

Is Electrolyte Maintenance Solution Required in Low-Risk Children with Gastroenteritis?

RESEARCH PROPOSAL

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1.OBJECTIVES/SPECIFIC AIMS

Hypothesis

There is likely no benefit from the routine use of Electrolyte Maintenance Solution (EMS) in low-risk children. In this population, those who are advised to replace all losses with Fluids As Tolerated (FAT) will not have a greater treatment failure rate than those who are encouraged to replace all losses with EMS.

Research Questions

Primary Research Question: For low-risk children who present to an Emergency Department (ED) with < 96 hours of vomiting or diarrhea, is the proportion of children who fail treatment significantly greater in those encouraged to replace all losses with FAT than in those encouraged to use an EMS?

Secondary Research Questions: We will also compare groups to answer the following questions:

1. Is there a difference in the percent weight change at the 72-84 hour follow-up visit?
2. Is there a difference in the proportion of children who receive intravenous rehydration?
3. Is there a difference in the proportion requiring hospitalization?
4. Is there a difference in the frequency of diarrhea and vomiting per 24 hour period?

Relationship to the Health of Children in Canada: Gastroenteritis continues to result in significant morbidity to Canadian children. The majority of such children routinely receive Oral Rehydration Therapy (ORT) with EMS at a considerable financial cost. The objective of this study is to clarify the current standard of care by determining if EMS is truly the optimal fluid to be used in this low-risk population by evaluating clinically important outcomes related to caregivers, clinicians and children. We believe that our results will enhance the success of ORT and potentially reduce our reliance on intravenous rehydration.

2. BACKGROUND/RATIONALE/PRESENT STATE of KNOWLEDGE

1. Importance of the Study

Gastroenteritis remains a major cause of morbidity amongst Canadian children, accounting for approximately 150,000 outpatient visits, 20,000 hospitalizations, and 30 deaths annually amongst Canadian children <5 years of age.¹ The mean annual total direct medical costs for diarrhea among children aged <5 years is approximately \$75 million/year, with \$300 million/year in total costs to society.¹ The primary treatment focus revolves around the use of Oral Rehydration Therapy (ORT) to treat dehydration and replace intravascular volume. This represents a unique situation, with protocols designed for developing countries changing the standard of care in industrialized countries.² Since diarrheal disease in Canadian children usually results in mild dehydration and minimal sodium losses, the use of low sodium Electrolyte Maintenance Solutions (EMS; ie. Pediatric Electrolyte[®]) has become the standard of care. However, given that North American children infrequently develop severe dehydration, it is unclear if the routine use of EMS is justified. When pediatricians directly dispense EMS, 16 children need to be treated to prevent 1 unscheduled office visit, however the upper bound of the 95% confidence interval is an astounding 508 patients.³ In addition, EMS is considered by some to be prohibitively expensive⁴ with 15% of pediatricians believing it to be too expensive for their patients to purchase. An additional 40% report that taste is a major barrier to consumption.⁵ As a result, oral fluid replenishment is often under utilized and IV rehydration employed instead.⁵⁻⁸ Our goal is to provide evidence to guide the selection of the optimal ORT fluids in low-risk children, thus increasing its use, enhancing its success, and reducing the reliance on intravenous rehydration.⁹ We hypothesize that the

strict adherence to EMS use in low-risk children may actually be counterproductive by resulting in reduced fluid intake and potentially increasing the use of intravenous rehydration.

2. **Background**

Burden of the Problem: In Canada there are over 2.2 million cases of diarrheal illness, costing approximately \$1.3 billion annually.^{1,10} In a population based study conducted in Hamilton, the estimated cost per case was \$1,089 with medication costs such as EMS accounting for 13% of the total cost of illness¹¹ and as much as \$732,744 annually per 100,000 population.¹¹

Choice & History of Oral Rehydration Solution (ORS): The term ORS has evolved over the years but remains synonymous with high sodium content rehydration solutions used primarily in underdeveloped countries. In 1943, an ORS containing 62 mmol/L of sodium was successfully used in Baltimore to treat patients with diarrhea.¹² A commercial product (Lytren), which was extensively used during the 1950s and was dispensed in powder form, was produced based on this information and contained 50 mmol/L of sodium and 80 gm/L carbohydrates. Simultaneously, hypernatremia was increasingly being reported throughout the United States.¹³ One or more of the following factors are felt to have contributed to the development of hypernatremia¹⁴:

- 1-High ORS carbohydrate content aggravated the diarrhea due to the osmotic load
- 2-Poor training and instructions resulted in incorrect ORS preparation resulting in very high sodium concentration solutions
- 3-The administration of high solute containing fluids such as boiled skim milk resulted in increased diarrhea due to the osmotic load.

As a result many pediatricians became reluctant to use ORS. Subsequent studies demonstrated that the absorption of sodium and glucose in the intestines is coupled¹⁵ and that optimal absorption of sodium and water occurs when the ORS contains 20-25 gm/L of glucose. In 1985, a study evaluating the composition of ORS randomized 140 outpatients requiring rehydration to receive solutions containing sodium at 90, 50, and 30 mmol/L;¹⁶ glucose concentrations varied from 20-50 gm/L. All groups performed similarly with respect to electrolyte abnormalities, duration of diarrhea and weight gain. However, the volume of fluid intake was greatest amongst those in the low sodium group (30 mmol/L), and all 3 treatment failures occurred in the high sodium groups (90 and 50 mmol/L). These findings, which were interpreted as indicating that high sodium ORS does not cause hypernatremia, also indicate that low sodium solutions (similar to present day EMS) perform just as well in children with mild dehydration. Subsequent trials¹⁷⁻¹⁹ have found that low sodium ORS is associated with less vomiting, less stool output, and a reduced need for unscheduled intravenous infusions amongst children requiring rehydration. Due to the low sodium losses seen in gastroenteritis in developed nations (30-40 mEq/L) compared with that seen in cholera (≥ 90 -120 mEq/L),²⁰ North American guidelines⁶ support the use of even lower sodium content Electrolyte Maintenance Solutions (EMS) such as Pediatric Electrolyte[®] which has a sodium concentration of 45 mEq/L (Appendix I). However, patients, even under physician supervision, frequently attempt rehydration with solutions bearing no resemblance to ORS, such as water, soda pop, and fruit juices.²¹

We recently completed a survey of members of Pediatric Emergency Research Canada (PERC) and the Pediatric Emergency Medicine Collaborative Research Consortium (PEM CRC) in the United States (manuscript under review). Of 227 respondents, 45% indicated that they believe that ORS palatability results in fluid refusal in greater than 25% of patients. Consequently, 30% report administering liquids aside from ORS (e.g. sports drinks, fruit juices, water) for oral rehydration to greater than 25% of the children they are treating. An additional 22% report adding flavouring to improve the palatability of

ORS (ie. adding water, juice, sugar, jello). Thus, what needs to be determined is how important the concentrations of sodium and glucose are for children requiring maintenance fluids and not rehydration to enable clinicians to make an evidence based decision to a common scenario encountered when treating a common disease.

Acute Gastroenteritis Management-Current Guidelines-Minimal/Mild Dehydration

Canadian Pediatric Society(CPS)²²: This organization recommends the administration of an age-appropriate diet with ORS used to replace ongoing losses once dehydration is corrected. Fluids containing non-physiological concentrations of glucose and electrolytes (carbonated drinks, sweetened fruit juices) are discouraged due to their high carbohydrate and very low electrolyte content and high osmolarity. The guidelines also discourage the offering of plain water.

American Academy of Pediatrics(AAP)/Centers for Disease Control¹: Although in 1996 the AAP stated that children without dehydration do not require ORS,²³ their latest position paper states that all families should have a supply of ORS at home at all times and to start therapy with ORS as soon as diarrhea begins.¹ They stress the need to replace fluid losses and to maintain adequate nutrient intake via an age-appropriate diet.¹ Infants should be offered more frequent breast or bottle feedings, and older children should be given more fluids.¹ Since losses cannot be easily measured at home, 10 mL/kg of ORS is recommended for each watery stool and 2 mL/kg for each episode of emesis.¹

These guidelines however, are not consistently followed: In recent survey conducted by the principal investigator (PI; SF) of 13 Canadian tertiary care pediatric hospitals, 3 (23%) routinely use non-ORS alternatives (Powerade[®], Gatorade[®], water, milk). Although The Hospital for Sick Children initially provides an EMS, a large number of children end up consuming apple juice, popsicles and water. In a survey of 104 U.S. pediatricians, 17% indicated that they routinely recommend the use of a sports drink, while 14% recommend clear liquids/soda/juice/tea/water.⁵ A survey of 142 Chairmen of Department of Pediatrics revealed that 78% of their institutions administer clear liquids and 58% offer fruit juices. This reality is reflected in the United Kingdom's guidelines which state that children who are not dehydrated should be allowed unrestricted access to fluids such as milk or water.²⁴

Taste Challenges: Forty percent of pediatricians maintain that children with minimal/mild dehydration refuse EMS because they do not like the taste.^{5,25,26} This is in keeping with the AAP and the CPS statements which indicate that children who are not dehydrated may refuse EMS because of its salty taste.²³ It is widely believed that improving the taste of EMS might lead to greater patient acceptance.^{26,27} However, this alters the electrolyte content and osmolality, with sodium content falling to 30-53 mmol/L²⁸ in addition to resulting in a significant reduction in intestinal salt and water absorption.²³ We therefore hypothesize that in the ED, EMS refusal even amongst mildly dehydrated children sometimes results in the administration of intravenous rehydration, a situation which may be avoided by a more liberal choice of replacement fluids.

We recently completed a prospective, triple-blind, randomized, crossover trial comparing the taste of 3 different EMSs (manuscript under review – Pediatrics). The primary outcome was a Visual Analog Score (0-10). We found that mean scores (N=64/solution) varied by over 225% and ranged from 2.8 – 6.4 out of 10. Thus, it is clear that while children have taste preferences for the solutions, even the most palatable EMS only received a score of 6 out of 10.

3. **Potential Advantages & Disadvantages**

ORS-The ability of EMS to achieve rehydration is its prime advantage. Their sodium:glucose ratio is crucial to drive the absorption of water from the intestines, across the cell's basolateral membrane and into the circulation (intestinal facilitated co-transport). Hence, even low osmolar solutions that maintain the 1:1 glucose to sodium ratio perform optimally as ORSs.¹ What is unknown is how solutions that deviate from this ratio will perform in children not requiring rehydration, but simply maintenance of euhydration.

The clinical benefits of EMS use has been extensively documented when compared with intravenous therapy (shorter length of stay, less staff time, and higher parental satisfaction).²⁹ However, no trial has compared EMS to non-EMS regimens in low-risk children. This is particularly important because the routine use of EMS in such children has several *potential disadvantages*: (1) **cost**: there are economic barriers to the use of EMS³⁰ which costs approximately \$10/liter, (2) **palatability**: children will frequently refuse to drink EMS²³ (3) **delayed refeeding**: Early feeding decreases changes in intestinal permeability, reduces illness duration, and improves nutritional outcomes.³¹⁻³³ Clinical trials have demonstrated that continued feeding during diarrheal episodes is safe, and actually reduces stool output and diarrhea duration.^{34,35} However, in a survey of 104 general pediatricians, 50% failed to advise prompt feeding in patients with diarrhea;⁵ in a group of 69 outpatients, normal feeding was reduced by professional advice and was attempted in only 39% of patients receiving advice from nurses and 35% receiving advice from doctors.³⁶ This delay in refeeding can be detrimental since weight gain is optimal when refeeding is instituted immediately following rehydration.³⁷ In low-risk children without evidence of dehydration, rehydration is not required, hence refeeding should occur immediately. We hypothesize that the focus on EMS and the perception by caregivers of it as a “drug” that will make their child better, may play a role in delayed refeeding. This perception may result in its adoption to the exclusion of other treatment modalities such as early refeeding.

We have selected Pediatric Electrolyte as it is readily available in apple flavour throughout North America. However its ratio of glucose:sodium (45:138) deviates substantially from the 1:1 ratio that is recommended.¹ While it is possible that the failure rate of ORT as currently practiced might be reduced with the use of a more optimal ORS, we hypothesize that the failure of ORT is primarily due to palatability and not because of physiologic issues. In a survey that we have recently completed of North American pediatric emergency medicine physicians, EMSs were identified as the solutions provided by 77% of Canadian and 74% of American physicians (manuscript under review). We have recently evaluated its palatability and found that it was preferred over another EMS (Enfalyte) (manuscript under review). While formulating and flavouring an ESPGHN like solution, with a better glucose:sodium ratio may be an option such a solution would not likely ever be commercially available in North America. Thus, we feel that Pediatric Electrolyte is the optimal solution for use in this study. Adding a third arm to this study to allow an evaluation of both Pediatric Electrolyte and an ESPGHN like solution would not be feasible given sample size and budgetary constraints.

Fluids as Tolerated (FAT)-There exists no direct data on the use of regular fluids in low-risk children. However, indirect evidence does exist: in a study comparing the safety and effectiveness of directly providing an EMS versus providing cereal-based EMS that had to be mixed, despite finding that 43% of patients in the cereal-based EMS group did not take any of the recommended liquid, there were no differences in clinical outcomes.⁹ Unfortunately this study was neither designed nor powered to look at those who did/did not consume EMS, yet the authors directly questioned the need for ORS at the onset of illness in minimally dehydrated children: “There are no data to answer this question. It is our clinical impression that the majority of children with acute gastroenteritis will do well even *without* ORS.”⁹

Additionally, amongst 75 adults hospitalized with dehydration, there was no difference in stool frequency or consistency or change in body weight between those randomized to received EMS and those who received Gatorade.³⁸ However, Gatorade's taste was preferred (mean VAS 8.2 vs. 5.5). An additional potential advantage of encouraging the intake of regular liquids may be an earlier return to a full diet. While it is unknown if the use of EMS delays the resumption of a full diet, this outcome remains to be assessed and correct feeding advice is required regardless of the fluid recommendations provided. The *theoretical disadvantage* from the use of non-EMS solutions to replace losses relates to its potential of increased diarrhea due to the high carbohydrate load, dehydration, and hyponatremia.³⁹ While there are case reports of the latter, the affected children are usually very young (< 3 months of age)⁴⁰ and they chronically consume excessive amounts of water or dilute formula.³⁹

The fluid that will be provided to the FAT group in the ED will be ½ strength apple juice. We have opted to use ½ strength due to reports associating full-strength apple juice with the development of chronic diarrhea.^{41,42} Additionally, it is known that the high carbohydrate content of full-strength juice may exceed the intestine's absorptive capacity, resulting in malabsorption. Thus, to minimize the potential of osmotic diarrhea occurring we will use ½ strength apple juice. While the palatability of ½ strength apple juice is inferior to full-strength juice, based on a recent survey that we conducted of North American pediatric emergency medicine physicians, that is the most frequently offered alternative when children refuse ORS (manuscript under review).

4. Impact on Health Costs

While a formal cost-effectiveness analysis is beyond the scope of the current proposal, it needs to be considered, given that in the 2003 calendar year, there are over 27,000 ED visits to Ontario EDs by children with acute gastroenteritis. At present, these children are treated with EMS at a cost of approximately \$10/liter with ½ strength apple juice (the intervention to be evaluated) costing under \$1/liter. Assuming each child is provided with ½ liter of liquid and that a province wide switch to FAT is made, the savings would exceed \$120,000 annually.

3. RESEARCH DESIGN/METHODS/ANALYSIS

1. Study Design

This will be a randomized, controlled, blinded, single-center, non-inferiority trial. While in the ED during the initial visit, all individuals will be blinded; unblinding of the caregiver will be necessary at the time of discharge to allow administration of the appropriate solutions following discharge.

2. Study Population and Setting (Appendix II)

Children aged 6-60 months presenting to the ED with vomiting or diarrhea who qualify for the initiation of ORT at triage and have none-some dehydration and <96 hours of symptoms.

3. Inclusion Criteria-Definitions

Initiation of ORT at Triage: Children must have a minimum of 3 episodes of vomiting or diarrhea in the preceding 24 hours in addition to meeting all other ORT protocol requirements (Appendix III).⁴³

None-Some Dehydration: It is recognized that distinguishing between mild and moderate dehydration is difficult, thus it is no longer recommended.¹ As such, we will employ a dehydration score developed and validated and which is currently in use in our ED to classify children as none-some (score 0 – 4) dehydration versus moderate-severe (5 – 8).⁴⁴⁻⁴⁶ This score will be assigned by trained triage nurses.

4. Exclusion Criteria

We have defined a “low-risk” population, and our inclusion/exclusion criteria in keeping with the recommendations provided by the Centers for Disease Control and Prevention in their guidelines for Managing Acute Gastroenteritis Among Children.¹ We will use the presence of any of the following to indicate that a child is “high-risk” (ie. not “low-risk”) and hence not eligible for this study:

1. Known gastrointestinal diseases (ie. inflammatory bowel disease, celiac) or any other underlying disease process that might place the child at an increased risk of treatment failure.
2. Age < 6 months
3. Weight < 8 kg
4. If premature, corrected gestational age < 30 weeks
5. Presence of hematochezia
6. Responsible physician judges the child requires immediate intravenous rehydration
7. English language is so limited that consent and/or follow-up is not possible.
8. Non-Ontario resident [Canadian Institute for Health Information (CIHI) follow-up data will not be available]

We have not set specific cut-offs for frequency of vomiting or diarrhea as children with frequent vomiting or diarrhea yet only have minimal-mild dehydration are the ideal study candidates. Including these children will allow us to determine if they are more likely to tolerate EMS or FAT.

7. Experimental Maneuvers (Appendix IV & V)

Sample Selection: On arrival, all potentially eligible children will be triaged. If deemed to be potentially eligible by the triage nurse, he/she will inform the caregiver that someone may be contacting them about a study related to their child’s symptoms. If the caregiver gives her/his approval, then the Research Assistant (RA-PRAISE program (Appendix II)) will be informed. An RA will be present in the ED 15 hours/day, 7 days/week to assess children for eligibility. If eligible, a trained Clinical Research Nurse Coordinator (CRNC) will be paged to obtain informed consent.

Once informed consent is obtained, a structured data collection form will be used to record baseline and historical co-variables that may affect outcomes and potentially confound the treatment comparison. Children will then be allocated to treatment and will begin ORT. All future treatment decisions will be at the discretion of the responsible physician. An electronic database of all potentially eligible children will be maintained, whether randomized or not. By recording the numbers of individuals screened, eligible and enrolled, as well as reasons for not enrolling eligible patients we will be able to judge whether there are differences between patients who were versus those who were not enrolled. If the two populations are similar, the generalisability of the trial will be increased and the probability of selection bias minimized. For those deemed ineligible, the criteria excluding them from the study will be documented.

Allocation: Enrolled children will be randomly allocated to either the EMS or FAT groups. Individuals will have an equal chance of allocation to either group. To ensure allocation concealment, the randomization table will be created and stored by an independent HSC pharmacist who will also prepare the solutions to be dispensed. The service will provide randomization using random block sizes. The experimental liquid provided (1/2 strength apple juice or apple Pediatric Electrolyte[®]) will be in opaque, identical appearing bottles to blind caregivers, RAs and ED staff and to optimize compliance. The Research Support pharmacy will colour match the solutions such that regardless of the method of administration (ie. cup, spoon, or syringe) blinding will be maintained. Patients who cross over and those who are enrolled and randomized but are later found to meet exclusion criteria will be followed and included in the analysis (both intention to treat, and per protocol).⁴⁷

EMS Group: The EMS group will form the control group as solutions such as Pediatric Electrolyte[®] are routinely recommended for use in children with gastroenteritis. Two liters of Pediatric Electrolyte[®] will be provided in a concealed unlabeled opaque container. Caregivers will be encouraged to provide the same liquid following disposition to replace ongoing losses. Since losses cannot be easily measured in outpatients, 10 mL of additional EMS should be administered/kg body weight for each watery stool and 2 mL/kg for each episode of emesis.¹ Caregivers will be informed about fluids to consume and dietary recommendations following discharge via an instructional letter (Appendix VI) provided to them in a concealed envelope upon disposition, thus maintaining blinding in the ED. Fluids containing non-physiological concentrations of glucose and electrolytes (carbonated drinks, sweetened fruit juices, water) will be discouraged.

FAT Group: Following randomization, caregivers will be provided with 2 liters of ½ strength apple juice, in a concealed unlabeled opaque container. Caregivers will be informed about fluids to consume and dietary recommendations following disposition via an instructional letter (Appendix VII) provided to them in a concealed envelope upon disposition, thus maintaining blinding in the ED. Following discharge, caregivers may provide liquids in keeping with their child's usual dietary pattern to replace fluid losses in order to truly compare FAT versus EMS. In the ED however, it is not feasible to provide more than one intervention and one control solution. However, if, following the initial assessment by the responsible physician, the child's oral consumption is felt to be inadequate (whether they are randomized to the FAT or EMS groups), the physician may choose to have the child consume an alternate solution. This will allow us to expand the choice of liquids offered to the FAT group, maintain blinding, and also not administer intravenous fluids unnecessarily (ie. when the physician's usual practice would be to offer an alternative to EMS when its consumption is insufficient). Should an alternative solution be provided, it will be recorded and the solution provided documented. If crossover occurs, EMS to FAT or FAT to EMS, this will be classified as a treatment failure. We do anticipate that crossover of EMS to FAT will be more common as the FAT group will most likely be provided an alternative FAT solution (ie. not EMS).

ED Care: All treatment recommendations aside from the intervention, will be in accordance with the AAP¹ and CPS²² recommendations. Treatment will be aimed at providing adequate fluids and continuing an age-appropriate diet. Following the initiation of ORT, all children will undergo evaluation by the ED physician with treatment provided as clinically warranted. All children will perform ORT employing frequent feeds (every 2-5 minutes) of small volumes (5 ml) of hydration fluid. Should vomiting occur during ORT, ondansetron oral disintegrating tablet will be administered from ED ward stock according to standard dosing protocol and guidelines (weight 8-15 kg: 2 mg; weight 15-30 kg: 4 mg; weight > 30 kg: 8 mg).⁴⁸ The administration of ondansetron to such children has become standard of care with numerous clinical trials documenting its effectiveness.⁴⁸⁻⁵² A recent meta-analysis concluded that ondansetron is effective at reducing the need for intravenous rehydration and hospitalization⁵³ and numerous reviews have concluded that ondansetron should be employed when treating children with vomiting secondary to acute gastroenteritis.⁵⁴⁻⁵⁶ To withhold such care might impede study approval by the Ethics Board and reduce support for the study from clinical staff. Lastly, we have data (manuscript under review), from a recent survey of 212 members of Pediatric Emergency Research Canada (PERC) and the Pediatric Emergency Medicine Collaborative Research Collaboration (PEM-CRC) indicating that over 80% of PERC members and 98% of PEM-CRC members administer an antiemetic agent to eligible children. In Canada, the agent chosen is ondansetron over 75% of the time while in the US it is ondansetron 100% of the time. Additionally, ondansetron administration in the outpatient office setting to children with gastroenteritis increased 7-fold between 2005 and 2008 indicating the even pediatricians and family physicians have begun administering it to optimize the success of ORT.⁵⁷ Thus, our use of

ondansetron, for children with vomiting despite an optimal ORT regimen (small, frequent volumes) is in keeping with current standards of care. Thus, by evaluating the success of EMS vs. FAT both pre and if necessary post-ondansetron administration, we will still be able to answer the question of “Does the use of FAT vs. EMS have any impact on subsequent vomiting?” while, at the same time, reducing the need for intravenous rehydration due to ongoing vomiting.

The following additional instructions will be provided to both groups at discharge (Appendix VIII):

- Modified discharge instructions, from www.aboutkidshealth.ca regarding vomiting/diarrhea will be provided with comments regarding the choice of liquids (EMS vs. FAT etc.) removed.
- A diary on which to record follow-up health care provider visits, diarrhea, vomiting, childcare, expenses, and fluids administered will be provided. This will be returned to the CRNCs at the final reassessment or mailed (postage-paid envelope) if it is not brought back to the CRNC.

ED Follow-Up: Routine follow-up will not be required as all enrolled children will return for reassessment by a CRNC in 72-84 hours with physician assessment performed if required. This time frame has been selected, as most revisits occur within 72 hours;^{48,58-60} thus the scheduled reassessment should not impact the outcome of interest. The time/date of the reassessment will be arranged prior to discharge. This will allow us to re-weigh subjects on the same scale and will act as a safety net to identify children whose condition may have deteriorated. Pertinent historical data variables will be collected, and a clinical dehydration assessment will be performed.⁴⁶ Caregivers will return all unused study liquids as well as their diaries at this visit. Unused supplies will be brought to The Hospital for Sick Children’s Research Support Pharmacy for destruction. Unscheduled physician assessments in the ED will be required for all children with $\geq 3\%$ weight loss from the enrolment weight, and for those with clinical dehydration scores ≥ 5 . Reassessments will occur every 48 hours until a stable weight (2 consecutive weights differ by $< 2\%$)⁶¹ is reached, and vomiting, diarrhea and poor intake have resolved.^{61,62} Caregivers will receive compensation for the inconvenience of the return visit.

Telephone Follow-up: Caregivers will be contacted DAILY to track progress, record symptoms and allow for tracking of outcomes (revisits, intravenous fluid administration, and hospitalization). In order to ensure the safety of all participants, calls will be made by the CRNC who will employ a standardized set of criteria which would require their advising the caregiver to return to the ED for re-assessment (Appendix IX). For children who do not attend the scheduled re-assessment, attempts will be made to contact the caregivers and collect all outcome data points to minimize loss to follow-up. Previous⁴⁸ and ongoing research in similar patient populations by the PI (SF) has had over 90% success with telephone follow-up at 7 days. To ensure that follow-up data is accurately collected, for all families not contacted by telephone after 7 days, a letter will be sent by registered mail requesting that the family either contacts the CRNC or that they complete a data form and return it in the stamped and addressed return envelope that will be provided. Follow-up calls will not be taped.

Database Follow-up: Lastly, to ensure that we capture all significant adverse events, we will request follow-up data from CIHI whose database includes information for all Ontario ED visits and all-hospital based and community-based ambulatory care. We will inform CIHI of all enrolled children and withdrawals on a monthly basis.

Blinding: The maintenance of blinding will occur by providing liquids in the ED that are identical appearing. Caregivers will be blinded in the ED (unless they taste the liquids); however they will become unblinded at the time of discharge as the instructions will state what liquids their child should receive following discharge. The primary outcome, treatment failure, is objective and unlikely to be

influenced by unblinding of the caregiver, who will be instructed not to reveal the randomization group to the CRNCs. If this does occur it will be recorded. To test blinding, the RA and physician will be asked which treatment he/she feels the child received and why.

Compliance: In ED: This will be enforced by limiting the consumption of liquids by the child to those provided by the RA or suggested by the ED supervising physician. If alternative liquids are consumed this will be recorded.

Following Discharge: This will not be an issue for the FAT group as they may consume whatever liquids they desire. This will be more difficult for the EMS group may be an issue, however, our design exceeds the standard of care by providing 2 liters of EMS to this group. This real world, effectiveness design, is important as a treatment that is not administered is likely ineffective. Thus, our trial takes a pragmatic approach which, is an important consideration in clinical trial designs.⁶³⁻⁶⁵ We will measure compliance during the follow-up visit allowing us to conduct an exploratory “as-treated” analysis to determine if those who were more compliant had superior outcomes. An individual will be determined to have been compliant if the caregiver reports that they attempted to administer increased fluids to replace losses > 75% of the time as assigned.

Data to be collected on families and children aged 6-60 months presenting to the ED with a minimum of 3 episodes of vomiting or diarrhea in the preceding 24 hours who qualify for the initiation of ORT at triage and have none-some dehydration and <96 hours of symptoms.

None-Some Dehydration: It is recognized that distinguishing between mild and moderate dehydration is difficult, thus it is no longer recommended.¹ As such, we will employ a dehydration score developed and validated and which is currently in use in our ED to classify children as none-some (score 0 – 4) dehydration versus moderate-severe (5 – 8).⁴⁴⁻⁴⁶ This score will be assigned by trained triage nurses.

Data will not be collected on “high-risk” (ie. not “low-risk”) children who are not eligible for this study:

1. Known gastrointestinal diseases (ie. inflammatory bowel disease, celiac) or any other underlying disease process that might place the child at an increased risk of treatment failure.
2. Age < 6 months
3. Weight < 8 kg
4. If premature, corrected gestational age < 30 weeks
5. Presence of hematochezia
6. Responsible physician judges the child requires immediate intravenous rehydration
7. Non-Ontario resident

Data to be collected will include (1) age in months, (2) outcomes from the ED visit (ondansetron administration, intravenous fluid administration, length of stay, disposition determination) and (3) future visits to SickKids in the subsequent 2 weeks. No information will be shared with nor requested from CIHI as it relates to these children. By collecting data on all similar patients attending the ED, including those who are not enrolled, we will be able to conduct a quality assurance evaluation of our protocol and recruitment process.

8. Outcome Measures

Primary: PROPORTION OF CHILDREN EXPERIENCING A TREATMENT FAILURE: We have chosen this outcome measure over weight (ie. % dehydration) as it is more clinically meaningful, particularly in a group of children in whom we do not expect to see a significant degree of dehydration

develop. This dichotomous outcome will be deemed to have occurred if any of the following events occur within 7 days of enrolment:

1. Requires an unscheduled visit after the initial encounter: This has been used as the primary outcome measure of EMS effectiveness³ and includes unscheduled office, urgent care, and ED visits for the same episode of diarrhea, vomiting, anorexia or fever, not requested by the initial physician.
2. Requires physician evaluation during a follow-up assessment. This would occur, if during CRNC assessment the child has a clinical dehydration score ≥ 5 (indicative of moderate dehydration)⁶¹ or has lost $\geq 3\%$ body weight since enrolment.
3. Hospitalization or Intravenous Rehydration: Either at the initial or subsequent visits.
4. Extended Symptomatology: The occurrence of ≥ 3 episodes of vomiting or diarrhea in a 24 hour period greater than 7 days (168 hours) after enrolment. Children whose have no (ie. zero) episodes of vomiting or diarrhea for ≥ 24 hours but then have a resumption of symptoms will be deemed to have two separate illnesses and not “extended symptomatology.
5. Failure to consume sufficient study fluid during the initial ED visit: Should children be encouraged to crossover during their index visit, they will be deemed to have failed treatment. This would occur if a child does not consume a sufficient volume of oral fluids and consequently the ED physician suggests trying an alternate liquid in order to avoid the use of intravenous rehydration. As blinding will be maintained, the ED physician will be unaware of the randomization liquid and they may choose to encourage the use of EMS or FAT.

Secondary Outcome Measures: The treatment groups will be compared with respect to the following:

1. Percent Weight Change: Weight change is the gold standard for measuring dehydration.^{61,66-72} We will determine the % weight change by calculating the difference between the enrolment weight and the 72-84 weight (during ED reassessment), dividing that by the lower weight, and transforming that into a percent weight loss. Children < 1 year of age will be weighed naked, those > 1 year of age will be weighed wearing only a diaper/underwear. They will be weighed 3 times at each visit with the median value used to represent the actual weight.
2. Proportion Receiving Intravenous Rehydration: While it is clear that children with minimal/mild dehydration should not routinely receive intravenous rehydration, it still occurs due to the under-use of ORT,¹ the worsening of a child’s condition, and the inherent limitations of ORT (ileus, excessive stool output, carbohydrate malabsorption, intractable vomiting).¹
3. Proportion Requiring Hospitalization: This outcome should be uncommon but is very important.
4. Frequency of diarrhea and vomiting episodes (per 24 hour period): Diarrhea is defined as a watery stool, able to take the shape of a container.⁴³ Vomiting is defined as an episode of forceful expulsion of stomach contents. Nonproductive retching, spilling of oral contents during feeding, and drooling are not considered vomiting episodes.

Other Outcome Measures: These outcomes will be explored but due to either inadequate power or lack of validated scores, they will not be considered as primary or secondary outcome measures.

1. Serum sodium, potassium, bicarbonate, urea, & creatinine: To be compared only amongst children who require intravenous rehydration at a revisit as it would be unethical to perform on all children.
2. Return to a 75% “normal diet”: During daily communication caregivers will be asked to estimate to what degree their child’s diet has returned to normal. While an individual caregiver’s ability to make this determination may be imprecise and the inter-observer reliability is unknown, given the large sample size and randomization, we anticipate equal reliability in both groups.
3. Caregiver satisfaction and ease of diet implementation: At the 1st ED follow-up visit caregivers will be asked to indicate their satisfaction with the discharge instructions they were given and the ease of implementation. Responses will be based on 7-point Likert-type.⁷³

4. *Duration of illness*: Defined as the time from presentation to the passage of the last diarrheal stool preceding the first formed stool.

9. **Trial Administration**

Trial Staff: One CRNC with ED gastroenteritis research expertise will be trained by the PI (SF) to the specifics of this study. She will work on the study as a 0.75 FTE for a 20 month consecutive period which will include two peak gastroenteritis seasons. This will allow her to provide ED coverage to obtain consent, conduct all the necessary follow-up visits and phone calls and provide all the back-up and administrative support that will be required to allow the PRAISE program volunteers (Appendix II) to identify eligible patients. As she will be working “on-call” and will not do primary screening of the ED, we anticipate that 30 hours per week should be sufficient to accomplish these tasks. If necessary on-call coverage will be shared with other “on-call” CRNCs employed by the PI.

Daily Follow-up Phone Calls: On days when ED reassessments are not scheduled, caregivers will receive a telephone follow-up call to enquire about ongoing symptoms, diarrhea/vomiting frequency, and the need for unscheduled follow-up appointments. This will continue until symptoms resolve. The CRNC will also address any parental concerns about the patients’ condition. Should there be questions regarding the need for unscheduled follow-up, if the child does not meet follow-up criteria as documented in Appendix IX, then a standard response will be employed (“Your child does not have any symptoms which would definitely require a follow-up visit, and as a Study Coordinator I cannot provide any medical advice regarding matters outside the scope of the study. Please contact your child’s physician or Telehealth Ontario (1-866-797-0000) with questions about his/her status.

Data Management and Feasibility: Please see Appendices X and XI.

10. **Sample Size and Power**

The methods proposed in the Sample Size and Analysis Sections are those appropriate for non-inferiority trials (ie. trials with non-zero null hypotheses)(Appendix XII).⁷⁴⁻⁷⁶ The null hypothesis for the primary analysis is $H_0: \mu_F - \mu_E \geq 7.5\%$ treatment failures, where μ_F and μ_E are the probabilities of a child meeting the study definition of treatment failure in the FAT and EMS groups respectively. Rejecting H_0 leads to the conclusion that there is evidence for adopting FAT as the standard treatment. That is, if FAT results in no more than a 7.5% increase in treatment failures, then its additional convenience may justify adoption. This implies that greater than 13 children would need to be treated with EMS in order to prevent one treatment failure. This margin of non-inferiority has been selected based on a survey conducted by the PI (SF) of ED and community pediatricians and is driven primarily by the excellent safety profile of the current standard of care (EMS), its entrenchment in numerous guidelines, the burden and cost of unnecessary visits, balanced against the cost and poor palatability of EMS. Responses from physicians surveyed included a mix of individuals suggesting 5% and 10%, thus the selection of 7.5%. While the non-inferiority margin for this study needs to be small to account for the “harm” associated with an unscheduled visit which includes financial cost, caregiver time (work absenteeism) and impact of the visit on the child, it is not feasible, based on sample size limitations to employ a lower margin (ie. a margin of 5% instead of 7.5% would increase the necessary sample size by 250%). Even with a significantly larger sample size, we would not be able to rule out the possibility of any adverse events ever occurring from the implementation of a FAT strategy. As such, the conclusions of this study will need to be disseminated meticulously to ensure that, if equivalent, FAT is adopted only for low-risk populations, such as is being included in our study.

The alternative hypothesis of interest is $H_A: \mu_F - \mu_E < 0\%$ (i.e. FAT is at least as effective as EMS). A sample size of 281 per group is required to achieve 80% power to reject H_0 using a one-sided $\alpha=0.025$ ⁴⁷ when the true difference in percent treatment failures between groups is 0. Our estimate of treatment

failure is based on a review of HSC's gastroenteritis data from 2003-07 which revealed that 14% of all children had a return visit to HSC's ED within 1 week with 39% of these receiving intravenous rehydration and 13% being hospitalized. While some of these return visits occurred in children with significant comorbidities who would be ineligible for this study, the baseline estimate does not include unscheduled visits to primary care providers and walk-in clinics. Thus, when taking those factors into account, we feel that 15% is a reasonable estimate of the primary outcome in the control group. Adjusting for a 10% loss to follow-up results in a final sample size of 624. A 10% loss to follow-up for the primary outcome is reasonable based on the PI's (SF) success (95%) with telephone follow-up in a previous, (and also in an ongoing) similarly designed study, which will enable capture of the primary outcome.⁴⁸

11. **Analysis**

All analyses will be undertaken by intention-to-treat and per protocol principles. The latter will be performed as blurring of the difference between treatment groups (unscheduled cross-over) will increase the chance of finding non-inferiority.⁴⁷

Baseline Variables: Baseline variables such as age at randomization, frequency and duration of vomiting and/or diarrhea, rotavirus vaccination status, and dehydration score, will be compared between randomization groups using the appropriate descriptive statistics. Frequency counts and percentages will be given for discrete variables, and means, medians, standard deviations and inter-quartile ranges for continuous variables. Concern regarding the confounding effects of a baseline variable will be based on the magnitude of observed between-group difference and the correlation with the outcome.

Primary Outcome: A 95% confidence interval for the difference between proportions ($\mu_F - \mu_E$) will be calculated and compared to the margin of equivalence of 7.5%. If the interval lies entirely on the left side of 7.5% (ie. we conclude with 95% certainty that the primary outcome occurs less than 7.5% more frequently amongst the FAT group), then non-inferiority will be concluded (Appendix XII). Following the recommendation of the Committee for Proprietary Medicinal Products⁷⁷ if inferiority is rejected then a test for superiority at the one-sided 2.5% level will be performed.

Secondary Outcomes: To account for the issue of multiple testing, statistical tests of hypotheses for the secondary outcomes will be set at the 0.01 level. The continuous variable (1) percent weight change will be analyzed using 2 sample t-tests. The binary secondary outcomes of (2) intravenous rehydration and (3) hospitalization will be analyzed using Fisher's exact test with adjustment for covariates facilitated by logistic regression. The continuous variables (4) frequency of diarrhea and vomiting are likely to follow a Poisson distribution,⁴⁸ hence they will be analyzed with a regression model following that assumption.

Exploratory analyses: A secondary analysis will be conducted to determine if age impacted on the outcomes of interest as there may be clinically important differences between children at the two extremes of our age spectrum. Logistic regression will be performed to determine the interaction between treatment group and age.

12. **Adverse Event Reporting**

All adverse events will be reported to the Hospital for Sick Children Research Ethics Board according to the Hospital for Sick Children's adverse event reporting requirements. All serious, unexpected adverse drug reactions to the study medication will be reported to Health Canada within 15 calendar days or for death or life-threatening events, within 7 calendar days. In the latter case, a follow-up report must be

filed within 8 calendar days. Adverse reactions will be managed according to the Hospital for Sick Children's standard clinical management practices.

13. Ethical Considerations

An independent Data Safety Monitoring Committee consisting of a biostatistician, a pediatrician, and an emergency medicine physician will be immediately advised of all adverse events, will be responsible for data monitoring, and will perform the interim data analysis following the enrolment of 200 children. Given the usual ethical and efficiency considerations for a trial large in size and long in duration,⁷⁸ we will adhere to the nominal significance levels proposed by Haybittle;⁷⁹ a probability value of 0.001 for the interim analysis and 0.025 for the final analysis. (See Appendix XIII)

14. Members of the Research Team/Relevant Work

Dr. Freedman is an ED pediatrician and Associate Scientist in the Child Health Evaluative Sciences Program at the HSC Research Institute. His research focus is on optimizing the management of pediatric gastroenteritis and dehydration. He has published several papers on dehydration, oral rehydration and antiemetics⁸⁰⁻⁸⁴ including a publication in the New England Journal of Medicine.⁴⁸ Dr. Schuh is a Senior Associate Scientist in the HSC Research Institute. She has published numerous funded trials studying the optimal ED management of acute asthma, bronchiolitis, and croup. Dr. Parkin is the Director of Research for the Division of Paediatric Medicine, an Associate Scientist with the Research Institute, and has previously developed and validated the clinical dehydration score that we will be employing.⁴⁴⁻⁴⁶ Dr. Boutis is an Associate Scientist at the HSC Research Institute with expertise in clinical trial methodology.

15. Potential Impact

The advisory panel which has guided study design and outcome measures has included pediatricians, pediatric gastroenterologists, and emergency medicine and infectious disease physicians from both the US and Canada. We will share the results of this trial with participants and health care practitioners; the latter via presentation at conferences, and publication in a peer-reviewed, freely accessible, journal. Community pediatricians and family physicians will be targeted for education via lectures, educational seminars and review articles. The results will clarify which ORT fluids should be recommended for low-risk children. Such information is crucial and will be incorporated into clinical management pathways and caregiver handouts (ie. Telehealth Ontario, aboutkidshealth.ca). Distribution strategies will include encouraging the use of this trial as the basis of management guidelines through the CPS, the Canadian Association of Emergency Physicians, and the AAP. Lastly, we will ensure that our dissemination strategy clearly recommends which children were evaluated to ensure that the results of this trial are applied to the appropriate patient population (ie. low-risk children) and not children with severe illness or environments without adequate medical support. We will ensure that the results of this study, if positive, do not replace all the preceding work and education on the use of EMS, by the use of appropriate cautionary statements and by clearly delineating the target population with the goal being to promote the success of home management of a common childhood illness.

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Appendix I

Electrolyte Content of Liquids Frequently Administered

The following table contains the electrolyte content of liquids frequently administered to children with acute gastroenteritis.

	Carbohydrate (gm/L)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Base (mmol/L)	Osmolarity (mOsm/L)
ORS						
WHO 2002 (<i>Gold Standard</i>)	13.5	75	20	65	30	245
WHO 1975	20	90	20	80	30	311
Enfalyte [®]	30	50	25	45	34	200
Pediatric Electrolyte [®]	25	45	20	35	20	250
Diet as Tolerated						
Apple juice	120	<1	44	45	-	730
½ Strength apple juice	60	0	22	22	-	365
Grape juice	160	1.0	40	-	32	1190
Orange juice	120	<1	50	-	50	
Coca-Cola Classic [®]	100	2.0	<1	-	13	650
Ginger Ale	90	3.5	0.1	-	3.6	565
Gatorade [®]	40	24	3	17	3	350
Chicken broth-canned	-	200	5	-	-	450

APPENDIX II

Study Setting

The Hospital for Sick Children's Division of Paediatric Emergency Medicine offers tertiary and quaternary level emergency and level 1 trauma services to the paediatric population of central Ontario and particularly the Greater Toronto Area. The emergency department also offers primary and secondary level services to the local population of downtown Toronto.

The emergency department continues to expand clinical research in the management of pediatric acute illnesses, in particular, pediatric gastroenteritis and dehydration. The emergency department, which sees on average 55,000 children per year, is well suited to the study of gastroenteritis as it sees almost 3,000 children with gastroenteritis/year.

The gastroenteritis/dehydration research program is spearheaded by Dr. Freedman. His research team includes 3 Clinical Research Nurse Coordinators, a Clinical Research Manager and several summer students. Additional support is provided by the Acute Care Research Group which includes the Critical Care Unit and Neonatal Intensive Care Unit, and is led by Dr. Jamie Hutchison with Laura Keating as the Research Manager. Ongoing prospective gastroenteritis studies include clinical (Rapid IV Rehydration (RIVR) for gastroenteritis; use of Probiotics in Pediatric gastroenteritis; a cross Canada gastroenteritis Practice Pattern Study) in addition to retrospective and cost-effectiveness studies (Trends in Gastroenteritis Management; Cost-Effectiveness of Ondansetron Administration; Optimal Dose of Oral Ondansetron; Hematemesis in Children).

We have increased our infrastructure to include a Pediatric Research Initiative At Sickkids Emergency (PRAISE) program. This program is intended to support the research initiatives of the Emergency Department. It is meant to represent a relatively unique opportunity for the undergraduate students to directly participate in the performance of clinical research, while also observing overall ED operations and interacting with physicians, nurses, and other health care personnel. Individuals selected to participate in this program will serve as Research Associates (RA) who will provide direct assistance with identification and collection of information from patients in the ED. The primary focus of these RA is on optimizing the success and rigor of clinical research in the ED. By consistently having PRAISE RAs present in the ED for 15 hours per day, nearly 365 days a year, the ability to enroll patients successfully in clinical studies protocols is greatly enhanced. It is anticipated that the program may grow to provide up to 24 hours per day of coverage, and currently includes double coverage during peak hours. These volunteer RAs will be directly supervised by the Clinical Research Nurse Coordinator who will supervise and be responsible for their participation in all aspects of the study. The use of the PRAISE program greatly enhances our ability to conduct high quality emergency department research in a cost-effective manner.

Appendix III

Oral Rehydration Therapy: Triage Inclusion Criteria

To be eligible to be included in this pathway, “YES” must be the response for each criteria.

Yes	No	Description
		≥3 episodes of vomiting or diarrhea in preceding 24 hours
		Duration of illness less than 96 hours
		Age 6 - 60 months
		Clinical suspicion of acute intestinal infectious process
		Weight ≥ 8 kg
		Clinical dehydration score < 5
		Capillary refill < 2 seconds
		Absence of bulging fontanelle
		Absence of bilious vomiting
		Absence of blood in diarrhea/emesis
		Absence of abdominal pain (if present reported as periumbilical in location)
		Absence of abdominal distension
		Absence of acute disease currently requiring treatment
		Absence of co-existing diseases (prematurity, cardiac, renal, neurological, metabolic, endocrine, immunodeficiency, trauma or history of ingestion)

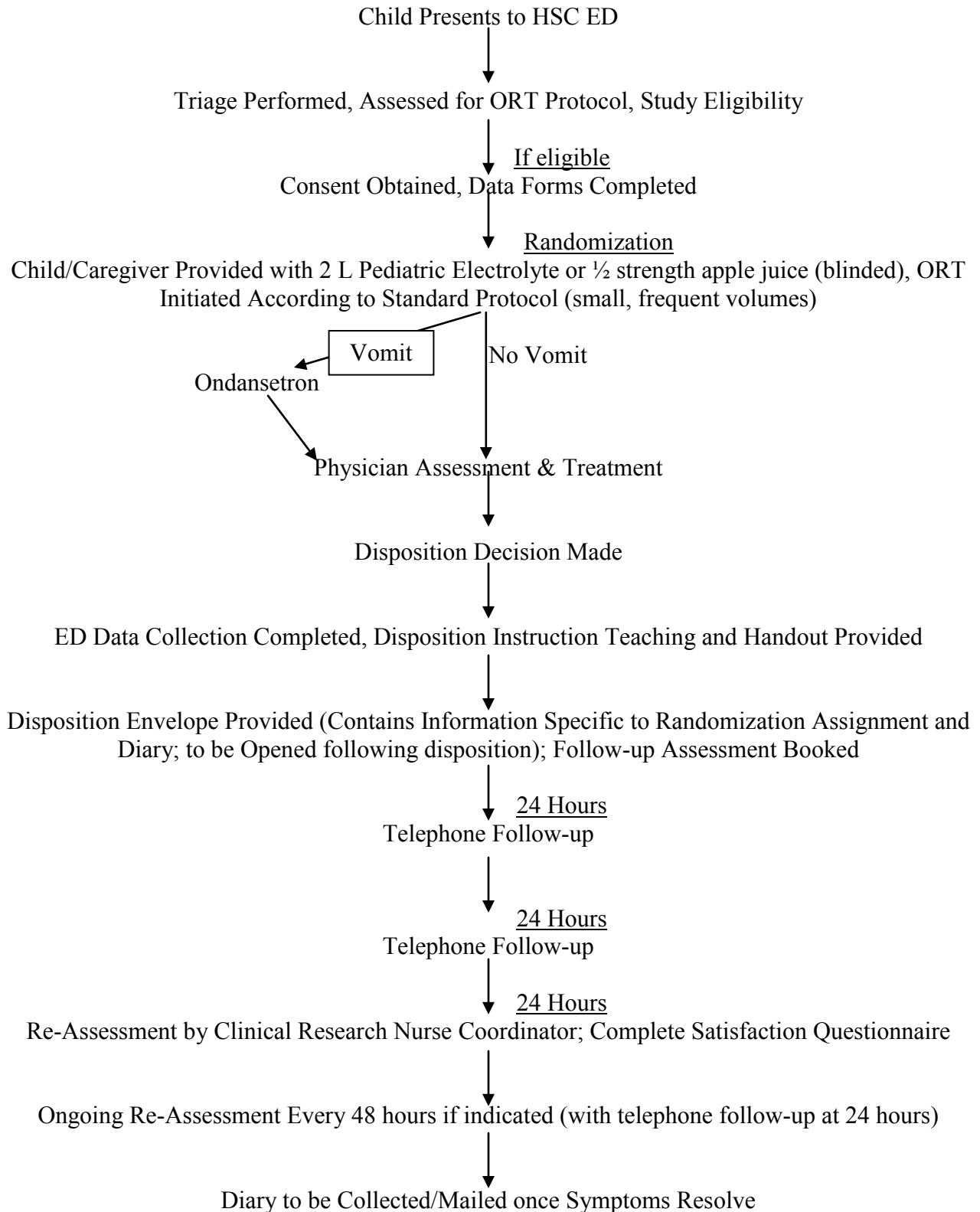
Triage Recommendation:

- Begin ORT Regime (attached)
- Medical Assessment prior to initiating ORT guideline
- Not Guideline eligible: Treat according to patient specific clinical indication

Signature of Triage RN

APPENDIX IV

Study Flow Diagram



APPENDIX V

Schedule of Assessments

Study Assessment	Screening	Randomization	Initial ED Assessment	ED Disposition	72-84 HR ED Reassessment	Q24HR PRN ED Reassessment	Q24 HR Phone Contact
Informed Consent	X						
Review of Eligibility Criteria	X						
History, Examination, Demographics	X						
Medication use	X						
Randomization		X					
Hydration Score	X				X	X	
Weight	X				X	X	
Rehydration Teaching		X			X	X	
Handouts/Instructions Provided				X			
Record Oral Fluids			X		X		
Rehydration Fluids Dispensed		X					
Serum Electrolytes ¹			X		X	X	
Intravenous Rehydration ¹			X		X	X	
Hospitalization ¹				X	X	X	
Blinding Assessment				X			
Satisfaction Survey					X		
Collect Completed Diary					X ²	X ²	
Adverse Event Assessment				X	X	X	X
Clinical Endpoint Assessment				X	X	X	X

1: If required based on clinical symptoms

2: Only to be collected if no further study follow-up is required

Appendix VI

Discharge Instructions to EMS Group

Your child has been assigned to drink Electrolyte Maintenance Solution (EMS). You should give your child the liquid we have provided to you (Pediatric Electrolyte) to replace all fluid losses (vomiting or diarrhea). For each episode of diarrhea please give him/her 10 ml/kg and for each episode of vomiting please give 2 ml/kg. Should your child not like the solution we have provided than you may purchase Pediatric Electrolyte with a different flavour or you may use a different solution such as Enfalyte, Gastrolyte, or Cera. Your child should consume a normal diet as soon as he/she desires it and may eat and drink whatever he/she would like however losses (vomiting and diarrhea) should be replaced using an Electrolyte Maintenance Solution. If your child vomits, then administer the Electrolyte Maintenance Solution only for 4 hours after which time you can resume a normal diet. However while the diarrhea or vomiting persists, please continue to replace all diarrhea and vomiting losses with an Electrolyte Maintenance Solution.

DO NOT you give your child soda pop (carbonated beverages such as ginger ale), fruit juice (apple, orange, grape) or water to replace their losses (vomiting or diarrhea).

Only you should know what type of liquid your child has been given to drink Please do not tell any one at the hospital what type of liquid your child has been given to drink, unless it is an emergency.

If you have questions you can contact the study nurse at 416-813-2163.
Please do not tell him/her what liquids your child is taking.

Please return all unused liquids, to the study nurse when you return for your follow-up visit.

Appendix VI

Discharge Instructions to FAT Group

Your child has been assigned to drink fluids as tolerated. Should your child not like the solution we have provided then you may provide your child with any fluids they desire to drink. You should give your child extra liquids to replace all fluid losses (vomiting or diarrhea). For each episode of diarrhea please give him/her 10 ml/kg and for each episode of vomiting please give 2 ml/kg. Your child should resume a normal diet as soon as possible.

DO NOT you give your child Electrolyte Maintenance Solutions (such as Pediatric Electrolyte, Enfalyte, Gastrolyte, Cera) to drink unless instructed to do so by a healthcare provider.

Only you should know what type of liquid your child has been given to drink Please do not tell any one at the hospital what type of liquid your child has been given to drink, unless it is an emergency.

If you have questions you can contact the study nurse at 416-813-2163.
Please do not tell him/her what liquids your child is taking.

Please return all unused liquids and the completed diary to the study nurse when you return for your follow-up visit.

Appendix VIII

Discharge Instruction Synopsis from AboutKidsHealth.Ca

These instructions are provided to you as part of the study to decide which liquids are best to give children with minimal dehydration.

Diarrhea can be caused by a virus or bacteria in your child's intestines. This makes your child's bowel movements looser and come more often. Most vomiting is caused by a viral infection of the lining of the stomach or if your child eats something that disagrees with him. Often, a child whose vomiting is caused by a virus also has diarrhea.

Encourage your child to drink the type of liquids assigned to them to replace all losses. Since dehydration, no matter what the cause, involves high loss of body water, the goal is to replace it. If your child is vomiting, give frequent small amounts of fluids rather than less frequent large amounts. Your child will be better able to keep the liquid down and will still get the same amount of fluid. Start with 1 teaspoon to 1 tablespoon every 5 minutes and increase gradually. After 4 hours without vomiting, double the amount each hour. If your child vomits using this treatment, rest the stomach completely for 1 hour and then start over but with smaller amounts. This one-swallow-at-a-time spoon fed approach rarely fails. A common error is to give as much fluid as your child wants rather than gradually increasing the amount. This almost always leads to continued vomiting.

If your child is assigned to, but refuses to drink the Electrolyte Maintenance Solution, you may administer juice diluted, 1:1, with water or saltine crackers with water. You should try to have your child resume a normal diet as soon as possible.

After 4 hours without vomiting, your child can gradually return to a normal diet. Infants can start with bland foods such as cereal. Older children can start with such foods as saltine crackers, cereals, white bread, rice, and mashed potatoes. Usually your child can be back on a normal diet within 24 hours after recovery from vomiting.

If your child has diarrhea, it is important to make sure your child does not lose too much water. You can do this by giving fluids more often than you would normally. Fluids prevent dehydration, but remember only give the type of fluids recommended by the study. You may give pretzels or salty crackers, rice cereal, oatmeal, bread, noodles, mashed potatoes, carrots, applesauce, and strained bananas to infants.

Call the study nurse at 416-813-2163 if you have questions or if:

- your child shows any signs of dehydration (such as no urine in over 8 hours, very dry mouth, no tears when crying)
- your child vomits up blood or there is blood in the diarrhea
- your child starts acting very sick
- the vomiting continues for more than 24 hours if your child is under age 2 years or 48 hours if over age 2
- your child is dizzy or unsteady while standing or walking
- your child appears less alert than usual
- your child refuses to drink fluids despite your encouragement

Appendix IX

Telephone Criteria for ED Revisit¹

1. Fever $\geq 39.0^{\circ}\text{C}$ for > 48 hours following initial assessment
2. Visible blood in stool
3. High output, including frequent (> 10) and substantial volumes of diarrhea (large according to caregiver)
4. Persistent vomiting, including frequent (> 5) and prolonged (> 2 days)
5. Caregiver report of signs of dehydration (ie. sunken eyes, decreased tears, dry mucous membranes, decreased urine output)
6. Change in mental status (ie. irritability, apathy, lethargy)
7. Inability of the caregiver to administer oral rehydration therapy

Reference

1. King CK, Glass R, Bresee JS, et al. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep 2003;52:1-16

Appendix X

Data Management

All data collected on enrolled patients will be reviewed within 48 hours of recruitment by the CRNC for completeness and appropriateness of enrollment. Regular e-mail, and weekly meetings for the first 6 weeks of the trial (biweekly thereafter) will be used to monitor start up and to obtain updates on recruitment and issues arising. All data will be entered within 1 week of being available into a Microsoft Access database which will be created by Research Institute staff (The Hospital for Sick Children) prior to commencing enrollment. Double data entry will be employed to ensure accuracy. All identifying information will be de-linked using coding for patient names and numbers. Computers and files will be password protected and maintained in locked offices. Paper data will be kept in a locked cabinet and office to which only the research teams will have access. Project coordination will be the responsibility of Dr. Stephen Freedman. Day to day activities will be coordinated by the study's CRNC. The CRNC will review the PRAISE schedule, organize payroll, promote the study, and will contact the Principal Investigator with any concerns. Weekly reports of the numbers of patients excluded, eligible, consented, missed, and randomized will be reviewed by the Principal Investigator.

Appendix XI

Recruitment/Feasibility

We performed a recruitment sensitivity analysis to estimate the likely necessary duration of the study in order to enroll our final total sample size of 624 subjects (312/year). Estimates are based on HSC data from 2002-2007 (annual variation not always available).

Total Number of Patients with Gastroenteritis/Year

Mean: 2723 Range: 2585 – 2871

Percent Age 6-60 Months

Based on 5 year HSC review: 68%

Percent Presenting Between 8:00 – 24:00

A 5 year review of our ED records indicate that approximately 85% of all children with gastroenteritis present between 8:00 – 24:00.

Mean: 85%

Percent Minimal/Mild Dehydration

A 5 year review of our ED records indicate that on average 22% of children with gastroenteritis have documented evidence of abnormal findings on one of the following domains: general appearance, dehydration, mucous membranes, tears, eyes, fontanelle, capillary refill, skin turgor. Thus our best point estimate will be slightly higher than 78% would have minimal/mild dehydration.

Weight < 8 kg

The 5 year chart review indicates that of those > 6 months of age, 5% will weigh < 8 kg.

Percent with Hematochezia

The 5 year chart review indicates that of those > 6 months of age, 3% will have hematochezia.

Percent with Requiring Immediate Initiation of Intravenous Rehydration

The 5 year chart review indicates that of those > 6 months of age, 5% will require the immediate initiation of intravenous rehydration.

Percent with ≥ 3 episodes of vomiting or diarrhea in preceding 24 hours

The 5 year chart review indicates that of those > 6 months of age, 70% will have ≥ 3 episodes of vomiting or diarrhea in preceding 24 hours.

Percent with Symptoms > 72 hours

The 5 year chart review indicates that of those > 6 months of age, 16% will have had symptoms for > 72 hours.

Consent

As most of these patients will be awaiting physician assessment when approached for consent, it is quite likely that consent rates will be high as the intervention is of minimal risk and may even provide the child with a more palatable solution to drink. The re-assessment may either aid or hinder consent however we hope this is offset by the financial incentive. We are in the process of conducting two other

clinical trials in pediatric gastroenteritis with non-overlapping patient populations. 204 children have been enrolled in a rapid intravenous rehydration study which requires, in addition to a 4 hour emergency department observation period and repeat bloodwork, follow-up phone calls on day #3 and 7. The consent rate in this study is currently at 83%. We are also conducting a probiotic study which requires that a diary be kept for 14 days, daily phone calls while symptoms persist, returning to the ED with stool samples, and mailing back unused sachets along with the diary on day #14. The consent rate for this cumbersome study is currently 79%. Thus, we believe that our best point estimate of 75% is reasonable.

While the follow-up for the proposed study is somewhat detailed, we have anticipated a 10% loss to follow-up which has been taken into account in our initial sample size calculations. It should be noted that our primary outcome (treatment failure), which has 4 elements, does not depend on complex follow-up and record keeping. The information required can be obtained from a simple follow-up telephone call on day #7. Previous⁴⁸ and ongoing research in similar patient populations by the Principal Investigator (SF) has had over 90% success with telephone follow-up at 7 days.

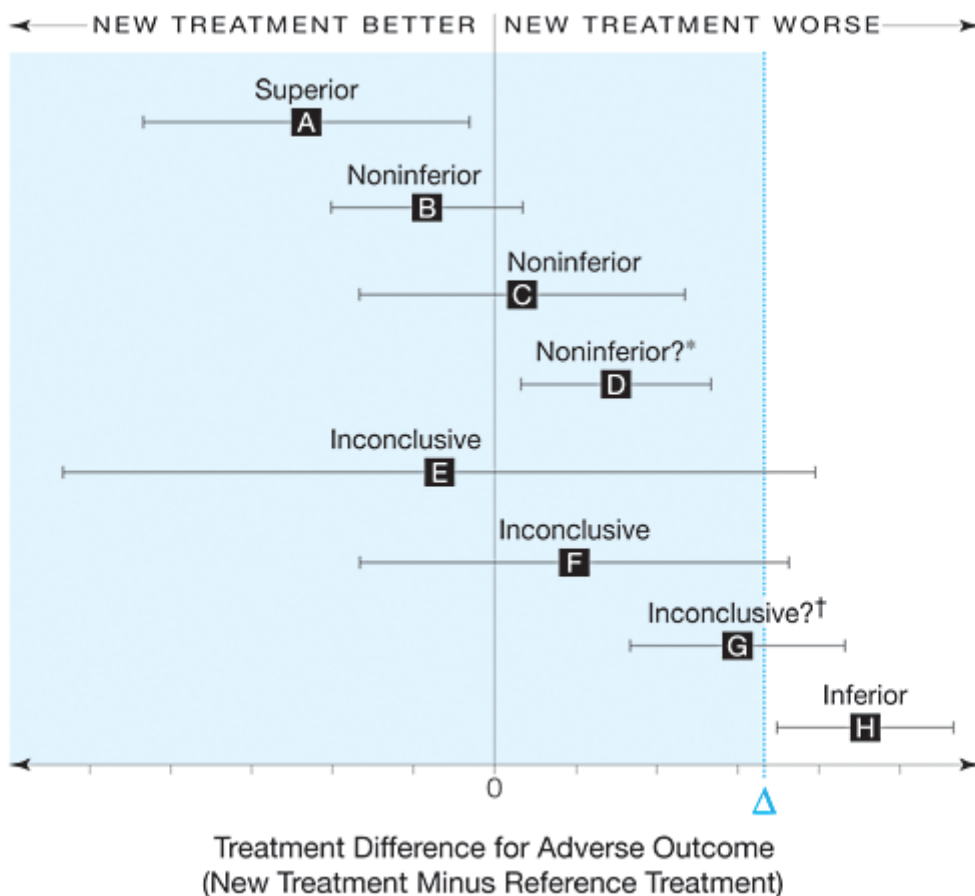
	Minimum Estimates	Best Point Estimates
Total # visits	2723	2723
% Age 6-60 Months	65	68
% Minimal/Mild Dehydration	75	78
% Weight \geq 8 kg	90	95
% without Hematochezia	95	97
% Requiring Immediate IV Rehydration	90	95
% \geq 3 episodes of vomit or diarrhea in preceding 24 hours	65	70
% symptoms < 72 hours	80	84
% Presenting Between 8-24	80	85
% Consenting	70	75
TOTAL ANNUAL ACRUAL	298	474
TOTAL ACCRUAL (2 Y)	596	948

Based on this recruitment sensitivity analysis, should we achieve our enrolment goal (624), using the best point estimate, after 16 months of recruitment. Thus, the requested 20 months of CRNC coverage should be adequate. In addition, there exists a cross-coverage scheme with CRNCs from other studies being able to provide coverage for this study, thus there should not be any difficulty in meeting the required sample size.

Appendix XII

Non-inferiority Randomized Trials

A non-inferiority trial seeks to determine if a new treatment is no worse than a reference treatment, ie. has as much efficacy as the standard or is worse by an amount less than a predetermined margin of non-inferiority. We accept this small margin of non-inferiority on the premise that the new treatment has some other advantage (better tasting, less expensive, greater availability, ease of administration). Because proof of an exact equality is impossible, a pre-stated margin of non-inferiority (Δ) for the treatment effect is required. In trials that investigate non-inferiority, the question of interest is not symmetric. The new treatment will be recommended if it is similar to or better than an existing one, but not if it is worse (by more than Δ). Superiority of the new treatment would be a bonus. Interpretation of the results of non-inferiority trials is described below (JAMA 2006;295(10):1152-60).



Appendix XIII

Ethical Considerations

Side effect data will be collected throughout the telephone follow-up period. Reporting will be in keeping with institutional Research Ethics Board guidelines and will include, the reporting of all unexpected adverse events along with a definition and grading, to the Hospital's Research Ethics Board. For unexpected adverse events, the Research Ethics Board will be informed within 7 days. For unexpected serious adverse events, the REB will be informed within 48 hours even if the information is incomplete. A complete follow-up adverse event report will be submitted no later than 7 days after the initial report.

Given our knowledge of the natural history of gastroenteritis in children without evidence of dehydration, we anticipate no serious outcomes. Nonetheless, a Data Safety Monitoring Committee will be established (Section 13). Following the completion of Year #1, we will examine the data for any significant differences between groups as it relates to adverse events and the primary outcome. The protocol additionally will be approved by The Hospital for Sick Children's Research Ethics Board prior to the commencing enrollment. Please see Appendix V for the consent form. Assent is not required for this study as all children will be < 4 years of age.