature measurement on diary card.

Stool Collection Guidelines

One looser-than-normal stool specimen should be collected using the following procedures as soon as possible following the beginning of illness (i.e., on the day the illness begins or the following day).

1. Scoop the stool from the diaper or cloth in which the baby is wrapped with the scoop on the lid of the stool collection container or the wooden spatula.
2. If the stool is watery and you cannot scoop it, then transfer it from where it is into the stool container as best you can by sliding it in.
3. The amount to be collected is marked with a black marker on the stool container. Please collect the stool specimen till that mark.
4. Screw the lid tightly on the specimen container.
5. Place the specimen container in the plastic bag provided by the field worker and seal it.
6. Enter the time and date of collection on the label affixed on the plastic bag containing the specimen container.
7. Notify your field worker that you have collected a stool OR, if you visit a study health facility, take the stool sample with you.
   * The stool specimen must be given to a field worker or other study staff member within 1 day (24 hours) of collection.

Day 5 of Diarrhea and/or Vomiting

Date: |____|____| |____|____|____| |____|____|
        dd   mmm   yy

Highest Temperature Morning: |____|____|.|____|°C Not Taken: ☐
Highest Temperature Night: |____|____|.|____|°C Not Taken: ☐

 Vomiting: Circle the number of times your child vomited last night and today.

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐	☐☐☐	☐☐☐

More than 6? How many? |____|

 Diarrhea: Circle the number of times your child had looser-than-normal or watery stools last night and today (if one or more occurred, take a stool sample).

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐	☐☐☐	☐☐☐

More than 6? How many? |____|

Medication (check one):
No Medication Given   ☐
Oral Rehydration (by mouth: home or sachet)   ☐
IV Rehydration   (by drip)   ☐
Oral & IV Rehydration (by mouth and drip)   ☐
Other, please specify: ☐
_____

Day 4 of Diarrhea and/or Vomiting

Date: |____|____| |____|____|____| |____|____|
                dd   mmm   yy

Highest Temperature Morning: |____|____|.|____|°C   Not Taken: ☐
Highest Temperature Night: |____|____|.|____|°C   Not Taken: ☐

Vomiting: Circle the number of times your child vomited last night and today.

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐☐

More than 6? How many? |____|

Diarrhea: Circle the number of times your child had looser-than-normal or watery stools last night and today (if one or more occurred, take a stool sample).

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐☐

More than 6? How many? |____|

Medication (check one):
No Medication Given   ☐
Oral Rehydration (by mouth: home or sachet)   ☐
IV Rehydration   (by drip)   ☐
Oral & IV Rehydration (by mouth and drip)   ☐
Other, please specify: ☐
_____

Day 1 of Diarrhea and/or Vomiting

Date: |____|____| |____|____|____| |____|____|
                dd   mmm   yy

Highest Temperature Morning: |____|____|.|____|°C   Not Taken: ☐
Highest Temperature Night: |____|____|.|____|°C   Not Taken: ☐

Vomiting: Circle the number of times your child vomited last night and today.

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐☐

More than 6? How many? |____|

Diarrhea: Circle the number of times your child had looser-than-normal or watery stools last night and today (if one or more occurred, take a stool sample).

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐☐

More than 6? How many? |____|

Medication (check one):
No Medication Given   ☐
Oral Rehydration (by mouth: home or sachet)   ☐
IV Rehydration   (by drip)   ☐
Oral & IV Rehydration (by mouth and drip)   ☐
Other, please specify: ☐
_____

Day 2 of Diarrhea and/or Vomiting

Date: |____|____| |____|____|____| |____|____|
　　　　　　dd　　　　　　mmm　　　　　　yy

Highest Temperature Morning: |____|____|.|____|°C   Not Taken: ☐
Highest Temperature Night: |____|____|.|____|°C   Not Taken: ☐

Vomiting: Circle the number of times your child vomited last night and today.

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐☐

More than 6? How many? |____|

Diarrhea: Circle the number of times your child had looser-than-normal or watery stools last night and today (if one or more occurred, take a stool sample).

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐☐

More than 6? How many? |____|

Medication (check one):
No Medication Given   ☐
Oral Rehydration (by mouth: home or sachet)   ☐
IV Rehydration   (by drip)   ☐
Oral & IV Rehydration (by mouth and drip)   ☐
Other, please specify: ☐
_____

Day 3 of Diarrhea and/or Vomiting

Date: |____|____| |____|____|____| |____|____|
　　　　　　dd　　　　　　mmm　　　　　　yy

Highest Temperature Morning: |____|____|.|____|°C   Not Taken: ☐
Highest Temperature Night: |____|____|.|____|°C   Not Taken: ☐

Vomiting: Circle the number of times your child vomited last night and today.

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐☐

More than 6? How many? |____|

Diarrhea: Circle the number of times your child had looser-than-normal or watery stools last night and today (if one or more occurred, take a stool sample).

None	One	Two	Three	Four	Five	Six
0	☐	☐☐	☐☐☐	☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐☐

More than 6? How many? |____|

Medication (check one):
No Medication Given   ☐
Oral Rehydration (by mouth: home or sachet)   ☐
IV Rehydration   (by drip)   ☐
Oral & IV Rehydration (by mouth and drip)   ☐
Other, please specify: ☐
_____

Appendix 4: Gastroenteritis Symptom Case Report Form

<ADD STUDY TITLE HERE>

Participant Identification Number: |__|__|__|__|

Health Facility: |__|__|__|__|

Date of Initial Presentation to Health Facility: |__|__| |__|__|__| |__|__|

                                                                              dd   mmm   yy

<ADD SITE SPECIFIC STUDY BACKGROUND DATA HERE>

1.   **Symptoms Occurring Prior to Presentation at Study Health Facility***

Record symptoms that occurred prior to presentation at a study health facility based on Diary Card review and parent interview.

Date and time of onset of <u>diarrhoea</u>: |__|__| |__|__|__| |__|__| |__|__|:|__|__| hrs (24 hour clock)
                                                    dd   mmm   yy

Date and time of onset of <u>vomiting</u>: |__|__| |__|__|__| |__|__| |__|__|:|__|__| hrs (24 hour clock)
                                                    dd   mmm   yy

Record maximum symptoms present in <u>any</u> 24 hour period on the days prior to the calendar day of presentation to study health facility:

	Looser-than-normal stools	**Vomiting**	**Temperature (°C)**
Maximum Number	|__|__|	|__|__|	|__|__| . |__| ☐ **Axillary** ☐ **Otic** ☐ **Oral** ☐ **Rectal** ☐ **Not Taken**
Duration*	_____ days	_____ days	

Only include days that each symptom occurred prior to presentation at a health facility. Do not include <u>today</u>.

Diary Card Available?   ☐ No ☐ Yes

Home ORS Use: Was ORS given within 24 hours prior to presentation? ☐ No   ☐ Yes

                          If yes, estimate total ORS intake prior to presentation: _____ ml

2. Symptoms at time of presentation to study health facility*

> *Assuming the child is stable and does not require immediate attention, complete this before administration of rehydration therapy (ORT or IV).*

A. Dehydration Assessment (Check one in each box-the worst symptom at time of presentation)

General Condition:	Eyes:
☐ Well/Alert ☐ Restless/Irritable ☐ Lethargic/Unconscious ☐ Unknown	☐ Normal ☐ Sunken (ensure child does not normally have sunken eyes) ☐ Grossly Sunken ☐ Unknown
Thirst:	**Skin Pinch**:
☐ Drinks normally/not thirsty ☐ Thirsty/Drinks Eagerly ☐ Drinks Poorly/Not Able to Drink ☐ Unknown	☐ Goes back quickly (immediately) ☐ Goes back slowly (fold visible for less than 2 seconds) ☐ Goes back very slowly (fold visible for more than 2 seconds) ☐ Unknown

B. Assess other symptoms and stool collection (complete first row of Section 3)

Stool collection date and time: |__|__| |__|__|__| |__|__| |__|__|:|__|__| hrs   dd   mmm   yy

C. Referral Information

Is the participant referred to another facility?   ☐ Yes   ☐ No

Referral Facility: |__|__|__|__|

3. Symptoms Present during Calendar Days Participant is at Health Facility:

Day	Date month year	Time (24 hour clock)	Number of looser-than-normal stools	Number of vomiting emesis	Vol. ORS Rehyd (mL)	Vol. IV Rehyd (mL)	Temperature °C ☐ Axillary ☐ Rectal ☐ Otic ☐ Oral
Day 1							
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 1 Summary							
|__|__| |__|__|__| |__|__|		|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 2							
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 2 Summary							
|__|__| |__|__|__| |__|__|		|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 3							
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 3 Summary							
|__|__| |__|__|__| |__|__|		|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 4							
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 4 Summary							
|__|__| |__|__|__| |__|__|		|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|

Date Day month year	Time (24 hour clock)	Number of looser-than-normal stools	Number of vomiting emesis	Vol. ORS Rehyd (mL)	Vol. IV Rehyd (mL)	Temperature °C ☐ Axillary ☐ Rectal ☐ Otic ☐ Oral
Day 5						
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 5 Summary						
		|__|__|	|__|__|	|__|__||__|__|	|__|__|__|__|	|__|__| . |__|
Day 6						
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 6 Summary						
		|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 7						
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 7 Summary						
|__|__| |__|__|__| |__|__|		|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 8						
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
|__|__| |__|__|__| |__|__|	|__|__|:|__|__|	|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|
Day 8 Summary						
|__|__| |__|__|__| |__|__|		|__|__|	|__|__|	|__|__|__|__|	|__|__|__|__|	|__|__| . |__|

4. Discharge Summary:

Date of discharge: |__|__| |__|__|__| |__|__| **Time of discharge:** |__|__|:|__|__| (24 hour clock)
                 dd   mmm   yy

Outcome at discharge (check one):   ☐ Fully Recovered   ☐ Not recovered   ☐ Death

Appendix 5: Reference List

Adegboyega, A. A., Onayade, A. A., & Salawu, O. (2005). Care-seeking behaviour of caregivers for

common childhood illnesses in Lagos Island Local Government Area, Nigeria. *Niger.J Med., 14*(1),

65-71.

Aloun, D. S., Nyambat, B., Phetsouvanh, R., Douangboupha, V., Keonakhone, P., Xoumphonhphakdy,

B.,....,Kilgore, P.E. (2009). Rotavirus diarrhoea among children aged less than 5 years at Mahosot

Hospital, Vientiane, Lao PDR. *Vaccine, 27 Suppl 5*, F85-F88. doi:S0264-410X(09)01307-3

[pii];10.1016/j.vaccine.2009.08.100 [doi]

Armah, G. E., Sow, S. O., Breiman, R. F., Dallas, M. J., Tapia, M. D., Feikin, D. R.,....,Neuzil, K.M. (2010).

Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in

developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled

trial. *Lancet*. doi:S0140-6736(10)60889-6 [pii];10.1016/S0140-6736(10)60889-6 [doi]

Atherly, D., Dreibelbis, R., Parashar, U. D., Levin, C., Wecker, J., & Rheingans, R. D. (2009). Rotavirus

vaccination: Cost-effectiveness and impact on child mortality in developing countries.

J.Infect.Dis., 200 Suppl 1, S28-S38. doi:10.1086/605033 [doi]

Binka, F. N., Anto, F. K., Oduro, A. R., Awini, E. A., Nazzar, A. K., Armah, G. E.,....,Iturriza-Gomara, M.

(2003). Incidence and risk factors of paediatric rotavirus diarrhoea in northern Ghana.

Trop.Med.Int.Health, 8(9), 840-846. doi:1097 [pii]

Black, R. E., & Lanata, C. F. (2007). Diarrheal Diseases. In K.E. Nelson & C. F. M. Williams (Eds.), *Infectious

disease epidemiology: Theory and practice* (pp. 759-786). Sudbury, MA: Jones and Bartlett

Publishers.

Black, R. E., Merson, M. H., Huq, I., Alim, A. R., & Yunus, M. (1981). Incidence and severity of rotavirus

and Escherichia coli diarrhoea in rural Bangladesh. Implications for vaccine development.

Lancet, 1(8212), 141-143.

Bresee, J., Fang, Z. Y., Wang, B., Nelson, E. A., Tam, J., Soenarto, Y.,....,Glass, R. (2004). First report from

the Asian Rotavirus Surveillance Network. *Emerg.Infect.Dis., 10*(6), 988-995.

Bryce, J., Boschi-Pinto, C., Shibuya, K., & Black, R. E. (2005). WHO estimates of the causes of death in

children. *Lancet, 365*(9465), 1147-1152. doi:S0140-6736(05)71877-8 [pii];10.1016/S0140-

6736(05)71877-8 [doi]

Centers for Disease Control and Prevention. (2007). Postmarketing monitoring of intussusception after

RotaTeq™ vaccination --- United States, February 1, 2006--February 15, 2007. *Morbidity and

Mortality Weekly, 56*(10), 218-222.

Clark, H. F., Bernstein, D. I., Dennehy, P. H., Offit, P., Pichichero, M., Treanor, J.,....,Heaton, P. (2004).

Safety, efficacy, and immunogenicity of a live, quadrivalent human-bovine reassortant rotavirus

vaccine in healthy infants. *J.Pediatr., 144*(2), 184-190. doi:10.1016/j.jpeds.2003.10.054

[doi];S0022347603007741 [pii]

Clark, H. F., Borian, F. E., Bell, L. M., Modesto, K., Gouvea, V., & Plotkin, S. A. (1988). Protective effect of

WC3 vaccine against rotavirus diarrhea in infants during a predominantly serotype 1 rotavirus

season. *J.Infect.Dis., 158*(3), 570-587.

Coffin, S. E., Elser, J., Marchant, C., Sawyer, M., Pollara, B., Fayorsey, R.,....,DiNubile, M.J. (2006). Impact

of acute rotavirus gastroenteritis on pediatric outpatient practices in the United States.

Pediatr.Infect.Dis.J, 25(7), 584-589. doi:10.1097/01.inf.0000220251.27595.74 [doi];00006454-

200607000-00004 [pii]

Cunliffe, N., & Nakagomi, O. (2007). Introduction of rotavirus vaccines in developing countries:

Remaining challenges. *Ann.Trop.Paediatr., 27*(3), 157-167. doi:10.1179/146532807X220262

[doi]

Cunliffe, N. A., Kilgore, P. E., Bresee, J. S., Steele, A. D., Luo, N., Hart, C. A., & Glass, R. I. (1998).

Epidemiology of rotavirus diarrhoea in Africa: a review to assess the need for rotavirus

immunization. *Bull.World Health Organ, 76*(5), 525-537.

de Palma, O., Cruz, L., Ramos, H., de Baires, A., Villatoro, N., Pastor, D.,....,Patel, M. (2010). Effectiveness

of rotavirus vaccination against childhood diarrhoea in El Salvador: case-control study. *BMJ, 340*,

c2825.

de Villiers, F. P., Sawyerr, T. N., & de Villiers, G. K. (2009). The incidence and clinical presentation of

infantile rotavirus diarrhoea in Sierra Leone. *S.Afr.Med.J, 99*(4), 249-252.

Duffy, L. C., Byers, T. E., Riepenhoff-Talty, M., La Scolea, L. J., Zielezny, M., & Ogra, P. L. (1986). The

effects of infant feeding on rotavirus-induced gastroenteritis: a prospective study. *Am.J.Public

Health, 76*(3), 259-263.

Feikin, D. R., Audi, A., Olack, B., Bigogo, G. M., Polyak, C., Burke, H.,...., Breiman, R.F. (2010). Evaluation

of the optimal recall period for disease symptoms in home-based morbidity surveillance in rural

and urban Kenya. *Int.J.Epidemiol., 39*(2), 450-458. doi:dyp374 [pii];10.1093/ije/dyp374 [doi]

Flores, J., Perez-Schael, I., Gonzalez, M., Garcia, D., Perez, M., Daoud, N.,....,Kapikian, A.Z. (1987).

Protection against severe rotavirus diarrhoea by rhesus rotavirus vaccine in Venezuelan infants.

Lancet, 1(8538), 882-884.

Fontaine, O. (2004). Gastroenteritis, acute viral. In D.L. Heymann (Ed.), *Control of communicable disease

manual* (18th ed., pp. 224-227). Washington, D.C.: American Public Health Association.

Georges, M. C., Wachsmuth, I. K., Meunier, D. M., Nebout, N., Didier, F., Siopathis, M. R., & Georges, A.

J. (1984). Parasitic, bacterial, and viral enteric pathogens associated with diarrhea in the Central

African Republic. *J Clin.Microbiol., 19*(5), 571-575.

Givon-Lavi, N., Greenberg, D., & Dagan, R. (2008). Comparison between two severity scoring scales

commonly used in the evaluation of rotavirus gastroenteritis in children. *Vaccine, 26*(46), 5798-

5801. doi:S0264-410X(08)01139-0 [pii];10.1016/j.vaccine.2008.08.030 [doi]

Glass, R. I., Parashar, U. D., Bresee, J. S., Turcios, R., Fischer, T. K., Widdowson, M. A.,....,Gentsch, J.R.

(2006). Rotavirus vaccines: current prospects and future challenges. *Lancet, 368*(9532), 323-332.

doi:S0140-6736(06)68815-6 [pii];10.1016/S0140-6736(06)68815-6 [doi]

Gothefors, L., Wadell, G., Juto, P., Taniguchi, K., Kapikian, A. Z., & Glass, R. I. (1989). Prolonged efficacy

of rhesus rotavirus vaccine in Swedish children. *J Infect.Dis., 159*(4), 753-757.

Grimwood, K., & Buttery, J. P. (2007). Clinical update: rotavirus gastroenteritis and its prevention.

Lancet, 370(9584), 302-304. doi:S0140-6736(07)61142-8 [pii];10.1016/S0140-6736(07)61142-8

[doi]

Hjelt, K., Grauballe, P. C., Andersen, L., Schiotz, P. O., Howitz, P., & Krasilnikoff, P. A. (1986). Antibody

response in serum and intestine in children up to six months after a naturally acquired rotavirus

gastroenteritis. *J Pediatr.Gastroenterol.Nutr, 5*(1), 74-80.

Huilan, S., Zhen, L. G., Mathan, M. M., Mathew, M. M., Olarte, J., Espejo, R.,....,Sami, Z. (1991). Etiology

of acute diarrhoea among children in developing countries: a multicentre study in five countries.

Bull.World Health Organ, 69(5), 549-555.

Iturriza, G. M., Simpson, R., Perault, A. M., Redpath, C., Lorgelly, P., Joshi, D.,....,Gray, J. (2008).

Structured surveillance of infantile gastroenteritis in East Anglia, UK: incidence of infection with

common viral gastroenteric pathogens. *Epidemiol.Infect., 136*(1), 23-33.

doi:S0950268807008059 [pii];10.1017/S0950268807008059 [doi]

Jenney, A., Tikoduadua, L., Buadromo, E., Barnes, G., Kirkwood, C. D., Boniface, K.,....,Russell, F. (2009).

The burden of hospitalised rotavirus infections in Fiji. *Vaccine, 27 Suppl 5*, F108-F111. doi:S0264-410X(09)01260-2 [pii];10.1016/j.vaccine.2009.08.071 [doi]

Kim, J. S., Kang, J. O., Cho, S. C., Jang, Y. T., Min, S. A., Park, T. H.,....,Kilgore, P.E. (2005). Epidemiological

profile of rotavirus infection in the Republic of Korea: results from prospective surveillance in

the Jeongeub District, 1 July 2002 through 30 June 2004. *J Infect.Dis., 192 Suppl 1*, S49-S56.

doi:JID33257 [pii];10.1086/431506 [doi]

Kosek, M., Bern, C., & Guerrant, R. L. (2003). The global burden of diarrhoeal disease, as estimated from

studies published between 1992 and 2000. *Bull.World Health Organ, 81*(3), 197-204. doi:S0042-96862003000300010 [pii]

Lewis, K.D.C., Dallas, M.J., Victor, J.C., Ciarlet, M., Mast, T.C., Ji, M., …,Neuzil, K.M. (2012). Comparison of

two clinical severity scoring systems in two multi-center, developing country rotavirus vaccine

trials in Africa and Asia. *Vaccine*, *30S*, A159-A166.

Madhi, S. A., Cunliffe, N. A., Steele, D., Witte, D., Kirsten, M., Louw, C.,....,Neuzil, K.M. (2010). Effect of

human rotavirus vaccine on severe diarrhea in African infants. *N.Engl.J.Med., 362*(4), 289-298.

doi:362/4/289 [pii];10.1056/NEJMoa0904797 [doi]

Maldonado, Y. A., & Yolken, R. H. (1990). Rotavirus. *Baillieres Clin.Gastroenterol., 4*(3), 609-625.

Mast, T. C., DeMuro-Mercon, C., Kelly, C. M., Floyd, L. E., & Walter, E. B. (2009). The impact of rotavirus

gastroenteritis on the family. *BMC.Pediatr., 9*, 11. doi:1471-2431-9-11 [pii];10.1186/1471-2431-9-11 [doi]

Naficy, A. B., Abu-Elyazeed, R., Holmes, J. L., Rao, M. R., Savarino, S. J., Kim, Y.,....,Clemens, J.D.(1999).

Epidemiology of rotavirus diarrhea in Egyptian children and implications for disease control.

Am.J.Epidemiol., 150(7), 770-777.

Nguyen, T. V., Le, V. P., Le, H. C., & Weintraub, A. (2004). Diarrhea caused by rotavirus in children less

than 5 years of age in Hanoi, Vietnam. *J Clin.Microbiol., 42*(12), 5745-5750. doi:42/12/5745

[pii];10.1128/JCM.42.12.5745-5750.2004 [doi]

Nkwi, P. N. (1994). Perceptions and treatment of diarrhoeal diseases in Cameroon. *J.Diarrhoeal Dis.Res.,*

12(1), 35-41.

Nokes, D. J., Abwao, J., Pamba, A., Peenze, I., Dewar, J., Maghenda, J. K.,....,Williams, T.N.(2008).

Incidence and clinical characteristics of group A rotavirus infections among children admitted to

hospital in Kilifi, Kenya. *PLoS.Med., 5*(7), e153. doi:07-PLME-RA-0331

[pii];10.1371/journal.pmed.0050153 [doi]

Nyambat, B., Meng, C. Y., Vansith, K., Vuthy, U., Rin, E., Kirkwood, C.,....,Kilgore, P.E. (2009). Hospital-

based surveillance for rotavirus diarrhoea in Phnom Penh, Cambodia, March 2005 through

February 2007. *Vaccine, 27 Suppl 5*, F81-F84. doi:S0264-410X(09)01296-1

[pii];10.1016/j.vaccine.2009.08.085 [doi]

Parashar, U. D., Alexander, J. P., & Glass, R. I. (2006). Prevention of rotavirus gastroenteritis among

infants and children. Recommendations of the Advisory Committee on Immunization Practices

(ACIP). *MMWR Recomm.Rep., 55*(RR-12), 1-13. doi:rr5512a1 [pii]

Parashar, U. D., Burton, A., Lanata, C., Boschi-Pinto, C., Shibuya, K., Steele, D.,....,Glass, R.I. (2009). Global

mortality associated with rotavirus disease among children in 2004. *J.Infect.Dis., 200 Suppl 1*, S9-

S15. doi:10.1086/605025 [doi]

Parashar, U. D., & Glass, R. I. (2009). Rotavirus vaccines--early success, remaining questions.

N.Engl.J.Med., 360(11), 1063-1065. doi:360/11/1063 [pii];10.1056/NEJMp0810154 [doi]

Parashar, U. D., Holman, R. C., Clarke, M. J., Bresee, J. S., & Glass, R. I. (1998). Hospitalizations associated

with rotavirus diarrhea in the United States, 1993 through 1995: surveillance based on the new

ICD-9-CM rotavirus-specific diagnostic code. *J Infect.Dis., 177*(1), 13-17.

Parashar, U. D., Hummelman, E. G., Bresee, J. S., Miller, M. A., & Glass, R. I. (2003). Global illness and

    deaths caused by rotavirus disease in children. *Emerg.Infect.Dis., 9*(5), 565-572.

Patel, M., Pedreira, C., De Oliveira, L. H., Tate, J., Orozco, M., Mercado, J.,....,Parashar, U. (2009).

    Association between pentavalent rotavirus vaccine and severe rotavirus diarrhea among

    children in Nicaragua. *JAMA, 301*(21), 2243-2251. doi:301/21/2243 [pii];10.1001/jama.2009.756

    [doi]

Qazi, R., Sultana, S., Sundar, S., Warraich, H., un-Nisa, T., Rais, A., & Zaidi, A. K. (2009). Population-based

    surveillance for severe rotavirus gastroenteritis in children in Karachi, Pakistan. *Vaccine, 27*

    Suppl 5, F25-F30. doi:S0264-410X(09)01267-5 [pii];10.1016/j.vaccine.2009.08.064 [doi]

Reither, K., Ignatius, R., Weitzel, T., Seidu-Korkor, A., Anyidoho, L., Saad, E.,....,Mockenhaupt, F.P. (2007).

    Acute childhood diarrhoea in northern Ghana: epidemiological, clinical and microbiological

    characteristics. *BMC.Infect.Dis., 7*, 104. doi:1471-2334-7-104 [pii];10.1186/1471-2334-7-104

    [doi]

Richardson, V., Hernandez-Pichardo, J., Quintanar-Solares, M., Esparza-Aguilar, M., Johnson, B., Gomez-

    Altamirano, C. M.,....,Patel, M. (2010). Effect of rotavirus vaccination on death from childhood

    diarrhea in Mexico. *N.Engl.J.Med., 362*(4), 299-305. doi:362/4/299

    [pii];10.1056/NEJMoa0905211 [doi]

Riepenhoff-Talty, M., Bogger-Goren, S., Li, P., Carmody, P. J., Barrett, H. J., & Ogra, P. L. (1981).

    Development of serum and intestinal antibody response to rotavirus after naturally acquired

    rotavirus infection in man. *J.Med.Virol., 8*(3), 215-222.

Rivest, P., Proulx, M., Lonergan, G., Lebel, M. H., & Bedard, L. (2004). Hospitalisations for gastroenteritis:

    the role of rotavirus. *Vaccine, 22*(15-16), 2013-2017. doi:10.1016/j.vaccine.2003.10.029

    [doi];S0264410X03007837 [pii]

Rodrigues, A., de Carvalho M., Monteiro, S., Mikkelsen, C. S., Aaby, P., Molbak, K., & Fischer, T. K. (2007).

Hospital surveillance of rotavirus infection and nosocomial transmission of rotavirus disease

among children in Guinea-Bissau. *Pediatr.Infect.Dis.J., 26*(3), 233-237.

Ruuska, T., & Vesikari, T. (1990). Rotavirus disease in Finnish children: use of numerical scores for clinical

severity of diarrhoeal episodes. *Scand.J.Infect.Dis., 22*(3), 259-267.

Senecal, M., Brisson, M., Lebel, M. H., Yaremko, J., Wong, R., Gallant, L. A.,....,Mansi, J.A. (2008).

Measuring the Impact of Rotavirus Acute Gastroenteritis Episodes (MIRAGE): A prospective

community-based study. *Can.J.Infect.Dis.Med.Microbiol., 19*(6), 397-404.

Staat, M. A., Azimi, P. H., Berke, T., Roberts, N., Bernstein, D. I., Ward, R. L.,....,Matson, D.O. (2002).

Clinical presentations of rotavirus infection among hospitalized children. *Pediatr.Infect.Dis.J,
21*(3), 221-227.

Suwatano, O. (1997). Acute diarrhea in under five-year-old children admitted to King Mongkut

Prachomklao Hospital, Phetchaburi province. *J Med.Assoc.Thai., 80*(1), 26-33.

Uhnoo, I., Olding-Stenkvist, E., & Kreuger, A. (1986). Clinical features of acute gastroenteritis associated

with rotavirus, enteric adenoviruses, and bacteria. *Arch.Dis.Child, 61*(8), 732-738.

UNICEF, & World Health Organization. (2009). *Diarrhoea: Why children are dying and what can be done*.

United Nations. (2005). *United Nations millennium development goals.* Retrieved from

http://www.un.org/millenniumgoals/#

Vaahtera, M., Kulmala, T., Maleta, K., Cullinan, T., Salin, M. L., & Ashorn, P. (2000). Epidemiology and

predictors of infant morbidity in rural Malawi. *Paediatr.Perinat.Epidemiol., 14*(4), 363-371.

Vesikari, T., Giaquinto, C., & Huppertz, H. I. (2006). Clinical trials of rotavirus vaccines in Europe.

Pediatr.Infect.Dis.J., 25(1 Suppl), S42-S47. doi:00006454-200601001-00006 [pii]

Vesikari, T., Isolauri, E., d'Hondt, E., Delem, A., Andre, F. E., & Zissis, G. (1984). Protection of infants

against rotavirus diarrhoea by RIT 4237 attenuated bovine rotavirus strain vaccine. *Lancet,*

1(8384), 977-981.

Vesikari, T., Isolauri, E., Delem, A., d'Hondt, E., Andre, F. E., Beards, G. M., & Flewett, T. H. (1985). Clinical

efficacy of the RIT 4237 live attenuated bovine rotavirus vaccine in infants vaccinated before a

rotavirus epidemic. *J Pediatr., 107*(2), 189-194.

Vesikari, T., Maki, M., Sarkkinen, H. K., Arstila, P. P., & Halonen, P. E. (1981). Rotavirus, adenovirus, and

non-viral enteropathogens in diarrhoea. *Arch.Dis.Child, 56*(4), 264-270.

Vesikari, T., Sarkkinen, H. K., & Maki, M. (1981). Quantitative aspects of rotavirus excretion in childhood

diarrhoea. *Acta Paediatr.Scand., 70*(5), 717-721.

Wildi-Runge, S., Allemann, S., Schaad, U. B., & Heininger, U. (2009). A 4-year study on clinical

characteristics of children hospitalized with rotavirus gastroenteritis. *Eur.J Pediatr., 168*(11),

1343-1348. doi:10.1007/s00431-009-0934-z [doi]

Wilopo, S. A., Soenarto, Y., Bresee, J. S., Tholib, A., Aminah, S., Cahyono, A.,....,Glass, R.I. (2009).

Rotavirus surveillance to determine disease burden and epidemiology in Java, Indonesia, August

2001 through April 2004. *Vaccine, 27 Suppl 5*, F61-F66. doi:S0264-410X(09)01328-0

[pii];10.1016/j.vaccine.2009.09.004 [doi]

World Health Organization. (2005). *Handbook : IMCI integrated management of childhood illness.*

Geneva, Switzerland: WHO. Retrieved from:

http://whqlibdoc.who.int/publiucations/2005/9241546441.pdf

World Health Organization. (2006). *Global deaths under age five attributable to rotavirus infection,*

2004. Retrieved from:

http://www.who.int/immunization_monitoring/burden/Global_national_estimates_2004_deat

hs_under_age_five_attributable_to_rotavirus_infection_2004.pdf

World Health Organization. (2007). Rotavirus vaccines WHO position paper. *Weekly Epidemiological Record, 82*(32), 285-296.

World Health Organization. (2008). *Generic protocol for monitoring impact of rotavirus vaccination on gastroenteritis disease burden and viral strains.* Geneva, Switzerland. Retrieved from: http://whqlibdoc.who.int/hq/2008/WHO_IVB_08.16_eng.pdf

World Health Organization, UNICEF, & World Bank. (2009). *State of the world's vaccine and immunization.* (3rd ed.). Geneva: World Health Organization.

Zaman, K., Anh, D. D., Victor, J. C., Shin, S., Yunus, M., Dallas, M. J.,...., Ciarlet, M. (2010). Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial. *Lancet*. doi:S0140-6736(10)60755-6 [pii];10.1016/S0140-6736(10)60755-6 [doi]

Zaman, K., Yunus, M., Faruque, A. S., El Arifeen, A. S., Hossain, I., Azim, T.,....,Sack, D.A.(2009). Surveillance of rotavirus in a rural diarrhoea treatment centre in Bangladesh, 2000-2006. *Vaccine, 27 Suppl 5*, F31-F34. doi:S0264-410X(09)01268-7 [pii];10.1016/j.vaccine.2009.08.063 [doi]