TEMPLATE

CLINICAL TRIAL PROTOCOL

Zinc acceptability study in children with acute diarrhoea

A prospective, open-label, (multi-centre) interventional study

Sponsor:

## Protocol authorized by

Name:

Affiliation:

Date:

Signature:

# PROTOCOL AGREEMENT FORM

I/We have read the Clinical Trial Protocol for this zinc sulfate acceptability study. I/We confirm it contains all the information for the conduct of the study in accordance with ICH E6, Good Clinical Practices (GCP) and local requirements. I/We am/are aware of the Investigator’s and (co-)Investigator´s responsibilities and I/we agree to conduct the study.

## INVESTIGATOR

Name:

Affiliation:

Date:

Signature:

## CO-INVESTIGATOR

Name:

Affiliation:

Date:

Signature:

## CO-INVESTIGATOR

Name:

Affiliation:

Date:

Signature:

Responsibilities and contacts

## INVESTIGATOR

## CO-INVESTIGATOR

## CO-INVESTIGATOR

(If a CRO is hired for the trial, name and contact information of CRO focal person should also be mentioned here.)

## SPONSOR CONTACT PERSON

Please mention the name(s) of Institutional Review Boards/Independent Ethics Committees [IRB/IECs] and their focal person(s), with contact information.

# Study Synopsis

|  |  |
| --- | --- |
| TITLE | Zinc sulfate (or other zinc salt) acceptability study in children with acute diarrhoea. A prospective, open-label, (multi-centre) interventional study |
| STUDY No. |  |
| STUDY DESIGN | Prospective, open label, (multi-centre) interventional study |
| STUDY OBJECTIVES | *Primary Endpoint:*  The adherence of children aged 3 to 59 months to the zinc sulfate product regimen.  *Secondary Endpoint:*  The palatability (taste) score of the zinc sulfate product |
| STUDY POPULATION | In total, 300 patients (150 patients below 18 months of age, 150 patients aged 18–59 months) |
| INCLUSION CRITERIA | Acute diarrhoea episode  Age 3–59 months  Signed informed consent  Caregiver must be accessible by mobile phone |
| EXCLUSION CRITERIA | Severe dehydration |
| INVESTIGATIONAL PRODUCT | Zinc sulfate (or other zinc salt)  [describe product format, tablet or syrup, strength] |
| DOSAGE | Children below 6 months: half of a 20 mg tablet, dissolved in a teaspoon of water or breast milk, once daily for 10 to 14 days  Children older than 6 months: full 20 mg tablet, dissolved in a teaspoon of water or breast milk, once daily for 10 to 14 days  (Revise this section as needed for syrup format.) |
| PRIMARY ENDPOINT | Acceptability of the zinc product. The treatment will be considered to have good acceptability if 80% of the prescribed treatment is taken by at least 70% of the children. |
| SECONDARY ENDPOINT | Taste palatability, i.e. a subjective evaluation measured on the basis of a caregiver’s report of his/her child’s behavior during the 10 to 14 days when the medicine is administered.  The caregivers are asked about the perception of taste of the zinc product given to the child.  A 5-point scale is used to classify response options. The choices are:   * 5 - Very well tolerated * 4 - Well tolerated * 3 - Tolerated * 2 - Poorly tolerated * 1 - Not tolerated   This measure is the overall response during the treatment period. Individual daily recorded responses will be helpful to arrive at the overall response value on the 5-point scale. |
| SAFETY EVALUATION | Adverse Events (AEs) identified from source data will be recorded on case report forms (CRFs). They should be reported to the Sponsor and the IRB/IEC. The Sponsor should report AEs to the local regulatory authority as required. |
| STATISTICAL CONSIDERATIONS | Statistical calculations for the primary and secondary endpoints should be outlined |

# Introduction

Zinc (Zn) is an essential mineral widely distributed within the human body in metalloproteins, Zn-binding proteins, etc. It is necessary for signal transduction, apoptosis, and also cell growth and proliferation via respective metallo- and Zn-dependent enzymes [[1](file:///C:\Users\Michelle\Documents\1.%20Yvonne%20Work\100%20Docs\1%20Originals%2031+13=44\NEXT%20to%20ck%20to%20temp-%20%23%20in%20DB%20B4%20copy%20in\57cvtr%20Zinc_Acceptability_SampleProtocol12Nov2014.docx#_ENREF_1)]. Zinc deficiency is related to many diseases, for example growth retardation, delayed sexual maturation or diarrhoea [[2](file:///C:\Users\Michelle\Documents\1.%20Yvonne%20Work\100%20Docs\1%20Originals%2031+13=44\NEXT%20to%20ck%20to%20temp-%20%23%20in%20DB%20B4%20copy%20in\57cvtr%20Zinc_Acceptability_SampleProtocol12Nov2014.docx#_ENREF_2)].

Diarrhoea is a leading killer of children, accounting for approximately 8 per cent of all deaths among children under age 5 worldwide in 2016. [[3](file:///C:\Users\Michelle\Documents\1.%20Yvonne%20Work\100%20Docs\1%20Originals%2031+13=44\NEXT%20to%20ck%20to%20temp-%20%23%20in%20DB%20B4%20copy%20in\57cvtr%20Zinc_Acceptability_SampleProtocol12Nov2014.docx#_ENREF_3)].

To combat this, the WHO and UNICEF recommend zinc supplementation (10 mg for infants less than 6 months old and 20 mg in 6–59 months old) combined with low-osmolarity oral rehydration salts [[4](file:///C:\Users\Michelle\Documents\1.%20Yvonne%20Work\100%20Docs\1%20Originals%2031+13=44\NEXT%20to%20ck%20to%20temp-%20%23%20in%20DB%20B4%20copy%20in\57cvtr%20Zinc_Acceptability_SampleProtocol12Nov2014.docx#_ENREF_4)]. Zinc supplementation during episodes of acute diarrhoea has been shown to significantly improve patient outcome and reduce diarrhoeal mortality [[5](file:///C:\Users\Michelle\Documents\1.%20Yvonne%20Work\100%20Docs\1%20Originals%2031+13=44\NEXT%20to%20ck%20to%20temp-%20%23%20in%20DB%20B4%20copy%20in\57cvtr%20Zinc_Acceptability_SampleProtocol12Nov2014.docx#_ENREF_5)].

To ensure acceptability of zinc supplements in the target population, the strong metallic aftertaste of zinc has to be masked using appropriate flavoring agents [[6](file:///C:\Users\Michelle\Documents\1.%20Yvonne%20Work\100%20Docs\1%20Originals%2031+13=44\NEXT%20to%20ck%20to%20temp-%20%23%20in%20DB%20B4%20copy%20in\57cvtr%20Zinc_Acceptability_SampleProtocol12Nov2014.docx#_ENREF_6)][[7](file:///C:\Users\Michelle\Documents\1.%20Yvonne%20Work\100%20Docs\1%20Originals%2031+13=44\NEXT%20to%20ck%20to%20temp-%20%23%20in%20DB%20B4%20copy%20in\57cvtr%20Zinc_Acceptability_SampleProtocol12Nov2014.docx#_ENREF_7)].

The chief adverse-effects of zinc sulfate include vomiting and regurgitation, which are usually transient adverse events [[8](file:///C:\Users\Michelle\Documents\1.%20Yvonne%20Work\100%20Docs\1%20Originals%2031+13=44\NEXT%20to%20ck%20to%20temp-%20%23%20in%20DB%20B4%20copy%20in\57cvtr%20Zinc_Acceptability_SampleProtocol12Nov2014.docx#_ENREF_8), [9](file:///C:\Users\Michelle\Documents\1.%20Yvonne%20Work\100%20Docs\1%20Originals%2031+13=44\NEXT%20to%20ck%20to%20temp-%20%23%20in%20DB%20B4%20copy%20in\57cvtr%20Zinc_Acceptability_SampleProtocol12Nov2014.docx#_ENREF_9)].

This protocol refers to zinc sulfate. However, other zinc salts are also invited and acceptable, per the current WHO Expression of Interest listing. The amount of elemental zinc delivered should approximate that delivered by zinc sulfate products.

# Study objectives

The primary objective of the study is to evaluate acceptability of the zinc product in management of childhood diarrhoea. The secondary objective is to assess palatability.

# Study treatments

## Investigational product: Zinc [description of zinc format, tablet or syrup, strength]

## Dosage: For tablets, half the tablet (10 mg) daily for children age 3–6 months or full tablet (20 mg) daily for children age 6–59 months. The dose will be dissolved in a teaspoon of water or breast milk and administered once daily for 10 to 14 days. For syrup, amounts of the zinc product corresponding to the above milligram doses for the appropriate age brackets.

## Packaging and labeling

Investigation product will be dispensed in a blister pack containing 10 or 14 tablets, or for syrup, in bottles.

## Randomization and unblinding procedures

### Treatment assignment

This is not a comparative study, no randomization will be conducted.

### Unblinding procedures

This is an open-label study.

## Drug accountability

The caregivers should bring the blister packs (even if all tablets are used), or bottles, to evaluate adherence at the follow up visit, if possible. The Study investigator will update accountability records of the investigational product according to ICH E6, GCP guideline.

Investigational product will not be provided to any third party.

# Study design

This is a prospective, open label, multi-center, interventional study.

# Selection of study population

## Number of subjects

A total of 300 patients will be enrolled (150 patients below 18 months and 150 patients aged 18–59 months). Additional patients may be enrolled according to local historical precedents for dropout rates, to avoid an underpowered study.

## Inclusion criteria

* Children of age 3-59 months with an acute diarrhoea episode who will be prescribed oral rehydration salts (ORS) and zinc per WHO guidelines. (Note: documentation of ORS administration is not required.)
* Documented informed consent by the caregivers
* Caregiver must be accessible by mobile phone

## Exclusion criteria

Severe dehydration (at least 2 of the following signs):

* Abnormally sleepy or lethargic.
* Sunken eyes.
* Drinking poorly or not at all.
* Skin pinch goes back very slowly (≥ 2 seconds)
* Known hypersensitivity to zinc sulfate.
* Having any medical condition that may interfere with the subject’s ability to sense or discriminate between tastes.

# Clinical procedures

## Description of study days

### Pre-trial evaluation

At the baseline visit, informed consent will be obtained, patients’ eligibility confirmed, demographic data recorded, and clinical symptoms of the diarrhoea episode evaluated. Instructions will be given regarding the dosage, acceptability criteria, evaluation and study procedure requirements.

### Study days

Patients will be followed at home with daily recordings of the 2 endpoints. Drug will be administered and evaluation will be done by the caregivers.

Phone calls to the caregivers should be done at around 5 days to assess any problems and encourage adherence to the full 10 to 14 day course. (A 10 to 14 day course of zinc has been shown to reduce the incidence of diarrhoea for 2 to 3 months.)

If the child vomits, another zinc dose should be given after a 2-hour interval.

Follow-up visit

Recording of the 2 endpoints may be done during an in-person or virtual visit, or by phone or text, following 10 to 14 days of treatment. Adverse events (e.g. vomiting) will be documented and drug accountability recorded.

## Safety monitoring

Safety will be monitored by the caregivers. The most common expected adverse event is vomiting.

# Methods of evaluation

The trial sponsor may collect data by in-person or virtual visit (visual media), or by phone or text, as circumstances require. Detailed records of all communications with caregivers must be kept, with date/time information, phone numbers, records of texts, responses for the primary and secondary endpoints, and adverse events (e.g. vomiting). These records will be audited by the WHO Inspection team after the trial is completed and prior to prequalification.

Sponsors should ensure they have adequate staffing to collect and keep records of study data.

All study documents should be kept in a format which can be inspected at a later date, including Institutional Review Board/Independent Ethics Committee (IRB/IEC) documents, Informed Consent Forms (ICF) and Case Report Forms (CRF).

## Adherence and Palatability

Adherence is the primary endpoint for the study. The dose given each day and the duration of treatment are recorded.

Adherence may be evaluated in person, by virtual (visual) visit, or by phone or text.

Palatability may also be evaluated in person, by virtual visit, or by phone or text. It is measured on the basis of a caregiver’s report of his/her child’s behavior when the medicine is administered. The caregivers are asked about their perception of the taste of the zinc tablet given to their child.

A 5-point scale is used to classify palatability response options. A hedonic scale “smiley face” line drawing with the 5 options may be used if preferred. The choices are:

* Very well tolerated
* Well tolerated
* Tolerated
* Poorly tolerated
* Not tolerated

This measure is the overall response during the treatment period. Individual daily recorded responses will be used to arrive at the overall average response value on the 5-point scale.

## Safety

## Vomiting is the most likely adverse event. The safety population will include all subjects who received at least one dose of the investigational product under study. Descriptive statistics will be used to summarize adverse events, safety results and demographic variables. Reasons for dropouts and timing will be documented. Any dosing errors should be described, with any adverse events resulting.

# Statistics

## Statistical analysis

Bivariate, crude analyses of association will involve chi-square and t-tests for categorical and continuous data respectively; p values of <0.05 will be considered to be statistically significant.

### Primary end-point analysis (Adherence)

The number of days (out of the total 10 to 14 days) the child took the protocol-prescribed dose of the medicine.

### The treatment will be considered to have good acceptability if at least 80% of the prescribed treatment is taken by at least 70% of the children over the duration of 10 to 14 days, per WHO guidelines.

### Secondary end-point analysis (Palatability)

The statistical analysis will comprise the calculation of the percentage of patients who found the investigational product to have “very well-tolerated, well-tolerated or tolerated” scores (i.e. any of the upper 3 possible scores). A 95% confidence interval, using the normal approximation of the binomial distribution, will be calculated for the percentage.

### Safety analysis

Descriptive statistics will be applied.

## Sample size justification

To identify a ± 7.5% minimal difference in acceptability between children aged over and below 18 months with an anticipated 70% acceptability (p), setting the level of confidence at 95% (z = 1.95), the resulting sample size estimate is 140 children per group. To adjust for potential drop-outs, it is necessary to add 10 children in each group, for a final target sample of 300 children (150 in each age-group). Additional patients may be enrolled according to local historical precedents for dropout rates, to avoid an underpowered study.

# Regulatory requirements

## Liabilities

If a bodily injury is sustained, resulting directly from the use of the study drug, the sponsor will reimburse for reasonable physician fees and medical expenses necessary for diagnostic and treatment of only the bodily injury which is not covered by the subject’s medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the study doctor and his/her staff, in which case the sponsor would cover associated fees.

The sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance obtained by the sponsor does not relieve the Investigator and the collaborators from maintaining their own liability insurance policy. A copy of the insurance certificate will be provided to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) or regulatory authorities in countries requiring this documentation.

## Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The investigators agree to provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate documents, including a copy of the protocol/amendments, case report forms (CRFs), informed consent forms (ICFs), advertising text (if any), investigator’s brochure (if any) and any other written information provided to caregivers of study subjects. The trial will not begin until the investigators have obtained the IRB/IEC favorable written approvals for all of the appropriate study documents.

In the event that the protocol is amended, the revised protocol must be approved by the IRB/IEC prior to its implementation, unless changes are simply administrative in nature. If a revised informed consent form is introduced during the study, each subject’s further consent must be obtained. The new version of the informed consent form must be approved by the IRB/IEC, prior to subsequently obtaining consent from the caregiver of each subject.

It is the sponsor’s responsibility to submit the protocol and its amendments (if any), and the informed consent forms to regulatory authorities when necessary.

## Informed consent form (ICF)

Before inclusion in the study, caregivers/parents/legal representatives of each prospective subject will be given a full oral and, if possible, written explanation of the purpose of the study, the procedures to be carried out and the potential hazards. Informed consent may be obtained in-person, virtually or by phone if necessary. In this case, confirmatory evidence must be present, in the form of electronic or printed records.

Once this essential information is provided to the caregivers/parents/legal representatives and once the physician in charge or designee has the conviction that they understand the implications of participating in the study, the caregivers/parents/legal representatives will be required to provide properly executed written or verbal (phone) informed consent prior to enrollment. Caregivers will be assured that they may withdraw the child from the study at any time without jeopardizing their medical care.

It is important to note that the ICF as approved by the IRB/IEC should be used to document consent taken from the caregivers/parents/legal representatives. The executed ICF documents may be the subject of on-site inspection, and must be retained appropriately.

## Case report form (CRF)

Per ICH E6 Good Clinical Practices, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject. The sponsor will supply specific instructions on the collection of the CRFs and handling of the data.

It is important to note that the CRF as approved by the IRB/IEC should be used to document study related observations. The executed CRFs (paper or electronic) must be retained and available for on-site inspection.

## Record retention

Per ICH E6 (R2), section 4.9.0, “The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site’s trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).”

The investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The investigator will retain the study documents 10 years after the completion or discontinuation of the clinical trial in line with national standards and/or local laws.

## Monitoring of the study

Monitors should be appointed by the sponsor. The sponsor should determine the appropriate extent and nature of monitoring. The monitor should ensure that the trial is conducted and documented properly. The monitor may visit the study facilities at any time (in-person or virtually) in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. Monitoring of the study should be conducted in line with ICH E6 requirements.

The executed monitor document (paper or electronic) should be retained for on-site inspection.

## Premature termination or suspension of a study

The study may be prematurely terminated in given circumstances:

* + - * if the information on the product leads to doubt as to the benefit/risk ratio
      * if the investigator has received from the sponsor all investigational product, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon
      * in the event the results of the clinical trial do not appear to be scientifically convincing to the sponsor
      * if the aim of the clinical trial has become outdated or is no longer of interest
      * in the event of breach by the investigator of a fundamental obligation under this agreement, including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for Good Clinical Practice;
      * if the total number of patients is reached earlier than expected.

# References

1. C. F. Mills, Zinc in human biology, London; New York: Springer-Verlag, 1988.
2. S. Prasad, Zinc deficiency in human subjects: proceedings of an International Symposium held in Ankara, Turkey, April 29–30, 1982, New York: A.R. Liss, 1983.
3. UNICEF 2018, Diarrhoea remains a leading killer of young children, despite the availability of a simple treatment solution.

https://data.unicef.org/topic/child-health/diarrhoeal-disease/#

1. W. U. J. Statement, "Clinical Management of Acute Diarrhoea," WHO and UNICEF, eds., 2004.
2. Z. A. Bhutta, R. E. Black, K. H. Brown, J. M. Gardner, S. Gore, A. Hidayat, F. Khatun, R. Martorell, N. X. Ninh, M. E. Penny, J. L. Rosado, S. K. Roy, M. Ruel, S. Sazawal, A. Shankar, and Z. I. C. G, “Prevention of diarrhoea and pneumonia by zinc supplementation in children in developing countries: Pooled analysis of randomized controlled trials,” Journal of Pediatrics, vol. 135, no. 6, pp. 689–697, Dec, 1999.
3. D. Nasrin, C. P. Larson, S. Sultana, and T. U. Khan, “Acceptability of and adherence to dispersible zinc tablet in the treatment of acute childhood diarrhoea,” Journal of Health Population and Nutrition, vol. 23, no. 3, pp. 215–221, Sep, 2005.
4. S. Awasthi, A. da Cunha, L. F. Dans, H. F. El Sayed, G. V. Gregorio, D. Jain, S. Lulseged, A. Madeiro, and I.-Z. Grp, “Zinc supplementation in acute diarrhoea is acceptable, does not interfere with oral rehydration, and reduces the use of other medications: A randomized trial in five countries,” Journal of Pediatric Gastroenterology and Nutrition, vol. 42, no. 3, pp. 300–305, Mar, 2006.
5. P. Larson, A. B. Hoque, C. P. Larson, A. M. Khan, and U. R. Saha, “Initiation of zinc treatment for acute childhood diarrhoea and risk for vomiting or regurgitation: a randomized, double-blind, placebo-controlled trial,” J Health Popul Nutr, vol. 23, no. 4, pp. 311–9, Dec, 2005.
6. M. Khan, C. P. Larson, A. S. Faruque, U. R. Saha, A. B. Hoque, N. U. Alam, and M. A. Salam, “Introduction of routine zinc therapy for children with diarrhoea: evaluation of safety,” J Health Popul Nutr, vol. 25, no. 2, pp. 127–33, Jun, 2007.