Clinical Protocol

204477

CONFIDENTIAL

SUMMARY INFORMATION

Title:	Clinical study to measure the impact of fortified malt based food on immunity outcomes in school children
Protocol Number:	204477
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH) Plot Number 67, Sector 32, Gurgaon, Haryana, India Ph - PPD
Product Name:	Fortified malt based food
Development Phase:	NA

Expert Advice Outside of Normal Working Hours:	Dr PPD, MD, GSKCH Tel: PPD

Key Protocol Authors:	
PRIMARY CONTACT **Clinical Study Manager:**	PPD, MSc., GSKCH Research & Development Centre, Plot no.67, Sector – 32, Gurgaon, 122001, Haryana, India Tel: PPD Fax: PPD
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Medical Lead:	Dr. PPD, MD, GSKCH
Other Protocol Authors:	

Clinical Supplies:	PPD, GSKCH
Data Manager:	PPD, M Pharm, GSKCH
Medical~~/ Dental~~ Expert:	Dr PPD, MBBS, MSc., GSKCH

Principal Investigator:	Dr Anuradha Khadilkar, MBBS, MD
Study Site Name & Address:	Jehangir Clinical Development Centre, Sassoon Road, Pune, Maharashtra, India Study Sites: ~~1. Genba Sopanrao Moze Prashala (English & Marathi Medium), 191/A Nagpur Chawl road, Maharashtra Co-operative Housing Board, Yerawada, Pune 411006~~ ~~Don Bosco high school, Shastri Nagar chowk, near IBM, Don Bosco road , Yerwada Pune Maharashtra 411006~~ **1. DON BOSCO HIGH SCHOOL SHASTRI NAGAR CHOWK, NEAR IBM, DON BOSCO ROAD, YERWADA, PUNE 411006** 2. Chaitanya English Medium School, Area No: 588, Rasta Peth, Pune Maharashtra 411011 ~~Utkarsh English Medium School, Area No: 278, next to community hall, opposite Saint Annes church,~~

	~~Solapur Bazar, Camp, Pune 411001~~ ~~Dhole Patil Government school, Dhole Patil road, Pune 411001~~ 3. **SANEGURUJI MARATHI MEDIUM SCHOOL, MAHARASHTRA AROGYA MANDAL, MALWADI HADAPSAR, PUNE 411028** 4. **FATHER AGNEL'S VIDYANKUR ENGLISH SCHOOL, VADGAONSHERI, PUNE 411026** **BACK-UP SCHOOL** ~~**ST FRANCIS HIGH SCHOOL, 25/2 NARVEER TANAJIWADI, SHIVAJINAGAR PUNE 411005**~~ 1. **PHOENIX ENGLISH MEDIUM SCHOOL, TUKARAM NAGAR, CHANDAN NAGAR, PUNE 411014** 2. **LATE BANDOJI KHANDOJI CHAVAN SCHOOL SURVEY NO 48 INDRAPRASTH NAGAR SHOBHAPUR, DHAYARI PUNE, MAHARASHTRA 411041**

Study Site Telephone Number:	PPD
Study Examiner(s):	NA

Clinical & Analytical Laboratory:	InterVein Laboratories Private Limited, Shapath IV, B501-502-503 S. G. Highway, Ahmedabad 380054, Gujarat, India

Contract Research Organisation (CRO):	ClinTec International Ltd. # 380, 2nd Floor ITTINA Center Service Road, Koramangala 3rd Block, Bangalore - 560 034, India

Regulatory Agency Identifier Number (if applicable):	NA

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol and any amendments and according to the current ICH GCP guidelines.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	Dr Anuradha Khadilkar
Investigator Qualifications:	MBBS, MD
Investigator Signature:	PPD
Date of Signature/ Agreement:	DD/MMM/YYYY

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PROCESS FOR AMENDING THE PROTOCOL

Protocol modifications to ongoing studies which could potentially adversely affect the safety of participants or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of participants treated, or subject selection criteria are considered major/substantial amendments and must be made only after appropriate consultation between an appropriate representative of GSKCH and the investigator.

Details of amendments to the protocols should be recorded on the following page. Protocol modifications must be prepared by a representative of GSKCH. All changes must be justified in the Reason for Amendment section of the following Protocol Amendment Page. Approval of amendments will be made by the original protocol signatories or their appropriate designees.

All major/substantial protocol modifications must be reviewed and approved by the appropriate IRB/IEC in accordance with local requirements, before the revised edition can be implemented.

All non-substantial/ minor/ administrative amendments should be submitted to the IRB/ IEC as per country specific requirements. In some countries pre-approval of a minor amendment is not required and will just be held on file by the sponsor and investigator.

PROTOCOL AMENDMENT PAGE

Details of all amendments should be recorded in the table below. Affected sections should be listed in the table; the actual amendment/ change should be made in the relevant section of the main protocol.
To highlight the change, the following features will be used:
To **add** text: Use of **CAPITAL LETTERS, BOLD AND UNDERLINE**
To **delete** text: Use of Strikethrough e.g. ~~strikethrough~~

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 1 **Protocol Version No.: 3.0**	Non-Substantial/Minor ☐ Substantial/ Major ☒	**Reduction in Zinc level on test product** Zinc level has been reduced so that its maximum value (including overages) in the test product anytime remains within both recommended and safe limits.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Section 12.2	Signature: PPD Date: PPD
Amendment No.: 2 **Protocol Version No.: 3.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Change in product formulation code** The test product formulation has been revised basis the revised Zn levels and so has	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No	1. Brief summary 2. Section 5.1	Signature: PPD Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
		been the formulation code.	CRF ☐ Yes ☒ No		
Amendment No.: 3 **Protocol Version No.: 3.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Inclusion of 'designated Contract Research Organisation (CRO)' in the text related to guiding policies and standard operating procedures under study governance** To clarify text with regards to CRO management activities.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Section 10.2 2. Section 10.3 3. Section 10.5	Signature: PPD Date: PPD
Amendment No.: 4 **Protocol Version No.: 4.0**	Non-Substantial/Minor ☐ Substantial/ Major ☒	**Putting measures in place in regard to storage and disposal of Human Biological Samples (HBS)** To clarify text with regard to storage and disposal of HBS, conditions such as a) issuance of study report, b) expiry of stability at -70℃	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Section 6.9	Signature: PPD Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
		and c) withdrawal of consent for analysis of samples, have been specified.			
Amendment No.: 5 **Protocol Version No.: 4.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Allowing supine position also for blood collection.** Collecting blood from children in lie down position on bed will be less painful and can avoid panic.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Section 6.9.1.3	Signature: PPD Date: PPD
Amendment No.: 6 **Protocol Version No.: 4.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Specifying types of topical anesthetic to be applied before collecting blood samples** For better clarity, examples for topical anesthetic ointment such as lidocain, tetracain *etc* are added.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Section 6.9.1.3	Signature: PPD Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 7 **Protocol Version No.: 4.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Selection criterion of schools being located in peri-urban areas has been removed.** To avoid any restriction and ambiguity and thus facilitating selection of schools, such criteria is omitted.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Section 3.4 2. Section 6.1	Signature: PPD Date: PPD
Amendment No.: 8 **Protocol Version No.: 4.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Severity classification of GI and respiratory illnesses as assessed by physician given in section 6.11.2 is to be modified and to be done as per criteria specified in appendix 5.** There is slight mismatch in severity classification by physician as described in section 6.11.2 and appendix	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Section 6.11.2	Signature: PPD Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
		5. To make it uniform, assessment of severity of illnesses is to be done as per criteria mentioned in appendix 5.			
Amendment No.: 9 **Protocol Version No.: 4.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**List of study sites (schools) is modified.** Some of previously selected schools have opted out of the study. New schools have now been selected including one as back up.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Summary Information	Signature: PPD Date: PPD
Amendment No.: 10 **Protocol Version No.: 4.0**	Non-Substantial/Minor ☒ Substantial/ Major ☒	**Vitamin B6 and C are removed from list of micronutrients to be analysed in blood.** Due to blood sample processing (centrifugation) requisites needed for	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Protocol synopsis 2. Section 2 3. Section 3.1 4. Section 9.3.3	Signature: PPD Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
		analytes, viz., Vitamin B6 and C, it would be difficult to maintain their stability in the collected samples. Thus considering feasibility, particularly at site (schools), Vitamin B6 and C have been dropped from the list of micronutrients planned to be analysed in the study.			
Amendment No.: 11 **Protocol Version No.: 4.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Full forms of abbreviations *e.g.* HBS and CTCAE are specified.** These abbreviations were missed to be defined in 'Abbreviations and Trademarks' appendix of previous version of protocol.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Section 12.1	Signature: PPD Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 12 **Protocol Version No.: 4.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Initial HBS storage temperature and duration specifications, immediately after its collection, have been changed** Immediately after collection of HBS it is more appropriate that they are stored for not more than 4 hrs at 2-8 C°. Thus initial HBS storage temperature and duration specifications, immediately after its collection, have been changed from 'less than 4 C° for no longer than 24 hrs' to '2-8 C° for no longer than 4 hrs'.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Section 6.9	Signature: PPD Date: PPD
Amendment No.: 13 **Protocol Version No.: 4.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Version number of Pulse COOximeter (Masimo Pronto), the instrument to be used to measure Hb, will be removed.** Newer version of non	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No	1. Section 6.9	Signature: PPD Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
		invasive spectrophotometry based instrument (Masimo Pronto 7 Pulse COOximeter) is available now. We may use a different (and not Pronto 7) version of this instrument in the study. Thus the version number of the instrument will not be specified in the protocol to avoid protocol deviation.	CRF ☐ Yes ☒ No		
Amendment No.: 14 **Protocol Version No.: 5.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Size of vacutainers to collect blood samples is changed** Instead of 7 ml sized vacutainer, blood samples will be collected in two 3.5 ml sized vacutainers. Total collected blood volume will remain same.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Section 6.9.1. 3	Signature: PPD Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 15 **Protocol Version No.: 5.0**	Non-Substantial/Minor ☒	**Typo error of blood collection time point is corrected** Blood collection timing is inadvertently mentioned at 'baseline and screening' instead of 'baseline and end of study'.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Section 6.9.1. 3	Signature: PPD Date: PPD
Amendment No.: 16 **Protocol Version No.: 5.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Type of vial to collect urine samples for lactulose mannitol is changed** Instead of specified cryo-vials, different vials (ria vials) will be used.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Section 6.9.1. 1	Signature: PPD Date: PPD
Amendment No.: 17 **Protocol Version No.: 5.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Type of vial to collect urine samples for urinary neopterin test is changed** Instead of specified cryo-vials, different vials (conical bottom tubes) will be used.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF	1. Section 6.9.1. 1	Signature: PPD Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
			☐ Yes ☒ No		
Amendment No.: 18 **Protocol Version No.: 5.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**List of study sites (schools) is modified.** Some of previously selected schools have opted out of the study. New schools have now been selected including two as back up.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Summary Information	Signature: PPD Date: PPD
Amendment No.: 19 **Protocol Version No.: 5.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Order of activities for baseline and end of study visit will not be specified.** Order of human biological samples (blood, saliva and urine) collection will be followed as per operational feasibility and convenience of children at sites.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	1. Protocol synopsis 2. Section 3.1 Study design	Signature: PPD Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 20 **Protocol Version No.: 5.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Last Study Physician Weekly Review conduct day of the study is specified.** Currently last SPWR conduct day is specified with respect to product administration only. Thus it is applicable to test group and not for control group. Thus, so as to standardize it in both the groups, last SPWR will be conducted on end of study visit day, even if symptoms are assessed for less than a week in symptom checklist form.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No		Signature: PPD Date: PPD
Amendment No.: 21 **Protocol Version No.: 5.0**	Non-Substantial/Minor ☒ Substantial/ Major ☐	**Timeline for writing statistical reporting and analysis plan of study is changed.** In compliance with GSK	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No	1. Section 9.3	Signature: PPD Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
		SOP, timeline of writing statistical reporting and analysis plan is changed from 'prior to study start (first subject first visit (FSFV)' to 'study analysis'.	CRF ☐ Yes ☒ No		

SCHEDULE OF EVENTS

Activity	Visit 1	Visit 2	Dietary Counselling Visits[1] Visit 3: Session 1-Day1-3 of Week 1 from BV Visit 4: Session 2-Week 2 from BV+ up to 3 days Visit 5: Session 3-Week 6 from BV+ up to 3 days Visit 6: Session 4-Week 10 from BV+ up to 3 days Visit 7: Session 5-Week 14 from BV+ up to 3 days Visit8: Session 6-Week 18 from BV + up to 3 days Visit 9: Session 7-Week 22 from BV + up to 3 days	SPWR & parent/LAR symptom checklist	Visit 10
	Screening Visit	Baseline Visit (+1 to 21 days post screening visit)			End of Study Visit (+ 1 to 7 days post end of 9 month from baseline visit)
Informed consent and assent[2]	X				
Demographics	X				
Medical history	X				
Current/concomitant medication	X	X	X		X
General physical examination	X				X
Vital signs	X				X
Hb assessment using Pronto	X				
Anthropometric measurements (height, weight, BMI and HAZ)	X				X
Inclusion/exclusion criteria evaluation	X				
Subject Eligibility	X				
24 hr dietary recall & Dietary Diversity Survey	X			SPWR will initiate 1 week (+up to 2 days) post first dietary counselling visit of the participant and will continue on a weekly basis (+ up to 2 days) until End of Study Visit.	X
Parental/LAR training to complete 'symptom check list'[3]	X				
Dispense blank Parent/LAR symptom checklist and Product Compliance Report Forms	X			Parent/LAR symptom checklist & Product Compliance Report Forms will be collected and reviewed for each weekly review with the physician	
Continued eligibility criteria		X	X		X
Sample collection for urinary neopterin test & lactulose/mannitol test		X			X
Sample collection for analysis of serum ferritin, sTfR, CRP, AGP, sIgA & nutritional biochemistry		X			X
Dietary counselling			X		
Product administration (applicable to test group only)[4]			X		
Product compliance check & collect empty product sachet (applicable to test group only)			X		
AE monitoring		X	X		X
Study Completion and medical sign off					X

[1] Session number 3, 4, 5, 6 and 7 can be postponed in view of long school holidays and exams. Session no 7 will not be conducted any later than the last day of 8th month of intervention period. A minimum of 4 weeks gap must be maintained between session number 2, 3, 4, 5, 6 and 7.

[2] Obtaining informed consent and assent and performing screening activities can be on different dates but informed consent and assent will be obtained prior to performing and applying any screening criteria or procedures. Screening activities should be within 60 days of obtaining consent and assent.

[3] Can be done anytime post obtaining Consent & Assent but prior to baseline visit.

[4] Intervention begins +1 to 3 days from baseline visit and continues for 9 months. Compliance check, test product empty sachets will be collected and AE will be recorded throughout the intervention period.

PROTOCOL SYNOPSIS FOR STUDY 204477

Brief Summary

The importance of public health intervention lies with the concept of the 'Continuum of care' approach. While there already exists a lot of information on the prevalence of nutritional inadequacy and its effects on morbidity and mortality from common childhood illnesses for children under 5 years of age, unfortunately, similar information on children older than 5 years of age is scarce. A nutritional intervention program will benefit an adolescent age group (11-19 years) only if there is continuity of care for primary school age children (6-10 years) also.

There is a wide-spread prevalence of concurrent micronutrient deficiencies, even in apparently normal school age children in India. Sometimes even apparently healthy school children may have sub-clinical deficiencies. Various studies and dietary surveys such as those conducted by the Indian Council of Medical Research indicate that the micronutrient intakes of school age children in India are much below the recommended levels.

Adequate amounts of micronutrients are required for the immune system to function effectively. Micronutrient deficiencies can have far-reaching health consequences, contributing to impairments in growth, neurobehavioral function, and immune competence, as well as increases in morbidity and mortality. Micronutrient deficiencies and childhood morbidities have been found to co-exist. Macronutrients also have significant role to play in proper functions of immune system. Protein-energy malnutrition is known to cause impaired immunity and increased susceptibility to infections. Many cells of the immune system depend for their function on metabolic pathways. In India, the most common diseases encountered during childhood are diarrhoea and acute respiratory illnesses (ARIs). These illnesses are a threat to the normal growth and development of a child.

The relationship between micronutrient deficiency and morbidities or mortalities from illness in school age children are well-documented; but, there is a dearth of evidence on the effectiveness of multiple nutrient (MN) supplementation on these parameters in school age children.

Therefore, this clinical study is proposed to test the hypothesis that a fortified malt based food may help improve immunity outcomes in school children 7 to 10 years of age. This study will be funded by GlaxoSmithKline Consumer Healthcare (GSKCH)

and will be run in India as a cluster randomised, open label controlled study. Participants will be recruited from schools in India.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the total number of ill days due to gastrointestinal (GI) and respiratory illnesses in participants receiving fortified malt based food (test product) with dietary counselling in comparison to participants receiving only dietary counselling over a period of nine months.	• Total number of ill days due to GI and respiratory illnesses.
Secondary	
• To compare the following parameters in participants receiving the fortified malt based food (test product) along with dietary counselling to participants receiving only dietary counselling over a period of nine months:	
1. Frequency of GI and respiratory illnesses.	1. Number of episodes of GI and respiratory illnesses.
2. Severity of GI and respiratory illnesses.	2. Severity of GI and respiratory illnesses.
3. School absenteeism due to GI and respiratory illnesses.	3. School absenteeism due to GI and respiratory illnesses.
4. Change from baseline (measured at screening) in body mass index (BMI).	4. BMI at screening and end of study.

5. Change from baseline in gut integrity/health as measured by Lactulose Mannitol test.	5. Gut integrity/health as measured by Lactulose Mannitol test at baseline and end of study.
6. Change from baseline in gut integrity/health as measured by Urinary Neopterin test.	6. Gut integrity/health as measured by Urinary Neopterin test at baseline and end of study.
7. Change from baseline in mucosal immunity as measured by Salivary Immunoglobulin A (IgA) status.	7. Salivary Immunoglobulin A (IgA) status at baseline and end of study.
8. Change from baseline in levels of micronutrients Vitamin A, ~~B6,~~ B12,~~C,~~ D (25-hydroxycholecalciferol), E, folate, of the trace elements selenium, zinc, copper, and iron as determined by blood draw and analysis.	8. Levels of micronutrients Vitamin A, ~~B6,~~ B12,~~C,~~ D (25-hydroxycholecalciferol), E, folate, of the trace elements selenium, zinc, copper, and iron at baseline and end of study
9. Change from baseline levels of ferritin, serum transferrin receptor (sTfR), C-reactive protein (CRP), and Alpha 1-acid glycoprotein (AGP) as determined by blood draw and analysis.	9. Levels of ferritin, serum transferrin receptor (sTfR), C-reactive protein (CRP), and Alpha 1-acid glycoprotein (AGP) at baseline and end of study.
10. Change from baseline (measured at screening) in dietary diversity score, assessed through 24-hour Individual Dietary Diversity Score (IDDS)	10. Dietary diversity score assessed through 24-hour IDDS at screening and end of study.
11. Change from baseline (measured at screening) in energy, protein, carbohydrates and fat consumption, assessed through	11. Intake of energy, protein, carbohydrate, and fat from 24-hour dietary recall survey at screening and end of study.

24-hour dietary recall survey	

Study Design

Overall Design
This is a single centre, multiple sites, open label, two-arm, parallel-group, stratified by gender, matched pair cluster randomised, controlled study.
Visit 1 - Screening Visit
The following assessments will be conducted in the order written post randomisation of clusters: • Informed consent and assent • Demographics • Medical history • Current/concomitant medications • General physical examination • Vital signs • Hb assessment using Pronto • Anthropometric measurements (height and weight) • Inclusion/exclusion criteria evaluation • Subject Eligibility • 24 hr dietary recall & dietary diversity survey • Parental/LAR training on the completion of the 'Symptom Check List' • Dispense blank Parent/LAR Symptom Checklist and Product Compliance Report Forms

Visit 2 - Baseline Visit
The following assessments will be conducted ~~in the order written~~: • Current/concomitant medications • Continued eligibility criteria • Sample collection for urinary Neopterin test & lactulose/mannitol test • Sample collection for analysis of serum ferritin, sTfR, CRP, AGP, sIgA & nutritional biochemistry (for micronutrients vitamins A, ~~B6,~~ B12, ~~C,~~ D, E, folate, and of the trace elements selenium, zinc, copper, and iron) • Adverse Event (AE) monitoring
Visit 3, 4, 5, 6, 7, 8, 9, SPWR and Product Administration Visits
The following assessments will be conducted: • Current/concomitant medications • Continued eligibility criteria • Dietary counselling will be administered to all study participants and their parents/LARs. • Test product will be administered to all study participants in the test group only. • SPWR visits will be conducted on a weekly basis until End of Study Visit. Parent/LAR symptom checklist & Product Compliance Report Forms will be collected and reviewed. • Adverse Event (AE) monitoring
Visit 10 - End of Study Visit
The following assessments will be conducted ~~in the order written~~: • Current/concomitant medication • General physical examination

- Vital signs
- Anthropometric measurements (height and weight)
- Continued eligibility criteria
- 24 hr dietary recall & dietary diversity survey
- Sample collection for urinary Neopterin test & lactulose/mannitol test
- Sample collection for analysis of serum ferritin, sTfR, CRP, AGP, sIgA & nutritional biochemistry (for micronutrients vitamins A, ~~B6,~~ B12,~~C,~~ D, E, folate, and of the trace elements selenium, zinc, copper, and iron)
- AE monitoring
- Study completion and medical sign-off

Type and Planned Number of Participants

Approximately 1300 participants will be screened in at least 4 clusters (with at least 2 clusters per study arm), to randomise approximately 924 participants to ensure 646 evaluable participants complete the entire study. This will ensure at least 323 evaluable participants per study arm.

Diagnosis and Main Criteria for Inclusion

Boys and girls, aged 7 to 10 years inclusive with HAZ of ≥-3 to ≤-1 will be invited to participate in this study.

Product Information

	Test Group	Control Group
Product Name	Fortified malt based food	No treatment
Product Formulation Code	CCI [redacted]	N/A
Dose	27 grams	N/A

Route of Administration	Oral	N/A
Dosing Instructions	27 grams powder made up in 150 mL lukewarm water administered twice daily	N/A

Statistical Methods

The primary efficacy variable of the study is the impact of treatments on the number of ill days. The number of ill days will be analysed using the analysis of variance (ANOVA). The ANOVA will have treatment, cluster (school) and gender as fixed effects. Comparisons will be made between test and control groups at 5% significance level. Ninety-five percent confidence intervals will also be constructed.

1. INTRODUCTION

The immune system is the body's defence against disease-causing organisms, malfunctioning cells, and foreign particles. Further, resistance to a disease-causing organism or harmful substance is termed "immunity". This ability to offer resistance to a disease can become compromised if nutrition is inadequate.

Substantial research has focused on the role of nutrition and especially on the contribution of vitamins and minerals to the optimum functioning of the immune system. It has been demonstrated that adequate amounts of micronutrients are required for the immune system to function effectively. Available data indicate a role for vitamins A, D, E, B6, B12, folate, and vitamin C, and of the trace elements selenium, zinc, copper, and iron in the proper working of the immune system [Wintergerst *et al* 2007].

Micronutrient deficiencies are widespread in many developing countries in whichstaple diets are predominately rice-based, intakes of animal-sourced foods are low [Winichagoon P 2002], and regional soil iodine and zinc levels are low [Wanaratna *et al*. 1997 & Alloway BJ 2004]. Children are particularly at risk for such deficiencies as a result of excessive losses of iron, zinc, and/or vitamin A arising from infectious diseases and/or parasitic infections [Filteau SM *et al*. 1994, Koski KG *et al*. 2001 & Egger RJ *et al*. 1990]. Interactions between co-existing deficiencies of vitamin A and iron [Bloem MW 1995 & Bloem MW *et al*. 1989] and vitamin A and zinc [Christian P *et al*. 1998 & Udomkesmalee E *et al*. 1992] may also occur, which may further exacerbate some of these micronutrient deficiency states. Such deficiencies can have far-reaching health consequences, contributing to impairments in growth, neurobehavioral function, and immune competence, and increases in morbidity and mortality [Viteri FE *et al*. 2002]. Macronutrients also have significant role to play in proper functions of immune system. Protein-energy malnutrition is known to cause impaired immunity and increase susceptibility to infection. The most consistent changes in immune competence in PEM are in cell-mediated immunity [McMurray DN *et al.* 1981, Chandra RK 1974]. Depression of cell mediated immunity by PEM could be the result of an absolute or relative deficiency of amino acids for cell multiplication. Moreover, children with PEM are known to have raised levels of plasma cortisol [Soliman AT *et al.* 2000], which can affect the thymic hormones synthesis from thymolymphatic system and result in repeated infections.

There is a wide-spread prevalence of concurrent micronutrient deficiencies, even in apparently normal school age children in India. According to a study by Sivakumar *et al* (2006), a staggering proportion of healthy school children have sub-clinical

deficiencies and/or inadequate micronutrient intakes. Approximately 45-65% of the school children had deficiencies of vitamins B2, B6, and B12. Studies so far have reported anaemia prevalence as high as 42 to 63% in this age group [Gomber *et al*. 2003, Kumar *et al*. 2003, Rao *et al*. 1980, Sethi *et al*. 2003, Sivakumar *et al*. 2006]. Furthermore, dietary surveys indicate that the micronutrient intakes of school age children in India are much below (approximately 30-70%) the recommended levels [Vijayraghavan *et al*. 2000, Sivakumar *et al*. 2006, NNMB 2006]. In a recent randomised, double blind, placebo controlled study conducted by an accredited academic institute in collaboration with GlaxoSmithKline (GSK) [Vaz *et al*. 2011], micronutrient deficiencies of riboflavin and B12 were found to be 88% and 17%, respectively, in apparently healthy school going children (7-10 years).

Micronutrient deficiencies and childhood morbidities have been found to co-exist [Patwari AK 1999]. In India, the most common diseases encountered during childhood are diarrhea and ARIs [Sarkar *et al*. 2013]. Other studies have shown these illnesses to be common across the developing world [Castro *et al*. 2003, Hussain *et al*. 1999]. These illnesses are a threat to the normal growth and development of a child.

Diarrhea and malnutrition often occur in a vicious cycle, with one condition perpetuating the other. It has been found that pre-existing nutritional deficits cause reduced turnover of epithelial cells of the gastrointestinal (GI) lining, resulting in delayed recovery [Patwari AK 1999]. Malnutrition can also compromise the body's defence mechanism thereby making the intestinal lining more vulnerable to colonisation by pathogenic microbes [Patwari AK 1999]. Diarrhea, in turn, causes further loss of nutrients [Bhandari *et al*. 2014, Thacker N. 2007] and hence an exacerbation of the diarrhea and the malnutrition. Several epidemiological studies have demonstrated a negative correlation between diarrhea and physical growth and development [Patwari AK 1999, Torres *et al*. 2000].

Like diarrhea, ARIs are also common illnesses during childhood [Couriel J 2002]. ARIs can further be categorised as upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs). The upper respiratory tract mucosa is the primary site for respiratory virus contact [Bartley J 2010]. URTIs are known to be the most common and include infections like rhinitis (common cold), sinusitis, ear infections, acute pharyngitis, epiglottis, and laryngitis [Simoes *et al*. Text Ch 25]. Such infections have the potential of leading to severe complications, thereby affecting the growth and development of a child.

Many studies have demonstrated the efficacy or the potential importance of single micronutrients in reducing the incidence, duration and or severity of these common illnesses in children. In a double-blind, randomised, placebo controlled trial conducted in Indian children; it was found that zinc administration, alone, significantly reduced the incidence of acute and prolonged diarrhea. It also reduced the recurrence of diarrhea in these children [Bhandari *et al*. 2014]. In a pooled analysis of randomised controlled trials, zinc administration was demonstrated to expedite recovery from diarrhea [Bhutta *et al*. 2000]. Vitamin D deficiency has been associated with increased incidence and duration of URTIs across ages [Uysalol *et al*. 2013, Cheng-Shiun *et al*. 2013]. In a study conducted in school age children in Bogota, Colombia, Vitamin A deficiency was found to be associated with increased risk of GI and respiratory morbidity [Thornton *et al*. 2014]. The proposed mechanism of action of Vitamin A in reducing respiratory infections is through increased expression of enzymes of the aldehyde dehydrogenase 1A family (ALDH1A) in respiratory tract epithelial cells [Rudraraju *et al*. 2014].

Though these studies demonstrate the importance or the potential importance of micronutrients in supporting the proper functioning of the immune system, in no study has the impact of an MN supplement on these parameters in school age children in India been investigated. Correcting nutritional inadequacy in school age children is critical for optimising child growth and capacity to learn, thereby building a solid foundation for the child's future. Increased morbidity from illnesses that are common in childhood (such as a greater frequency of illnesses, a longer duration of illness, or increased illness severity) is likely to result in increased school absenteeism, thereby negatively impacting total learning days and ability. Therefore, it is of utmost significance to evaluate the effect of MN supplementation in this age group, given that deficiencies are chronic and widely prevalent.

To test the hypothesis that MN supplementation can favorably impact immune functioning relative to no MN supplementation, in the proposed clinical study, children will be randomly allocated to either fortified malt based food (test) group or a control (reference) group[5]. All study participants (irrespective of group allocation), as well as their teachers and their parents or legally acceptable representatives (LARs), also will receive age-specific dietary counseling to optimise nutritional intakes, based on the Dietary Guidelines for Indians, established by the Indian

[5] To achieve double-blinding, the children in the control group would have to be administered an unfortified calorie free product. However, it was determined that it would be unethical to administer an "empty-calorie" product to growing children, as the consumption of the empty-calorie product may result in the displacement of more nutritious foods in the diet.

Council of Medical Research (National Institute of Nutrition). Thus, the test group will be administered the test product (fortified malt based food) while dietary advice shall be matched in both the test and control groups with respect to the quality, content and duration.

This proposed randomised controlled clinical study is intended to test the hypothesis that a fortified malt based food may improve immunity outcomes in 7-10 year old school age children.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine the total number of ill days due to GI and respiratory illnesses in participants receiving fortified malt based food (test product) with dietary counselling in comparison to participants receiving only dietary counselling over a period of nine months.	• Total number of ill days due to GI and respiratory illnesses.
Secondary	
• To compare the following parameters in participants receiving the fortified malt based food (test product) along with dietary counselling to participants receiving only dietary counselling over a period of nine months: 1. Frequency of GI and respiratory illnesses. 2. Severity of GI and respiratory illnesses. 3. School absenteeism due to GI and respiratory illnesses.	 1. Number of episodes of GI and respiratory illnesses. 2. Severity of GI and respiratory illnesses. 3. School absenteeism due to GI and respiratory illnesses.

4. Change from baseline (measured at screening) in body mass index (BMI).	4. BMI at screening and end of study.
5. Change from baseline in gut integrity/health as measured by Lactulose Mannitol test.	5. Gut integrity/health as measured by Lactulose Mannitol test at baseline and end of study.
6. Change from baseline in gut integrity/health as measured by Urinary Neopterin test.	6. Gut integrity/health as measured by Urinary Neopterin test at baseline and end of study.
7. Change from baseline in mucosal immunity as measured by Salivary Immunoglobulin A (IgA) status.	7. Salivary Immunoglobulin A (IgA) status at baseline and end of study.
8. Change from baseline in levels of micronutrients Vitamin A, ~~B6,~~ B12, ~~C,~~ D (25-hydroxycholecalciferol), E, folate, of the trace elements selenium, zinc, copper, and iron as determined by blood draw and analysis.	8. Levels of micronutrients Vitamin A, ~~B6,~~ B12, ~~C,~~ D (25-hydroxycholecalciferol), E, folate, of the trace elements selenium, zinc, copper, and iron at baseline and end of study.
9. Change from baseline levels of ferritin, serum transferrin receptor (sTfR), C-reactive protein (CRP), and Alpha 1-acid glycoprotein (AGP) as determined by blood draw and analysis.	9. Levels of ferritin, serum transferrin receptor (sTfR), C-reactive protein (CRP), and Alpha 1-acid glycoprotein (AGP) at baseline and end of study.
10. Change from baseline (measured at screening) in dietary diversity score, assessed through 24-hour Individual Dietary Diversity Score (IDDS).	10. Dietary diversity score assessed through 24-hour IDDS at screening and end of study.

11. Change from baseline (measured at screening) in energy, protein, carbohydrates and fat consumption, assessed through 24-hour dietary recall survey.	11. Intake of energy, protein, carbohydrate, and fat from 24-hour dietary recall survey at screening and end of study.

3. STUDY PLAN

3.1. Study Design

Overall Design
This is a single centre, multiple sites, open label, two-arm, parallel-group, stratified by gender, matched pair cluster randomised, controlled study.
Visit 1 - Screening Visit
The following assessments will be conducted in the order written: • Informed consent and assent • Demographics • Medical history • Current/concomitant medications • General physical examination • Vital signs • Hb assessment using Pronto • Anthropometric measurements (height and weight) • Inclusion/exclusion criteria evaluation • Subject Eligibility • 24 hr dietary recall & dietary diversity survey • Parental/LAR training on the completion of the 'Symptom Check List'

- Dispense blank Parent/LAR Symptom Checklist and Product Compliance Report Forms

Visit 2 - Baseline Visit

The following assessments will be conducted ~~in the order written~~:

- Current/concomitant medications
- Continued eligibility criteria
- Sample collection for urinary Neopterin test & lactulose/mannitol test
- Sample collection for analysis of serum ferritin, sTfR, CRP, AGP, sIgA & nutritional biochemistry (for micronutrients vitamins A, ~~B6,~~ B12, ~~C,~~ D, E, folate, and of the trace elements selenium, zinc, copper, and iron)
- AE monitoring

Visit 3, 4, 5, 6, 7, 8, 9, SPWR and Product Administration Visits

The following assessments will be conducted:

- Current/concomitant medications
- Continued eligibility criteria
- Dietary counselling will be administered to all study participants and their parents/LARs.
- Test product will be administered to all study participants in the test group.
- SPWR visits will be conducted on a weekly basis until End of Study Visit. Parent/LAR symptom checklist & Product Compliance Report Forms will be collected and reviewed.
- AE monitoring

Visit 10 - End of Study Visit

The following assessments will be conducted ~~in the order written~~:

- Current/concomitant medication

- General physical examination
- Vital signs
- Anthropometric measurements (height and weight)
- Continued eligibility criteria
- 24 hr dietary recall & dietary diversity survey
- Sample collection for urinary Neopterin test & lactulose/mannitol test
- Sample collection for analysis of serum ferritin, sTfR, CRP, AGP, sIgA & nutritional biochemistry (for micronutrients vitamins A, ~~B6,~~ B12,~~ C,~~ D, E, folate, and of the trace elements selenium, zinc, copper, and iron)
- AE monitoring
- Study completion and medical sign-off

3.2. Subject Restrictions

Lifestyle/ Dietary
The following lifestyle/dietary restrictions apply to study participants, post enrolment after screening: • Participants should report to the study site in a 3-hour fasted state on the day of lactulose/mannitol testing. Participants will be allowed to return to their regular diet 30 minutes after ingestion of the lactulose/mannitol test solution. • Participants must abstain from the use of all other nutritional supplements. • Participants must abstain from use of all other health food supplements.
Medications and Treatments
There are no restrictions with regards to medication use and medical treatment. As GI and respiratory illnesses are the outcomes of interest, it is expected that some of the participants may require pharmacological management of their symptoms or other

medical treatment. Use of immunosuppressive therapy *e.g.*, oral corticosteroids or chemotherapy during the course of study will be considered a protocol violation and will result in the removal of the subject from the efficacy analyses.

3.3. Type and Planned Number of Participants

Participants will be recruited from schools in the areas of the study centre. Study staff may address parents/Legally Acceptable Representatives (LARs) in parents-teachers' meetings. It is not anticipated that any advertising such as posters, leaflets, radio, etc. will be required to aid recruitment. However, these methods may be used if required.

Approximately 1300 participants will be screened in at least 4 schools (with at least 2 schools per study group), to randomise approximately 924 participants to ensure 646 evaluable participants complete the entire study. This will ensure at least 323 evaluable participants per study group.

3.4. Study Design and Dose Justification

Rationale for Study Design

This is a single centre, multiple sites, open label, two-arm, parallel-group, stratified by gender, matched pair cluster randomised, controlled study in children aged 7-10 years (inclusive).

There are several factors including ethical, administrative, compliance etc in the study which mandate randomisation at cluster level rather than at individual level. Firstly, to achieve double-blinding, the children in the control group would have to be administered an unfortified calorie free product. However, it was determined that it would be unethical to administer an "empty-calorie" product to growing children, as the consumption of the empty-calorie product may result in the displacement of more nutritious foods in the diet. Thus the control group has been decided to be not given any product. Secondly, it would not be realistic & practical to randomise individual students in a school to different treatments. Thus administrating the intervention at cluster level will increase administrative efficiency. Thirdly, there are high chances of sharing of test product (contamination) from un-blinded participants in test group to un-blinded participants in control group if they belong to same cluster (school). Contamination of control participants can have two related effects i.e. it can reduce the point estimate of an intervention's effectiveness and consequently the apparent reduction may lead to a type II error—that is, increase in chances of rejection of an

effective intervention as ineffective because the observed effect size will neither be statistically nor clinically significant. Thus with such nature of intervention it itself dictates its application at cluster level.

Schools with the following characteristics will be invited to participate in the study:

- ~~Located in peri urban areas~~
- No government or sponsored micronutrient supplementation scheme running in the past 6 months
- Mixed-gender education/co-education system of education
- No history of any outbreak or clustering of cases of infectious diseases in last month

Matching creates comparable groups at baseline and will provide 'face validity' regarding balance between treatment arms. Thus matching the clusters prior to random allocation will improve causal effect estimation by improving intergroup homogeneity. Cluster (schools) will be matched for cluster size (in context to the number of children in 7-10 yrs age group), socioeconomic profiles of students, and type of school (government subsidised or private).

After obtaining informed consent and assent, school children aged 7-10 years will be screened to identify eligibility based on the pre-defined inclusion and exclusion criteria. The children will then be allocated to their respective groups, based on the random allocation of the school to which they belong.

Nutritional deficiency and the resulting immunity outcomes can be influenced by dietetic interventions which aim to improve nutritional intakes. These interventions primarily include dietary advice to improve the nutritional quality of the diet and oral nutritional supplement intake.

To test the hypothesis that MN supplementation can improve immunological/clinical outcomes, it is pertinent that the two treatment groups are matched in terms of their background diets. Thus the test group will be administered the test product (fortified malt based food), while both the test and control groups will receive dietary advice (the quality, content and duration of the nutritional counselling will be equivalent for the two groups). Dietary counselling is intended to improve knowledge, attitude and practices as they relate to nutrition and diet, with the overall aim of improving the quality of the diet. Since the impact of parenting on diet is greatest in the early years,

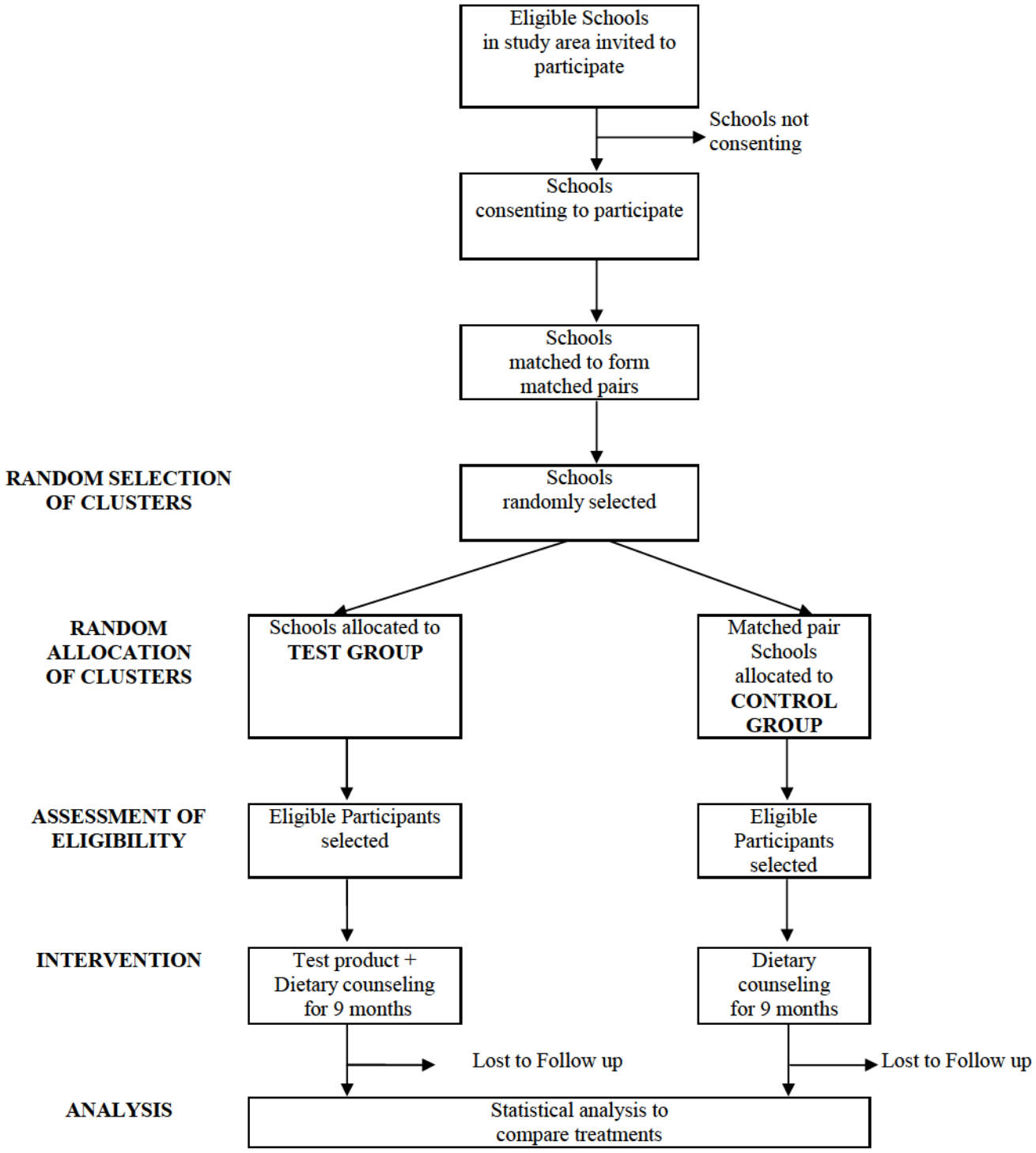
and also, as children spend significant amounts of time with school teachers, both parents and teachers will also be part of the dietary counselling. Dietary counseling will be based on the Dietary Guidelines for Indians, established by the Indian Council of Medical Research (National Institute of Nutrition).

Background diets and changes in background diets may distort the true relationship between the intervention and the outcome. To eliminate such possible confounding, it is imperative that quality of dietary intakes is assessed both at start and end of study. Since, quality of a diet is impacted by food quantity and diversity; both these variables will be assessed for all study participants. For quantitative assessment of food consumption, 24-hour dietary recall will be used. To understand the diversity of foods that the child is consuming, a 24-hour Individual Dietary Diversity Score (IDDS) [FAO guidelines dietary diversity, 2011] will be used.

Cluster sampling design may impact effective sample size, which can be mitigated using more numbers of clusters. Thus, considering feasibility, at least 2 schools per study group will be selected.

To control for possible effects of gender, a balanced ratio of boys and girls in the test and control groups will be targeted. The study will be stratified by gender to recruit a target ratio of 50% girls and 50% boys, with a minimum of 40% of either gender and a maximum of 60% of either gender.

The study flowchart will be as follows:



Rationale for Participants' Inclusion and Exclusion:

With the assumption that the study population is normally distributed for World Health Organisation (WHO) height-for-age z-scores (HAZ), reference populations within -2 to +2 standard deviations (or z score) represent 95.4 % population. But for the study participants in developing countries like India, the median for the HAZ in comparison to WHO growth standards is towards the lower side which falls at approximately -2 SD of the WHO standard curve at age 5 years [National Family Health Survey -3] [Indian Academy of Paediatrics Growth Charts Committee, 2015]. Thus a Z-score between -3 to -1 (rather than -2 to +2) would cover the representative population of developing countries like India.

Children with a prior or present diagnosis of a disease or condition which may affect immune function or nutritional status (*e.g.,* tuberculosis, AIDS, diarrheal diseases) cannot be included in the study. Usage of medications that can affect nutritional status or immune function (*e.g.,* immunosuppressive therapies, such as oral corticosteroids or chemotherapy) also will result in study ineligibility.

Rationale for Dose

Children in schools that have been randomised to receive the fortified malt based food will be administered two doses of the test product daily for 9 months. Each dose will be prepared by reconstituting a sachet of the fortified malt based food (27 grams powder) with 150 mL of lukewarm water. Thus, per day, participants in schools that have been randomised to receive the fortified malt based food will consume a total of approximately 300 mL of the product each day. The total daily dose will result in the intake of micronutrients at levels within Recommended Dietary Allowances (RDAs), as established by the WHO and also below the upper tolerable levels of the respective micronutrients, as established by Food and Nutrition Board, Institute of Medicine, National Academies.

To prevent stomach fullness as a deterrent against compliance, the interval between the two doses will be maximised during all school days. Study staff will make efforts to administer one dose as soon as the participants enter the school and the second dose will be provided just prior to school dismissal. At home, each day one dose will be administered preferably in the morning and the second dose will be administered preferably in evening, by parents/LARs.

Rationale for Schedule of Dietary Counselling Sessions

Dietary counselling shall be imparted in two phases. In first phase, complete contents of dietary education and advices will be delivered in two sessions in first two weeks of study period. While second phase, will mainly deal with the follow up of contents delivered in session 1 and 2. Follow up sessions will be conducted to reinforce the contents delivered and also to solve and satisfy any query/problem arisen while following the dietary practices. A total of five follow up sessions will be conducted post completion of two content delivery sessions.

A minimum of 4 weeks of gap between consecutive content delivery session and follow up session (i.e. between session 2 and 3); and two consecutive follow up dietary counselling sessions (i.e. between session 2, 3, 4, 5, 6 and 7) must be maintained. A gap of 4 weeks will provide adequate time to participants/ parents/LARs to practice the teaching of dietary counselling, thus enhancing efficiency and efficacy of dietary counselling.

In view of long study period, it is expected that school academic examinations dates may clash with the scheduled dietary counseling sessions. Thus, it will not be ethical to expect either participants or their parents/LARs to attend dietary counseling sessions during participant's school exams. In case, if any dietary counseling session is not conducted due to reasons such as school exams, long school holidays etc, the next session for dietary counseling will be postponed and conducted as soon as participant is available in school and exams are finished.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the safety statement.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria are established:

1. Consent and Assent
   Demonstrates understanding of the study and willingness to participate as evidenced by the parent's and/or LAR's voluntary written informed consent as well as written assent by the child and has received a signed and dated copy of the informed consent form as well as the assent form.

2. Age and Gender
   Boys and girls aged between 7-10 yrs, inclusive

3. Compliance
   Child and parent/LAR understand and are willing, able and likely to comply with all study procedures and restrictions.

4. General Health
   Good general and mental health with, in the opinion of the investigator or medically qualified designee:
   a) No clinically significant and relevant abnormalities in medical history or upon physical examination.

   b) Absence of any condition that could affect the child's safety or wellbeing or their ability to understand and follow study procedures and requirements.

5. Participants with HAZ of $\geq$-3 to $\leq$-1.

4.2. Exclusion Criteria

1. Children in Care (CiC): A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a CiC can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a CiC does not include a child who is adopted or has an appointed legal guardian.

2. Allergy/Intolerance
   Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.

3. Indication that child is likely to move out of geographical range of the study within the period of study intervention and activities, thus hindering the child's compliance to study activities.

4. Clinical Study/Experimental Medication
   a) Participation in another clinical study or receipt of an investigational drug within 30 days of the screening visit.

   b) Participation in any nutritional study or didactic nutrition education in the last 6 months of the screening visit.

   c) Previous participation in this study.

5. Child with severe anaemia (Hemoglobin <8g/dL).

6. Children with history of use of immunosuppressive therapy *e.g.*, oral corticosteroids or chemotherapy in past six months prior to the screening visit.

7. Current or relevant history of any serious, severe or unstable physical or psychiatric illness or any medical disorder that would make the participant unlikely to fully complete the study or any condition that presents undue risk from the test product or procedures, on the discretion of study physician.

8. Recent history [2 months] of serious infections, injuries and/ or surgeries in the opinion of the investigator.

9. Children consuming nutritional supplements and/or health food drinks on a regular basis (≥3 times a week) in last 3 months.

10. Personnel
    a. Child belonging to an employee of the sponsor or the study site or members of their immediate family.
    b. Sibling of a child already enrolled in the study.

4.3. Screening/ Baseline Failures

Screen failures are defined as participants who consent to participate in the study but never subsequently receive study intervention. In order to ensure transparent reporting of screen failure participants, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events. Re-screening of participants will not be allowed in this study.

4.4. Withdrawal/ Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. If a subject withdraws or is withdrawn from the study, all human biological samples collected before they left will be analysed and reported unless the subject requests otherwise. A participant may request for their human biological samples to be destroyed. In these cases, the investigator must document this in the site study records and the samples should not be used for any further research.

If the reason for removal of a subject from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the electronic case report form (CRF). If a subject is withdrawn from the study because of a product limiting AE, thorough efforts should be clearly made to document the outcome. Any AEs ongoing at the final visit will be followed up until resolved, the condition stabilises, is otherwise explained, or the subject is lost to follow-up.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed ‘lost to follow up’, the investigator or designee must make every effort to regain contact with the subject (where possible, at least 2 telephone calls). The contact attempt should be documented in the subject’s record.

- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

4.5. Subject Replacement

Participant who withdraws from the study post-randomisation will not be replaced.

4.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the date of the last subject's last visit.

5. PRODUCT INFORMATION

5.1. Study Product

The following study product will be supplied by the Clinical Supplies Department, GSKCH:

	Test Product
Product Name	Fortified malt based food
Product Formulation Code	CCI [redacted]
Dose	27 grams
Route of Administration	Oral
Dosing Instructions	27 grams powder made up in 150 mL lukewarm water, administered twice daily

Other items to be supplied by the Clinical Supplies Department, GSKCH:

Name of Item	**Purpose**
Tumblers	To assist with the addition of the correct volume of lukewarm water during the

	preparation of daily test dose and to assist with the assessment of compliance (volume remaining)
Stirrers	To assist mixing during the preparation of daily test dose

5.2. Dose Schedule

Participants will be administered two doses of the drink (approx 150 mL each) daily for 9 months. To maximise the interval between the two doses, during all school days study staff will make efforts to administer one dose as soon as the participants enter the school and the second dose will be provided just prior to school dismissal. At home, each day one dose will be administered preferably in the morning and the second dose will be administered preferably in evening, by parents/LARs.

5.3. Dose Administration

The graduated tumbler will be filled with luke-warm water up to the 150 mL mark. The entire contents of one sachet will be gradually emptied in the water filled tumbler with intermittent stirring to avoid formation of lumps. The reconstituted test product will be provided to the participants immediately for oral consumption.

On all school days, two test product doses (each dose of 27g in 150mL lukewarm water) will be provided to the participants at schools, under the supervision of trained research personnel. At schools, the test product will be reconstituted by site staff using bottled water. The participants will be given counted number of single serve sachets (27grams each) for consumption over weekends and during other school holidays and school absenteeism. The participant's parents/LARs will be informed during the consenting process on how to prepare the product in lukewarm water (boiled water will be recommended).

5.4. Dose Modification

No modification to the dosing regimen will be allowed. Any variation from the dosing regimen will be reported to the study site personnel and details will be entered on the test product administration log and then entered into the CRF.

5.5. Product Compliance

For doses administered at school, study-personnel will supervise and ensure complete consumption of test products. Random home visits will be made by site staff to ensure compliance of product consumption at home. Details of daily product consumption (including weekends, school holidays and school absenteeism) will be entered in the CRF.

In the unlikely event that the test product is incompletely consumed (due to accidental spillage, for instance) or not administered, this will also be noted in the CRF along with the product volume that was not consumed (in case of incomplete consumption). In case this happens at home, parents/LAR will need to enter details in the Product Compliance Report (Appendix 4). Site staff will dispense as many blank reports as appropriate for recording details. Each report will be numbered in an ascending order (for each participant) and records should be maintained to track the total number of reports dispensed and collected. Participant will be considered as non-compliant if the participant consumes less than 70% of the total amount of recommended (for the entire study duration) dose.

5.6. Precautions

No special precautions are necessary provided the test product is used in accordance with the protocol and the usage instructions.

5.7. Overdose

An overdose is a deliberate or inadvertent administration of a product at a dose higher than specified in the protocol.

Overdose is not likely to occur in this study. Limited quantities of the product will be supplied, and closely monitored by the site for each subject.

Overdose per se is not an AE. However, any clinical sequelae of an overdose should be reported as an AE (and serious adverse event (SAE), if appropriate). For reporting, follow the AE and SAE reporting instructions.

5.8. Rescue Therapy

No rescue therapy is required in this study.

5.9. Product Assignment

Prior to the start of the study, schools within matched pairs will be assigned to test and control group in accordance with the randomisation schedule generated by the Biostatistics Department, GSKCH, using validated internal software.

5.9.1 Randomisation

A unique screening number will identify each participant screened for study participation. At each school, screening numbers will be assigned in ascending numerical order as each participant's parent/LAR signs their consent form.

This study will follow cluster randomisation where in schools will be termed as clusters and then matched pairs will be formed on the basis of criteria defined in Section 6.1. As schools are determined to be fully eligible and matched pairs are formed, schools within the matched pairs will be randomised according to the randomisation schedule provided to the study centres. Each matched pair will be assigned a randomisation number in ascending numerical order as each matched pair is formed.

Once 60% of participants from any gender have been enrolled within a study group, recruitment into that gender will stop to ensure that there is a maximum 60% of either male or female. Remaining 40% of participants will be recruited from other gender.

The randomisation schedule will be provided by the Biostatistics Department, GSKCH.

5.9.2 Blinding

This is an open-label study; hence there will be no requirement for blinding of study personnel at site and sponsor/CRO.

The study centre will receive a randomisation schedule to be used by the centre for randomisation of matched-pair clusters. This schedule will have a randomisation number for a matched pair of clusters followed by the study group (test/control) for intervention within clusters.

5.9.3 Code Breaks

Since the investigator is un-blinded to the treatment there will be no requirement of breaking the code in the study by/for investigator.

5.10. Packaging and Labelling

The test product will be supplied in plain white sachets with a study label affixed to each sachet. Each subject will receive a subject carton with sufficient sachets to cover the duration of the intervention period.

The contents of the label will be in accordance with all applicable regulatory requirements and will be the responsibility of the Clinical Supplies Department, GSKCH.

All sundry items will be supplied in their commercial packaging for use throughout the study as required.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study. Participants should be instructed to not remove or deface any part of the study label.

5.10.1. Accountability of Product

All products supplied are for use only in this clinical study and should not be used for any other purpose.

The investigator or designee will maintain a full record of test product accountability. A Product Dispensing Log must be kept current and will contain the following information:

- The identification of the subject to whom the test product was dispensed.
- The dates and quantity of the test product dispensed to the subject.
- The dates and quantity of the test product/empty sachets returned by the subject (if applicable).

The inventory must be available for inspection by the study monitor during the study. During and at the end of the study, test product supplies will be verified by the monitor. Test product supplies will then be either collected by the study monitor or returned by the investigator or designee to the GSKCH Clinical Supplies Department or designated vendor.

5.10.2. Storage of Product

Study product supplies must be stored in compliance with the label requirements in a secure place with limited or controlled access.

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Schedule of Events section.

Adherence to the study design requirements, including all assessments and procedures are essential and required for study conduct.

6.1. Matched Pair Formation

Each school will be deemed as a cluster. Schools with following characteristics will be invited to participate in the study:

- ~~Located in peri urban areas~~
- No government or sponsored micronutrient supplementation scheme running in past 6 months
- Mixed-gender education/co-education system of education
- No history of any outbreak or clustering of cases of infectious diseases in last month

Schools which agree to participate will be selected and will be subsequently matched for cluster size (in context to the number of children in 7-10 yrs age group), socioeconomic profiles of students, and type of school; government subsidised or private.

6.2. Informed Consent and Assent

The investigator, or designee, must obtain written (signed and dated) informed consent from each participant's parent *or* LAR and/or impartial witness, participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The investigator, or designee, must also explain to the participant's parents or participant's LAR that they are completely free to refuse for their child to enter the study or to withdraw from it at any time. They will also be notified that they are free to withdraw consent for a collected biological sample to be

used after the collection. The investigator may contact the parents/LARs during parents-teachers meeting to inform them about the study. Consent will be obtained from interested parents/LARs on the same day of parents-teachers meeting if possible or they will be provided with alternate appointment dates to come for consenting and screening activities.

Once the parental or LAR consent process is over, separate assent will be obtained from the prospective study participants, whose parents/ LARs have consented. If participants do not give assent despite parental/LAR consent, they will be excluded from the study. Assent will always be obtained only after consent is obtained from Parents/LAR.

Appropriate forms for documenting a written consent and assent-will be provided by the investigator or by GSKCH or by CRO. The investigator, or designee, should sign and date the consent and assent-form to confirm that the process was completed correctly.

A copy of the signed and dated consent and assent-forms will be provided to the participant's parents / LARs along with any other written information and they will be instructed to retain these documents.

Obtaining informed consent and assent and performing screening activities can be on different dates but informed consent and assent will be obtained prior to performing and applying any screening criteria or procedures. Screening activities should be within 60 days of obtaining consent-and assent. A participant will be considered to be enrolled in the study after obtaining consent and assent, he/she has been found eligible for study basis all study screening criteria and procedures.

If, during a participant's participation in the study, any new information becomes available that may affect the participant's/parents or LARs willingness to participate in the study, each ongoing participant's parent or LAR should receive a copy of this new information and be re-consented into the study. Re-assent will also be sought from participants Participant's parents or LAR should be provided with a copy of the signed and dated amended consent and assent-form.

6.3. Demographics

The following demographic parameters will be captured by the Investigator or designee and recorded on the CRF: year of birth, gender and race.

6.4. Medical History and Concomitant Medication

For each participant, the medical history will be taken and reviewed by the Investigator or medically qualified designee. Details of any relevant medical or surgical history (in the last six months), including allergies or drug sensitivity, will be recorded. Any concomitant therapy taken in the 30 days prior to the Screening Visit and throughout the study will also be recorded.

6.5. General Physical Examination

The Investigator or their designee will perform a physical examination which should include assessment of the following body systems as appropriate: Central Nervous System (CNS); eyes; ears, nose and throat (ENT); respiratory; cardiovascular; GI; musculoskeletal; neurological; endocrine/metabolic; haematopoietic/lymphatic; dermatological.

The outcome of these assessments will be documented in the CRF and any abnormalities will be described. The Investigator can interpret individual findings based on the participant's age, physical state and level of fitness. Participants with clinically significant findings outside the normal range should be excluded from the study based on investigator's discretion. This decision will be documented on the Comments page of the CRF.

6.6. Vital Signs

Qualified site staff will record participant's heart rate and oral body temperature when participants are resting in a sitting position, checked against the following normal ranges (which are given as a guide) and recorded in appropriate forms.

Heart rate:

70-110 beats per minute.

Oral body Temperature:

97.7–99.5 °F

The Investigator can interpret individual findings based on the participant's age, physical state and level of fitness. Participants with clinically significant readings outside the normal range should be excluded from the study based on investigator's discretion. This decision will be documented on the Comments page of the eCRF.

6.7. Anthropometric Measurements (Height, Weight, BMI and HAZ)

All anthropometric measurements will be performed using the guidelines adopted at the National Institute of Health sponsored Arlie Conference [Anthropometric Reference Manual, 1988].

Height will be measured using a portable stadio-meter (SECA 213), with the subject standing bare-foot, to the nearest 0.1 cm. An average of 3 measurements will be recorded.

Weight will be measured in standard clothing on standardised weighing scale (SECA 874) to the nearest 0.1 kg. Weight will be measured in the unit kg and an average of 3 measurements will be recorded.

BMI will be calculated using the following formula:

$BMI = Weight_{kg} / (Height_{m})^2$

HAZ will be obtained using the World Health Organisation (WHO) Anthroplus software available at http://www.who.int/growthref/tools/en/ (WHO AnthroPlus for personal computers Manual: Software for assessing growth of the world's children and adolescents. Geneva: WHO, 2009).

6.8. Hb Assessment

A non-invasive spectrophotometry based instrument (Masimo Pronto ~~7~~ Pulse CO-Oximeter) will be used for Hb assessment. The Masimo Pronto ~~7~~ Pulse CO-Oximeter uses signal extraction technology pulse oximetry.

Site staff will select an appropriate sized sensor. The sensor will be placed on the nail of ring finger of the left hand, followed by assessment of haemoglobin by pressing the test button. Appropriate care will be taken by the site staff to ensure that the participant's test finger nail does not contain any nail paint.

6.9. Collection, Storage, Assessment and Destruction of Human Biological Samples

Human biological samples will be collected with prior consent (from parents/LARs) and assent (from participants) as per the study schedule.

All collected samples will be coded with unique identifiers and tracked until destruction. Samples must be clearly labeled with the screening number, protocol number, site/centre number, and visit date. Under no circumstances should a collected sample be left unidentified. Details for the preparation and shipment of samples will be provided in the laboratory manual.

~~Samples will be stored in requisite storage conditions mentioned for respective samples. Samples will be processed and shipped to laboratory as per details mentioned in the laboratory manual.~~

IMMEDIATELY AFTER COLLECTION, SAMPLES WILL BE FROZEN AT OR BELOW -20°C. IF FREEZING IS NOT POSSIBLE, THEY WILL BE REFRIGERATED IMMEDIATELY AT 2-8°C AND MAINTAINED AT THIS TEMPERATURE FOR NO LONGER THAN 4 HOURS, BEFORE SERUM SEPARATION AND SUBSEQUENT FREEZING AT OR BELOW -20°C. SAMPLES IF STORED FOR A PERIOD BEYOND EXPIRY OF STABILITY AT -20°C SHOULD BE FROZEN AT OR BELOW -70°C.

ALL SAMPLES (BASELINE AND END-LINE) WILL BE ANALYSED IN BATCHES, IN PERIODICITY BASED ON THEIR STABILITY AT -20 °C OR -70 °C (IF STORED FOR A PERIOD BEYOND EXPIRY OF STABILITY OF SAMPLES AT -20° C).

HBS TO BE STORED TILL IT IS PROPERLY DISPOSED OF AT THE END OF ITS RETENTION PERIOD (I.E. TILL STUDY REPORT IS ISSUED), OR USEFUL LIFE (I.E. TILL EXPIRY OF STABILITY AT -70°C), OR UPON RECEIPT OF A REQUEST TO DESTROY THE HBS DUE TO WITHDRAWAL OF CONSENT. NO SAMPLE WILL BE RETAINED BEYOND 1 YEAR FROM LAST PARTICIPANT LAST VISIT.

6.9.1. Collection and Storage of Human Biological Samples

6.9.1. 1. Urine Samples

Urine samples will be collected for Lactulose:Mannitol test and Urinary Neopterin test.

For Urinary Neopterin test, spontaneous random urine will be collected. As this test does not require any solution to be administered, urine sample for this test will be collected prior to administration of Lactulose/Mannitol solution.

A urine volume of 2mL per participant will be stored in ~~coded cryovials~~ **CONICAL BOTTOM TUBES** and then will be transferred to laboratory ~~and stored under -80ºC~~ for further analysis.

For Lactulose:Mannitol test, The Lactulose-Mannitol solution to be used includes 250 mg/mL of lactulose and 50 mg/mL of mannitol (1002 mOsm/L), and will be administered at a dose of 2 mL/kg up to a maximum of 20 mL. All urine passed over duration of 2 ½ hours [Akram S *et al.*, 1998, Sequeira IR *et al*, 2014] will be collected after administration of Lactulose:Mannitol solution. A prior 3 hours fasting is essential before administration of test solution. Participants will be allowed to return to their regular diet 30 minutes after ingestion of the lactulose:mannitol test solution. During the 2 ½ hour time, participants will be offered liquids frequently in order to permit collection of an adequate volume of urine. The start and stop time for the 2 ½ hour duration will be recorded for each participant. After 2 ½ hour urine collection total urine volume will be measured and recorded.

From the entire collection of urine in a container, 2 mL well mixed urine sample will be transferred in ~~coded cryovials~~ **RIA VIALS**. Remaining urine samples will be discarded as bio medical waste. The designated study staff will place all urine samples into a zip-lock bag containing absorbent toweling. All specimens will be refrigerated (or kept cold in a cooler with a frozen ice pack) until transported to the laboratory for analysis. The cooler will be securely sealed with tape and sent to the Laboratory, preferably on the same day as collection.

~~Immediately after collection, freeze samples at or below -20°C. If freezing is not possible, refrigerate immediately at 4°C and maintain at this temperature for no longer than 24 hours (ideally less than 2 hours) before freezing at or below -20°C.~~

~~All samples (baseline and end line) will be analysed in batches, in periodicity based on their stability data at -20 °C.~~

6.9.1. 2. Saliva Samples

Saliva sample will be collected for assessment of sIgA. Whole saliva is the gold standard when collecting oral fluid for biological testing. Since sIgA is location dependant [Beltzer, E.K. *et al*, 2010] [Crawford, J.M *et al*, 1975], whole saliva sample avoids localised secretions of specific salivary glands providing a more consistent specimen. Thus, saliva samples will be collected from each participant using passive drool method with Saliva Collection Aid (SCA)as described by the manufacturer) (Salimetrics, State College, PA).

Saliva will be collected using SCA. Ribbed-end of the SCA will be securely placed into a pre-labeled collection vial. Participants will be instructed to pool the saliva in mouth. SCA will be placed on mouth entry. Then, participants will be asked to tilt the head forward, and gently force saliva through the SCA into the vial to fill with at least 50 µL of volume. A small amount of air space will be reserved in the vial to accommodate liquid expansion during freezing. After collection of sample, SCA will be removed and discarded and cap will be attached to collection vial and tightened.

~~Immediately after collection, freeze samples at or below -20°C. If freezing is not possible, refrigerate immediately at 4°C and maintain at this temperature for no longer than 24 hours (ideally less than 2 hours) before freezing at or below -20°C. Samples if stored for more than 4 months should be frozen at -80°C.~~

~~All samples (baseline and end line) will be analysed in batches, in periodicity based on their stability at -20 °C (if stored for less than 4 months) or -80 °C (if stored for more than 4 months).~~

6.9.1. 3. Blood Samples

After application of an anesthetic patch/ointment ***E.G.*** **LIDOCAIN, TETRACAIN** ***ETC*** to reduce discomfort, a total volume of approximately 7 mL (each at ~~screening and~~ baseline visit **AND END OF STUDY VISIT**, total of approximately 14 mL) of whole blood will be collected from each participant by a certified phlebotomist for biochemical and micronutrient analysis.

The participant will be made to **LIE DOWN ON BED** or sit comfortably on a chair with his arm stretched on the table. He/she will be asked to exercise the arm so as to make the ante-cubital vein prominent. A tourniquet will be tied about 2 inches above the vein on the upper arm. The vein will be palpated, and the area will be sterilised. The vein will be pricked and vacutainer placed in position to collect sample. Blood samples will be collected in ~~single vial (7 ml each)~~ **TWO VIALS (3.5 ML EACH)** by designated staff.

~~After collection, all blood samples will be coded and refrigerated immediately at temperature ≤ 4°C and will be maintained at this temperature for no longer than 24 hours (ideally less than 2 hours). At the laboratory, these samples will be converted into serum and then preserved in aliquots at ≤ -20 °C, until further required analyses are performed.~~

~~All samples (baseline and end-line) will be analysed in batches, in periodicity based on their stability data at -20 °C.~~

6.9.2. Laboratory Assessment and Destruction of Human Biological Samples

All samples will be analysed at the end of study as per standard operating procedures and validated techniques / methods. All protocol required laboratory assessments, must be conducted in accordance with the Laboratory Manual or according to the laboratory section of the Protocol, and Protocol Schedule of Events.

~~Post laboratory assessment, all samples will be stored in requisite storage conditions mentioned for respective samples and will be destroyed within one year after last participant last visit.~~ No biological samples should be destroyed without a prior written agreement between GSKCH and the study centres.

6.10. Dietary Counselling

Dietary counselling sessions will be administered at school. It will be administered to all study participants and their parents/LARs. It is preferable that both parents of participants are provided dietary counseling, but in case if it is not possible then either of mother or father will be provided dietary counselling. Separate sessions of dietary counseling will be held for participants and parents/LARs. Attendance by the school teachers will be strongly encouraged. Study dieticians will administer, supervise and ensure delivery of counselling as per the schedule.

A total of 7, separate sessions for study participants and parents/LAR as described in table below:

Session No	Nutritional Educational Counselling	Duration (in min)
Session 1	Delivery of contents	60 + up to 10 min
Session 2		60 + up to 10 min
Session 3	Follow up of contents delivered in Session 1 and 2: Reinforcement and Problem Solving	30 + up to 10 min
Session 4		30 + up to 10 min
Session 5		30 + up to 10 min

Session 6		30 + up to 10 min
Session 7		30 + up to 10 min

Counseling will be provided by dietician/nutritionist, well versed with local language and with effective education and counseling skills. Contents of the dietary counseling will be socio-culturally acceptable and explained in the language participants, parents and teachers can understand. Contents of dietary counseling will be based on the Dietary Guidelines for Indians, established by the Indian Council of Medical Research (National Institute of Nutrition), and will be provided as per Appendix 8. Study dietician/nutritionist will be instructed to cover each topic described under each session, adequately so as to finish the session within the stipulated time. Start time and end time of each session will be captured in eCRF.

Each session will be followed by up to 10 min of question-answer session. Respectful, science-based answers to participants' questions will be delivered.

Each participant/parent (either of mother or father)/LAR is required to attend all dietary counseling sessions on 'delivery of contents' (i.e. session number 1 & 2) and minimum of three out of five 'follow up' dietary counselling sessions (i.e. session number 3, 4, 5, 6 & 7). Participant will be considered as non-compliant if the participant/parent/LAR does not attend either of session number1 & 2 OR three or more sessions out of session number 3, 4, 5, 6 & 7.

In case, if any dietary counselling session is not conducted due to reasons such as school exams, long school holidays etc, the next session for dietary counseling will be postponed and conducted as soon as participant is available in school and exams are finished. However, last dietary counselling session (i.e. session no 7), in any scenario, will not be conducted any later than the last day of 8th month of intervention period of a particular subject. A minimum of 4 weeks of gap between consecutive content delivery session and follow up session (i.e. between session 2 and 3); and two consecutive follow up dietary counselling sessions (i.e. between session 2, 3, 4, 5, 6 and 7) must be maintained.

6.11. Clinical Outcomes Assessment

6.11.1. Case/Illness definition

For the purpose of study, GI and respiratory illnesses will be evaluated. These study illnesses are defined as follows:

A. **GI illness:** An acute illness that includes any of following symptoms: 3 or more loose/liquid/watery stools and/or any vomiting in 24 hours [WHO, 2016] [Azor-Martinez E *et al*, 2014].

   Diarrhea, vomiting arising due to non-infectious causes, such as Irritable Bowel Syndrome (IBS), and medications will be excluded from the diagnosis.

B. **Respiratory illness:** An acute illness that included ≥1 of the following symptoms: runny nose, stuffy or blocked nose, cough, fever or chills, sore throat, or sneezing [Sandora *et al.* 2016].

   Symptoms arising due to non-infectious causes (e.g., allergy) will be excluded from the diagnosis.

6.11.2. Morbidity Outcomes Definitions

Following morbidity outcomes with respect to GI and respiratory illnesses are going to be evaluated in the study:

A. **Number of illness days**: Number of days a participant is ill because of GI and/or respiratory illnesses as diagnosed by study physician, as per the criteria defined, over the intervention duration. This corresponds to total number of days (symptomatic or asymptomatic) in an episode of illness.

B. **Frequency of illnesses**: Total number of illness episodes of GI and/or respiratory illnesses, divided by duration of intervention, where each episode is defined as each incidence of illness followed by at least 3 symptom free days [Azor-Martínez *et al*., 2014] [Barreto ML *et al*., 1994] [Sur D *et al*., 2003].

   For the purpose of study, each occurrence of an illness is defined as an event which incorporates a period which includes all illness days uninterrupted by any symptom free day. Thus, an episode may consist of one or more than one occurrences of illness.

C. **Severity of an illness episode:** Intensity of GI and/or respiratory illnesses; **WILL BE EVALUATED AND CLASSIFIED AS PER CRITERIA SPECIFIED IN APPENDIX-5 (BASED ON CTCAE 2010)**~~which is evaluated and classified as follows:~~

   ~~➢ Severity of GI illnesses [CTCAE 2010]~~

   ~~a. Diarrhoea:~~

- ~~Mild, ≤3 loose stools/day~~
- ~~Moderate, 4 to 6 loose stools/day~~
- ~~Severe, ≥7 loose stools/day~~

~~b. Vomiting:~~

- ~~Mild, 1 to 2 bouts/day~~
- ~~Moderate, 3 to 5 bouts/day~~
- ~~Severe, ≥6 bouts/day~~

➢ ~~Severity of respiratory illnesses~~

- ~~Mild Easily tolerated, causing minimal discomfort and not interfering with normal everyday activities.~~
- ~~Moderate Sufficiently discomforting to interfere with normal everyday activities.~~
- ~~Severe Any event that prevents normal everyday activities.~~

D. School absenteeism: Number of days when a child fails to attend school because of GI and/or respiratory illnesses.

6.11.3. Clinical Evaluation Tools

A. Parent/LAR reported Symptom Checklist

At the beginning of the study, parents/LARs will be provided with blank 'symptom checklist' forms. The symptom checklist to be used by the parents/LARs has been appended (Appendix 3). When a symptom is observed in the participant during the intervention period, the parents will be required to fill the symptom checklist as trained by study staff. The severity/intensity of severity assessment of the symptoms e.g. sore throat, dry cough, wet cough, runny nose, stuffy/blocked nose and sneezing will be made by parents/LARs as per the following criteria:

- Mild – Easily tolerated, causing minimal discomfort and not interfering with normal everyday activities.
- Moderate – Sufficiently discomforting to interfere with normal everyday activities.
- Severe – Any event that prevents normal everyday activities.

Parents/LARs will be trained by study staff to assess the symptoms based on above criteria. For the assessment of other symptoms e.g. diarrhea/loose stools, vomiting and fever, the criteria are already mentioned in the symptom checklist which are in

line with assessment done as per CTCAE 2010. Parents/LARs will also be provided with digital thermometers to check temperature in case if fever is observed.

In cases where parents/LARs do not observe any symptoms in the participant, they will be asked to mark the relevant ('No') box mentioned for each symptom for each day in the symptom checklist. The symptom checklist will be handed to study physician on weekly basis for review by physician. The physician will then evaluate the symptoms, if any, to determine diagnosis.

Those requiring hospitalisation or specialised care will be referred to the secondary or tertiary care hospital, as deemed necessary by the study physician. The determined diagnosis will be captured in the CRF, and the severity will be graded based on the criterion indicated in Appendix 5.

B. Diagnosis Form

Diagnosis form (DF) will used to note the diagnosis, severity and school absenteeism due to GI and respiratory illnesses only, as defined in the study protocol. DF will also be used to capture start and end date of all occurrences of GI and respiratory illnesses in the week.

Other morbidity outcomes such as number of illness days, number of episodes, frequency due to GI and respiratory illnesses, as defined in the study protocol, will be calculated programmatically using statistical analysis software (SAS).

Data on diagnosis and morbidity outcomes by study physician on the DF will be used for analysis. DF will be filled as per the details obtained from:

- Symptom checklist filled by parents/LARs
- External clinical record, if treated by an external physician
- Direct information by participants/parents/LARs
- Clinical history and examination by study physician

6.12. Study Physician Weekly Review

To ensure that no case is missed, a weekly review (SPWR) will be scheduled by the study physician to check symptom checklist from all participants.

SPWR will initiate 1 week (+up to 2 days) post first dietary counselling visit of the participant and will continue on a weekly basis (+ up to 2 days) until end of study visit. ~~At least one weekly review with the study physician will occur after product administration stops~~ **LAST SPWR WILL BE CONDUCTED ON END OF STUDY VISIT DAY, EVEN IF SYMPTOMS ARE ASSESSED FOR LESS THAN A WEEK IN SYMPTOM CHECKLIST FORM**.

In case the SPWR of a participant is not conducted due to reasons such as absenteeism, long holidays etc for a week, then every attempt will be made to contact and collect symptom checklist from participant/parents/LARs, either telephonically or visiting them at home. If any participant is not accessible for consecutive 4 weeks, he/she will be considered as lost to follow up.

6.12.1. Collection of Symptom Checklist

Parent/LAR-reported symptom checklist will be collected on each weekly review. Physician will review the parent/LAR Symptom checklist and conduct clinical examination of only those participants who present with symptoms on the symptom checklist or inform the physician directly.

6.12.2. Study Physician Clinical History and Examination

Study physician will be made available at school on all school days during school timings.

When the participant **falls sick at school** during school timings with the pre-specified symptoms related to GI and respiratory illnesses, participant will be presented to the study physician. Study physician will collect relevant clinical history from participants and parents/LARs (if available). Study physician will systematically evaluate the symptoms using well-defined, pre-established criteria and will make objective diagnosis of the clinical outcomes, as defined in the study protocol.

When study participant **fall sick but are not at school** (e.g. during holidays, after school dismissal etc), with the pre-specified symptoms related to GI and respiratory illnesses, parents/LARs would need to complete the 'symptom checklist' provided to them. Symptom checklist would be presented to study physician by the participants/ parents/ LARs. In case, if an external physician is consulted for the treatment, clinical record form from the same would also be presented to the study physician along with symptom checklist. Study physician will collect relevant clinical history from participants and parents/LARs (if available). Study physician will evaluate and verify parent reported data on symptom checklist and clinical record form from external

physician. Study physician will systematically evaluate the symptoms (if still present in the participants) using well-defined, pre-established criteria and will make objective diagnosis of the clinical outcomes, as defined in the study protocol.

Diagnosis by study physician on DF will be used for analysis. In case of a conflict between parent-reported symptoms, external physician's reported diagnosis and study physician's diagnosis, the study physician's diagnosis will supersede.

Availability of physician will also ensure the children are provided with timely care, which could include the advice to use a hydration formula and/or medications (*e.g.,* antibiotic, nasal decongestant) to help manage their symptoms/infection. If and when needed, and, if possible, the same type of hydration formulas and medications would be provided to children – *e.g.*, the same type of antibiotic, the same type of nasal decongestant, *etc*.

6.13. 24 hr Dietary Recall & Dietary Diversity Survey

6.13.1. 24 hr Dietary Recall

This method involves a structured interview and will be conducted as per the questionnaire provided in Appendix 6. Since children, invariably tend to overestimate, parents/LARs should be present at the 24-hour recalls. Majority of the information should come from the parent/LARs, with the child making additions to fill in the gaps.

Respondents (participant/ Parents/LARs) will also be asked whether or not the day recalled is typical of their usual food consumption, or if it was unusual or restricted in any way e.g. fast, festival etc. If the day is not the representative of a typical day then the participant may be called for another day.

On confirmation of the day being a representative of a typical day, a trained study staff will ask the respondents (participant/ parents/LARs) to recall all food and beverage consumed by the child during previous 24 hours. For homemade food and beverage, following information will be recorded:

- List of ingredients: e.g. water, oil, herbs, spices.
- Amounts of ingredients: This can be in household measures, weights or using portion sizes.
- Cooking method: Record some brief information on how the dish was prepared and cooked.

The food or beverage items which are bought, name of the brand will be enquired. A portion size can be described in terms of either household measures (e.g. one level teaspoon of sugar, bowl, cup etc) or weights.

Calculation on energy and the macronutrients (protein, carbohydrates and fat) will be made using application/software. For the purpose latest available Dietsoft software available at http://dietsoft.in/ based on Indian data (NIN and ICMR) will be used.

6.13.2. Dietary Diversity Survey

Household dietary diversity refers to the number of different food groups consumed over a given reference period [Hoddinott and Yohannes, 2002]. This measure is important because a diversified diet is associated with many health benefits, including more optimal child anthropometric status and improved Hb concentrations [Swindale and Bilinsky, 2006].

Dietary diversity can be assessed at the level of the household or at the level of the individual, resulting in either a Household Dietary Diversity Score (HDDS) or an Individual Dietary Diversity Score (IDDS). The HDDS is a measure of the socioeconomic status of the family; the IDDS is a measure of the nutritional quality of the individual's diet. For the proposed clinical study, it is important to understand the child's IDDS; hence, the CDDS will be determined.

IDDS will be assessed based on the 'Guidelines for measuring household and individual dietary diversity' prepared by Food and Agriculture Organisation (FAO) of the United Nations [FAO guidelines dietary diversity, 2011]. Detailed information on translation and adaptation, instructions for administering the questionnaire and analyzing dietary diversity data will be used as recommended in the guidelines.

Based on data on foods and beverages consumed in last 24 hr as captured by 24 hr dietary survey, appropriate food groups in questionnaire in Appendix 7, will be selected.

Dietary diversity scores are calculated by summing the number of food groups consumed by the child over the 24-hour recall period. The score ranges from 0 to 9, with one point awarded for foods that are consumed from each of the following food groups in the previous 24 hours:

1. Starchy staples
2. Dark green leafy vegetables

3. Other vitamin A rich fruits and vegetables
4. Other fruits and vegetables
5. Organ meat
6. Meat and fish
7. Eggs
8. Legumes, nuts and seeds
9. Milk and milk products

Depending upon IDDS, study participants would be categorised into three groups as following:

- ≤ 3 food groups - Lowest dietary diversity
- 4 and 5 food groups - Medium dietary diversity
- ≥ 6 food groups - High dietary diversity

6.13. Study Conclusion

Participants will be evaluated to determine if they completed all study procedures or if they were discontinued from the study early. If the subject discontinued at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page of the CRF by selecting one of the options below.

1. Subject did not meet study criteria
2. Adverse Event
3. Lost to Follow Up
4. Protocol Violation
5. Withdrawal of Consent
6. Other

7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

Adverse Event Definition:

- An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of an investigational product or investigational invasive procedures, whether or not considered related to the investigational or investigational invasive procedures.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational product or investigational invasive procedures.

Events meeting AE definition include:

- Any abnormal laboratory test results (if applicable) or other safety assessments, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition(s) detected or diagnosed after study product administration or investigational invasive procedures even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder/ condition being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

7.1.2. Serious Adverse Events

Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:
A. Results in death
B. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
C. Requires hospitalisation or prolongation of existing hospitalisation NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered

serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

D. Results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

E. Is a congenital anomaly/birth defect

F. Other Situations

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse or reports of spontaneous abortion.

7.2. Recording Adverse Events and Serious Adverse Events

Recording of adverse events and serious adverse events:

- The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

- The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF.

- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception

of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

- AEs will be collected from the start of the administration of investigational product or investigational invasive procedures and until 7 days following last administration of the study product or investigational invasive procedures.

- SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

- Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:

The investigator or designee will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities

- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be

assessed as severe.

Note: An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality:

- The investigator is obligated to assess the relationship between study product and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes (source document) or CRF that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.4. Reporting Adverse Events and Serious Adverse Events

AE Reporting to GSKCH:

- AEs will be recorded in the AE section of the CRF.
- Medical conditions recorded by the subject on a diary card or similar document that meet the definition of an AE must also be recorded in the AE section of the CRF, if not previously well-characterised by the investigator in the subject's medical history.
- AEs elicited by the investigator in a standard manner at the study visits should also be recorded in the AE section of the CRF. The investigator or designee must ask the subject the following question during each visit including any follow-up visits: "***Have you felt unwell, experienced any symptoms or taken any medication (since your last visit) (today) (since your last dose) (since the last session)?***"
- The medically qualified investigator should review adverse events in a timely manner; this review should be documented in writing in the source document or in the CRF.
- After the study is completed at a given site, and the site has received their study data on Compact Discs (CDs), the electronic data collection tool will be removed from the internet to prevent the entry of new data or changes to existing data.

SAE Reporting to GSKCH:

A paper copy of the SAE form provided in the investigator study master file should be completed as fully as possible.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject's demography
- Description of events, with diagnosis if available

- Investigator opinion of relationship to study product (see section 8.3)
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and GSKCH assessment of the SAE report:

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken on study product
- Outcome if known

The SAE form, completed as fully as possible, and SAE fax cover sheet must be faxed or e-mailed to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. The GSKCH Study Manager should be notified of the situation by telephone or email.

Fax Serious Adverse Events to:

India: PPD

The GSKCH Study Manager will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Phamacovigilance, the Medical Director responsible for the study and other GSKCH personnel as appropriate via email.

The initial report will be followed up with more information as relevant, or as requested by the GSKCH study manager.

7.5. Follow-up of Adverse Events and Serious Adverse Events

Follow-up of AEs and SAEs:
• After the initial report, the investigator is required to proactively follow up

with each subject and provide further information on the subject's condition.

- All AEs/SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the subject is lost to follow-up.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- Investigators are not obliged to actively seek AEs or SAEs in former participants. However, if the investigator learns of any SAE, including the death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the investigational product or study participation, the investigator will promptly notify GSKCH.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Regulatory and ethics reporting requirements for SAEs:

- The investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of participants are met.
- GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.
- Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.
- An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from

GSKCH will file it with the Investigator Brochure (or safety statement) and will notify the IRB or IEC, if appropriate according to local requirements.

8. DATA MANAGEMENT

For this study, subject data will be entered into an electronic case report form, using a GSKCH validated data system.

8.1. Source Documents/ Data

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified in the Source Document Designation Form. In some cases the CRF can be used as a source document.

Each subject will be assigned and identified by a unique Screening Number. Any reference made to an individual subject within the study must be done using the unique Screening Number.

8.2. Electronic Case Report Form

A 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.

For each subject who has given informed consent/assent and has been screened, CRF must be completed and signed by the Principal Investigator (or authorised designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with applicable GSKCH standards and data cleaning procedures to ensure the integrity of the data e.g. removing errors and inconsistencies in the data.

In order to protect the privacy of participants, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded in the CRF or as part of the query text.

Adverse events and concomitant medications terms (if applicable) will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

Subject data will be entered into GSKCH defined CRFs and transmitted electronically to GSKCH in a validated (21 CFR Part 11 compliant) web-based electronic data capture system (InForm™).

All CRF pages should be completed during a subject assessment when the CRF has been designated as the source. Data that is sourced elsewhere should be entered into the CRF in an agreed upon timeframe between the Investigator and Sponsor.

The CRFs (including queries, query responses and audit trails) will be retained by GSKCH. Site data archived compact discs (CD(s)) prepared by a third party will be sent to the investigator to maintain as the investigator copy following the decommissioning of the study.

8.3. Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance. Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

8.3.1. Data Queries

Programmed edit checks will be generated automatically, as the data is being entered into the system. Data Management will also run reports and listings on the CRF data, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (Adverse Events and Drugs) are reported appropriately.

The study monitor at the study site will review the CRFs in accordance with the monitoring plan, and any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. Monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction

8.4. Processing Patient Reported Outcomes

Patient reported outcome (PRO) data are collected directly from the subject PRO measures e.g. diary cards, questionnaires etc, and entered into the sponsor's clinical data management system (DMS) by the study site representative. In instances where the PRO data is entered into the DMS by GSKCH, the PROs will be anonymised, and forwarded to GSKCH for entry, as agreed and documented ahead of the study starting. PROs that are source will be retained by the investigator and certified copies will be sent to GSKCH.

In order to protect the privacy of participants, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded on all PRO's that will be forwarded to GSKCH.

8.5. External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSKCH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed upon quality control process is performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSKCH via secured web portal or CD/DVD via mail carrier with tracking capabilities.

Proper reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1 Sample Size Determination

The primary efficacy variable of the study is the total number of ill days due to GI and respiratory illnesses. The sample size has been calculated based on the assumption of an average of 7 ill days in the control group with a difference of 10% between the treatments.

Years Lost due to Disability (YLD) is a measure of the burden of disease from its morbidity. Below are data that are specific to India: As per the data from Global Burden Disease, WHO 2010 study (GBD, WHO, 2012; IHME, 2013) and Census India, 2011, YLD per child in the 5-9 year age group, due to diarrhea, LRTIs, other infectious disease and nutritional deficiencies is 8.274 days/child per year or 6.21 days/child per 9 months.

Thus, based on above data, approximately 7 ill days due to GI and respiratory illnesses per 9 months has been assumed in this proposed study population of 7-10 year olds.

The sample size is based on the primary endpoint. No sample size considerations have been taken into account for secondary objectives.

The simulated data were also used based upon the assumption of a Poisson distribution per study treatment. On observation of these simulated data, it was considered that these Poisson distributions were not heavily skewed and, as a result, normal distributions may be assumed. Consequently, a normality assumption has been adopted for both the generation of sample size and the intended approach to the statistical analysis.

Because of assumption of poisson distribution, estimates of variability were calculated as square root of mean.

Mean of control was assumed to be 7.0 and standard deviation (SD) was 2.65, mean of test group was 6.3 and SD was 2.51. To be able to achieve 80% power, 215 participants per treatment arm (Total = 430) will be required to complete the study in case of individual randomisation. This assumes 5% level of significance (two tailed t-test).

As this study is using cluster randomisation, and design effect (DE) needs to be considered for sample size calculations. Scientific literature suggests, DE due to cluster sampling strategy can be assumed to be 1.5 [Rosner, B, 1986]. Same has been assumed in one study, which used three-stage systematic cluster sampling [Dandona R *et al*, 2008].

Using the following formula from Hemming *et al*, 2011:

$$N^* = N \times DE$$

Where N*=Number of participants required for cluster randomised trial

N = Number of participants required for individual randomisation

DE = Design Effect

And assuming DE to be 1.5, the number of evaluable participants completing the study required would be 323 per arm (Total=646).

To allow for 30% drop-out rate, a total of 924 participants will be randomised.

Approximately 1300 participants will be screened to randomise approximately 924 participants in order to obtain 646 participants completing the study.

9.2. General Considerations

9.2.1. Definition of Analysis Populations

All participants who receive the study product will be considered evaluable for the safety population.

All participants in the safety population with any post-treatment assessment will be included in Intent-to-treat (ITT) population. ITT population will be the primary population for efficacy analysis.

Per protocol (PP) population will consist of participants who have all post-treatment assessments and do not have any protocol violations that would affect efficacy assessments. PP analyses will be performed only if there is more than 5% difference between number of study participants in ITT and PP population. A final decision on whether a PP analysis will be performed will be made prior to study un-blinding.

9.2.2. Exclusion of Data from Analysis

Prior to database lock and breaking of the study blind, review listings will be defined and reviewed by the Biostatistician and Medical Director (or designee) to identify protocol violations and to determine their level of impact on efficacy analyses. Further details of these review listings will be provided in the statistical analysis plan (SAP) and review listing specification document. The review listings may include, but will not be necessarily limited to, the following:

- Violation of inclusion or exclusion criteria that are deemed to affect efficacy.
- Use of prohibited treatment (e.g. usage of immunosuppressive therapy *e.g.*, oral corticosteroids or chemotherapy during the course of study) or medication before or during the study, which is felt to affect the assessment of efficacy.

- Non-compliance with product administration.
- Comments.

9.2.3. Criteria for Assessing Efficacy

The study will be deemed to be successful if a statistically significant decrease is demonstrated in number of ill days during nine (9) months of intervention in the test product group compared to the control product of the study.

9.2.4. Criteria for Assessing Tolerability

Safety will be assessed by reporting adverse events (AEs) by all participants taking the test product vs. control product of the study.

9.2.5. Handling of Dropouts and Missing Data

No data will be imputed in case of dropouts or missing data.

9.2.6. Other Issues

There will be no interim analysis.

9.3. Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalisation of the protocol and prior to **STUDY ANALYSIS** ~~study start (first subject first visit (FSFV))~~.

9.3.1. Demographic and Baseline Characteristics

Participant demographics information will include age, gender, and race.

Baseline characteristics will include height, weight, and HAZ.

Categorical measures (gender, race, and HAZ (for ranges: -3 to -2 and -2 to -1)) will be summarised by number and percent of participants in each category.

Descriptive statistics for continuous measures (age, height, weight, BMI and HAZ) will include the number of participants (N), mean, median, standard deviation (SD), minimum, and maximum.

9.3.2. Primary Analyses

The primary efficacy variable of the study is the number of ill days. The number of ill days is defined as number of days a subject is ill because of GI and/or respiratory illnesses as diagnosed by study physician, as per the criteria defined in Section 6.11.1 and 6.11.2, over the intervention period.

For this variable, primary analysis will be performed on participants in ITT population who have completed the entire study for 9 months.

The null hypothesis of interest is:

H_0: There is no difference in the number of ill days.

The alternative hypothesis of interest is:

H_1: There is a difference in the number of ill days.

The number of ill days will be summarised in terms of number (N), mean, standard deviation, minimum, and maximum for both the treatment groups.

The number of ill days will be analysed using the analysis of variance (ANOVA). The ANOVA will have treatment, cluster (school), and gender as fixed effects.

Adjusted means, 95% confidence intervals, within treatment p-values for each treatment group, treatment group difference, 95% confidence interval of the difference and the between-treatment p-values based on the statistical model described above will also be presented.

All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

The simulated data used for the sample size calculations were based upon the assumption of a Poisson distribution per study treatment. However, on observation of these simulated data, it was considered that these Poisson distributions were not heavily skewed and, as a result, normal distributions may be assumed. Consequently, a normality assumption has been adopted for both the generation of sample size and the intended approach to the statistical analysis. However, the assumptions of normality and homogeneity of variance will be investigated and violation of these assumptions may be overcome using suitable transformation (for example, log or square root). If transformed data is also non-normal, then alternative analyses relevant to Poisson distributed data will be investigated (further details will be

provided in the SAP). If none of these options are considered appropriate for the data, then appropriate non-parametric tests will be performed.

9.3.3. Secondary Analyses

Following secondary efficacy variables will be analysed for both completers (those who completed entire 9 months of study) and ITT population.

The secondary efficacy variables are:

- Frequency of GI and respiratory illnesses defined as total number of illness episodes of GI and/or respiratory illnesses, divided by duration of intervention, where each episode is defined as each incidence of illness followed by at least 3 symptom free days (Section 6.11.2).

  The same model outlined above for primary outcome variable will be used for this secondary outcome.

- Severity of GI and respiratory illnesses (Mild, moderate, or severe intensity as captured in DF) (See Section 6.11.2 for details on capturing severity of illness).

  This will be will be captured by study physician as per severity grading outlined in Appendix 5. Frequencies of intensity (Mild, moderate, or severe) by treatment groups will be compared using chi-square test (if frequencies are greater than 5%). If frequencies are $\leq$ 5% in any treatment groups, then these will be compared using Fisher's exact test between treatment groups.

- School absenteeism due to GI and respiratory illnesses as identified from DF.

  The same model outlined above for primary outcome variable will be used for this secondary outcome.

- Change from baseline (measured at screening visit) in BMI.

  This will be analysed using an analysis of covariance (ANCOVA) model. The model will include the fixed factors for treatment, cluster (school) and gender; baseline BMI assessment recorded at screening visit as covariate.

- Change from baseline in gut integrity/health as measured by Lactulose:Mannitol test and Urinary Neopterin test defined in Section 6.9.1.1 respectively.

These will be analysed using an ANCOVA model. The model will include the fixed factors for treatment, cluster (school) and gender; baseline gut integrity/health assessment at baseline as covariate.

- Change from baseline in salivary IgA as defined in Section 6.9.1.2.

  This will be analysed using an ANCOVA model. The model will include the fixed factors for treatment, cluster (school), and gender; baseline salivary IgA assessment at baseline as covariate.

- Change from baseline in levels of micronutrients Vitamin A, ~~B6,~~ B12, ~~C,~~ D (25 Hydroxy chole calciferol), E, folate, of the trace elements selenium, zinc, copper, and iron as determined by blood draw and analysis (Section 6.9.1.3).

  These will be analysed using an ANCOVA model. The model will include the fixed factors for treatment, cluster (school) and gender; baseline assessments at baseline as covariate.

- Change from baseline in levels of ferritin, serum transferrin receptor (sTfR), C-reactive protein (CRP), and Alpha 1-acid glycoprotein (AGP) as determined by blood draw and analysis (Section 6.9.1.3).

  These will be analysed using an ANCOVA model. The model will include the fixed factors for treatment, cluster (school) and gender; baseline assessments at baseline as covariate.

- Change from baseline in dietary diversity score as assessed through 24-hour IDDS (Section 6.12.2).

  These will be analysed using an ANCOVA model. The model will include the fixed factors for treatment, cluster (school) and gender; baseline assessments at screening as covariate.

- Change from baseline in energy, protein, carbohydrate and fat from 24-hour dietary recall survey (Section 6.12.1).

  These will be analysed using an ANCOVA model. The model will include the fixed factors for treatment, cluster (school) and gender; baseline assessments at screening as covariate.

Adjusted means, 95% confidence intervals, within treatment p-values for each treatment group, treatment group difference, 95% confidence interval of the difference and the between-treatment p-values based on the statistical model described above for each secondary outcome will also be presented.

All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

The assumptions of normality and homogeneity of variance will be investigated. Violation of these assumptions may be overcome using suitable transformation (for example, log) or performing appropriate non-parametric tests.

9.3.4. Safety Analyses

All participants who receive treatment will be included in the safety analysis and reporting of safety data. AEs (including severity/relationship to study treatment) will be summarised by treatment group. AEs reported prior to product administration will be regarded as pre-treatment and will be included in AE data listing. AEs will be regarded as treatment emergent if they occur during or after the first dose of product administration (i.e. +1 to 3 days post randomisation at Baseline Visit.

9.3.5 Other Analyses

As exploratory analysis, following analyses will also be performed:

- Analysis on number of ill days will be performed for those participants in ITT population who have completed the study for 3 months and 6 months separately.
- Analysis on number of ill days will be performed on GI and respiratory illnesses separately on those participants who are in ITT population and have completed the study for 3months, 6 months and 9 months.
- Total number of ill days (GI and respiratory illnesses), number of episodes (GI and respiratory illnesses), and severity of GI and respiratory illnesses by gender will also be analysed.
- Total number of ill days (GI and respiratory illnesses), number of episodes (GI and respiratory illnesses), and severity of GI and respiratory illnesses by screening, end of study, and change from baseline in DDS, energy, protein, carbohydrate and fat will also be analysed.

The same model outlined above for primary outcome variable (Section 9.3.2) will be used for this secondary outcome.

Adjusted means, 95% confidence intervals, within treatment p-values for each treatment group, treatment group difference, 95% confidence interval of the difference and the between-treatment p-values based on the statistical model described above for each secondary outcome will also be presented.

All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

The assumptions of normality and homogeneity of variance will be investigated. Violation of these assumptions may be overcome using suitable transformation (for example, log) or performing appropriate non-parametric tests.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trials Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of participants begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK**/DESIGNATED CRO** policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol (including amendments), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), investigator brochure/ safety statement (including any updates) and any other written information to be provided to participants. A letter or certificate of approval

will be sent by the investigator to the sponsor prior to initiation of the study, and also when subsequent amendments to the protocol are made.

- Signed informed consent to be obtained for each subject's parent/LAR and signed assent to be obtained from each subject. Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

- GSK will provide full details of the above procedures, either verbally, in writing, or both.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK**/DESIGNATED CRO** procedures, GSK or designee (i.e. third party vendor) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK **AND/OR CRO** requirements.

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK or designee will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.

- Safety and rights of participants are being protected.

- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The extent and nature of monitoring will be described in a written monitoring plan on file at GSKCH. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

The sponsor will be available to help investigators prepare for an inspection.

10.5. Conditions for Terminating the Study

Upon completion or premature discontinuation of the study, the GSKCH monitor **OR DESIGNEE (I.E. THIRD PARTY VENDOR)** will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSKCH/**CRO** Standard Operating Procedures.

Both GSKCH and the Investigator reserve the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies (if applicable), this can occur at one or more or at all sites.

If the trial is prematurely terminated or suspended for any reason, the investigator site should promptly inform the trial participants and should assure appropriate therapy/ follow-up for the participants. Where required by the applicable regulatory requirements, GSKCH should inform the regulatory authority (ies).

In addition:

- If the investigator terminates or suspends a trial without prior agreement of GSKCH, the investigator site should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.
- If the GSKCH terminates or suspends a trial, the investigator should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.
- If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial, the investigator should promptly notify the GSKCH and provide GSKCH with a detailed written explanation of the termination or suspension.

10.6. Records Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSKCH, participants should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of participants' codes, names and addresses. Documents not for submission to GSKCH, e.g. participants' written consent forms, should be maintained by the investigator in strict confidence.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements (GSKCH recommends that documents be kept for 10 years). The investigator is also required to keep subject identification codes on file for at least 15 years after completion or discontinuation of the study. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSKCH and the investigator. The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or

transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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12. APPENDICES

12.1. Appendix 1 - Abbreviations and Trademarks

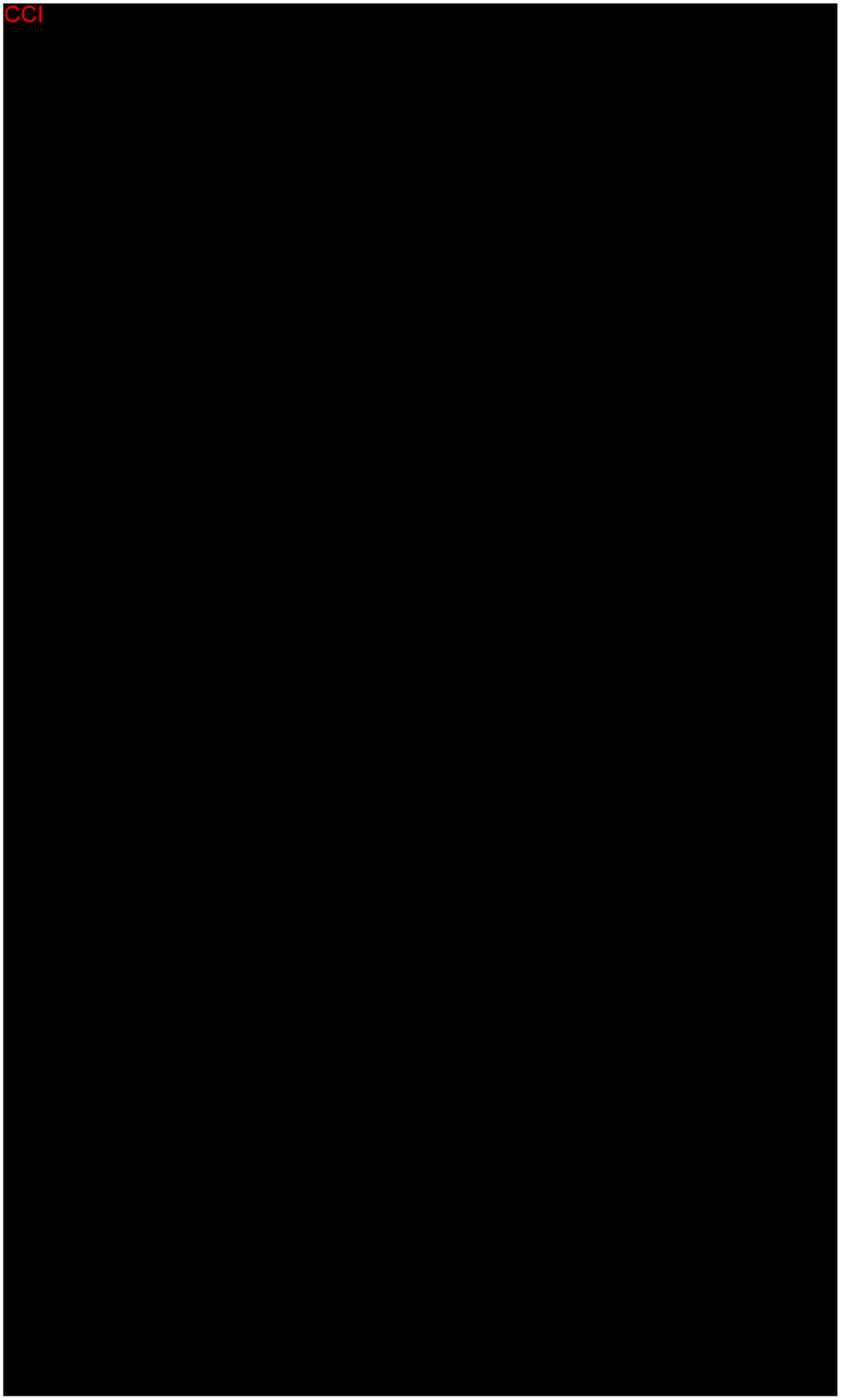
Abbreviations

AAGP2	Acid glycoprotein Gen.2
AE	adverse event
AGP	Alpha 1-acid glycoprotein
ALDH1A	Aldehyde dehydrogenase 1A family
ANOVA	Analysis of variance
ARI	Acute respiratory illnesses
BMI	Body mass index
CD	compact disc
CiC	Children in Care
CRF	Case report form
CRP	C-reactive protein
CNS	Central nervous system
CTCAE	**COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS**
DF	Diagnosis form
ENT	ears, nose and throat
FSFV	first subject first visit
g	Gram
GI	gastrointestinal
GSK	GlaxoSmithKline
GSKCH	GlaxoSmithKline Consumer Healthcare
HAZ	height-for-age Z-scores
HBS	**HUMAN BIOLOGICAL SAMPLES**
ICH	international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IEC	independent ethics committee
IRB	institutional review board
ITT	intention to treat
LAR	legally appropriate representative
LM	lactulose:mannitol
LRTI	lower respiratory tract infection

LSLV	last subject last visit
MFC	master formulation code
mg	Milligram
ml	Milliliter
MMN	multiple micronutrient
MN	multiple nutrient
NIN	National Institute of Nutrition
°C	degree centigrade
°F	degree Fahrenheit
PII	personally identifiable information
PP	per protocol
PRO	patient reported outcome
RDA	Recommended Dietary Allowance
SAE	serious adverse event
SCA	Saliva Collection Aid
SD	standard deviation
sIGA	salivary immunoglobulin A
SAP	statistical analysis plan
SOS	SalivaBio Oral Swab
SP	Study Physician
DF	Diagnosis Form
SPWR	Study Physician Weekly Review
sTfR	serum transferrin receptor
URTI	upper respiratory tract infection
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organisation
YLD	Years lost due to Disability
yrs	years

12.2. Appendix 2 - Product Nutritional Profile

CCI



12.3. Appendix 3 - Parent/LAR reported Symptom Checklist

Screening Number ____________ Week: From __ __/ __ __ __/__ __ __ __
To __ __/ __ __ __/__ __ __ __

Dear Parent/LAR,
Please report to study staff any other symptoms not listed below.
Please use DD/MM/YYYY format for entering dates.
Please use the following guidelines to grade intensity-

[1]Mild – easily tolerated, causing minimal discomfort and not interfering with normal everyday activities.

[2]Moderate – sufficiently discomforting to interfere with normal everyday activities.

[3]Severe – any event that prevents normal everyday activities.

Symptom	**Date**	**Yes**	**No**	**No of loose stools passed in a day** 3	4-6	≥7
Diarrhea/ Loose stool	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
Symptom	**Date**	**Yes**	**No**	**No of bouts in a day** 1-2	**3-5**	**≥6**
Vomiting	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐
	_ _/_ _ _/_ _ _ _	☐	☐	☐	☐	☐

Screening Number _____ **Week: From** __ __/ __ __ __/__ __ __ __
To __ __/ __ __ __/__ __ __ __

Symptom	Date	Yes	No	Oral body temperature reading 99.6-101.4°F	101.5-103.2°F	≥103.4°F
Fever	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
Symptom	**Date**	**Yes**	**No**	**Intensity** Mild[1]	Moderate[2]	Severe[3]
Dry cough	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
Symptom	**Date**	**Yes**	**No**	**Intensity** Mild[1]	Moderate[2]	Severe[3]
Wet cough	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐

Screening Number _____ **Week: From** __ __/ __ __ __/__ __ __ __
To __ __/ __ __ __/__ __ __ __

Symptom	Date	Yes	No	Mild[1]	Moderate[2]	Severe[3]
Sore throat	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
Symptom	**Date**	**Yes**	**No**	**Mild[1]**	**Moderate[2]**	**Severe[3]**
Runny Nose	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
Symptom	**Date**	**Yes**	**No**	**Mild[1]**	**Moderate[2]**	**Severe[3]**
Sneezing	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐
	__/___/____	☐	☐	☐	☐	☐

Completed by:
Name: Signature & Date:

12.4. Appendix 4 - Product Compliance Report

(For home use only)

Screening Number _____ Form Number _____

Dear Parent/LAR,
Please retain the empty product sachet and
Please enter below in case your child did not take at all/took partially any of the study drink doses that you gave at home.

Date *(DD/MMM/YYYY)*	**Dose** *(Please tick)*	**Volume of leftover drink** *(mL)*
	1st ☐	
	2nd ☐	
	1st ☐	
	2nd ☐	
	1st ☐	
	2nd ☐	
	1st ☐	
	2nd ☐	
	1st ☐	
	2nd ☐	
	1st ☐	
	2nd ☐	
	1st ☐	
	2nd ☐	
	1st ☐	
	2nd ☐	
	1st ☐	
	2nd ☐	
	1st ☐	
	2nd ☐	

Completed by:

Name: Signature & Date:

12.5. Appendix 5 - Diagnosis Form (DF)

Screening Number _____ Week: From __ __/ __ __ __/__ __ __ __
To __ __/ __ __ __/__ __ __ __

1. Was a parent/LAR symptom checklist received for this week? Yes/No
2. Did the subject inform the study physician directly of any Symptoms? Yes/No
3. If any symptoms were confirmed, was a diagnosis for GI and respiratory illnesses provided by the study physician? Yes/No/Not applicable

Note:

a) If applicable, fill out the following diagnosis chart
b) No. of ill days will be calculated programmatically for GI and respiratory illnesses reported in the study.
c) School absenteeism in the DF will be marked for absenteeism due to GI and respiratory illnesses only.
d) Number of episodes of illness for a particular week will be determined programmatically.
e) Parents/LAR will also be asked to report to the study physician/study staff any other symptoms observed in participants but are not listed parent/LAR symptom checklist and will be entered in the AE forms.

Diagnosis / Occurrences in this week	GI Illnesses (Yes ☐ No ☐)		Respiratory Illnesses (Yes ☐ No ☐)
	Diarrhea ☐	Vomiting ☐	
First Occurrence			
AE Report Number (from paper AE form)			
Start Date			
End Date			
Severity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
School absenteeism (No. of days in this week)			
AE Number (from eCRF)			
Second Occurrence			
AE Report Number (from paper AE form)			
Start Date			
End Date			
Severity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
School absenteeism[1] (No. of days in this week)			
AE Number (from eCRF)			
Third Occurrence			
AE Report Number (from paper AE form)			
Start Date			
End Date			
Severity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
School absenteeism (No. of days in this week)			
AE Number (from eCRF)			
Fourth Occurrence			
AE Report Number (from paper AE form)			
Start Date			
End Date			
Severity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
School absenteeism (No. of days in this week)			
AE Number (from eCRF)			

Severity of GI and respiratory illnesses will be captured by study physician as per severity grading captured below [CTCAE 2010]:

Illness	Mild*	Moderate**	Severe***
GI illnesses			
Diarrhea	□ Increase of <4 stools per day over baseline	□ Increase of 4-6 stools per day over baseline	□ Increase of ≥7 stools per day over baseline; incontinence; hospitalisation indicated; life-threatening consequences; urgent intervention needed
Vomiting	□ 1-2 episodes (separated by 5 minutes) in 24 hrs	□ 3-5 episodes (separated by 5 minutes) in 24 hrs	□ ≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, total parenteral nutrition or hospitalisation indicated; life-threatening consequences; urgent intervention indicated
Respiratory illnesses			
ARI	□ Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	□ Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refer to school attendance, playing, studying, participating in school activities.	□ Severe or medically significant, but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL. Life-threatening consequences; urgent indication indicated.

***Mild** (Grade 1 as per CTCAE 2010) - Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

****Moderate** (Grade 2 as per CTCAE 2010) - Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refer to school attendance, playing, studying, participating in school activities.

*****Severe** (Grade 3 & 4 as per CTCAE 2010) - (Grade 3) Severe or medically significant, but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL. (Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.) (Grade 4) Life-threatening consequences; urgent indication indicated.

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12.6. Appendix 6 - 24 hour Dietary Recall

Screening Number _____ Visit Number _____

Date: ___/____/_____ *(DD/MMM/YYYY)*

Is this a typical day? Yes or No _____

To parents/LARs

"I am going to ask you about everything that (NAME OF CHILD) ate and drank yesterday. By this I mean, 24 hours from midnight to midnight. I would like to know exactly what was eaten and drank and how much (NAME OF CHILD) had."

To Child

"I will ask you to tell me about any foods and drinks which your (MUM, DAD (main food provider)) does not know about or cannot remember. Is that okay? [Wait for agreement]."

	Food/beverage Item	**Description (Homemade/Bought)**	**Portion Size**	**Recipe[1]** *([1]Applicable only if homemade)*	**Brand[2]** *([2]Applicable only if bought)*
Morning					
Morning Snacks					

	Food/beverage Item	Description (Homemade/Bought)	Portion Size	Recipe[1] *([1]Applicable only if homemade)*	Brand[2] *([2]Applicable only if bought)*
Lunch					
Evening Snacks					
Dinner					

	Food/beverage Item	Description (Homemade/Bought)	Portion Size	Recipe[1] *([1]Applicable only if homemade)*	Brand[2] *([2]Applicable only if bought)*
Any other Food/Beverage					

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12.7. Appendix 7 - Dietary Diversity Questionnaire

Screening Number _____ Visit Number _____

Date: ___/____/_____ *(DD/MMM/YYYY)*

To be filled based on the information recorded in 24 hr dietary recall. For any food groups not mentioned, ask the respondent if a food item from this group was consumed.

Question number	Food group	Examples	YES=1 NO=0
1	CEREALS	corn/maize, rice, wheat, sorghum, millet or any other grains or foods made from these (e.g. bread, noodles, porridge or other grain products) + *any other local foods*	
2	WHITE ROOTS AND TUBERS	white potatoes, white yam, white cassava, or other foods made from roots	
3	VITAMIN A RICH VEGETABLES AND TUBERS	pumpkin, carrot, squash, or sweet potato that are orange inside + *other locally available vitamin A rich vegetables (e.g. red sweet pepper)*	
4	DARK GREEN LEAFY VEGETABLES	dark green leafy vegetables, including wild forms + *locally available vitamin A rich leaves such as amaranth, cassava leaves, kale, spinach*	
5	OTHER VEGETABLES	other vegetables (e.g. tomato, onion, eggplant) + *other locally available vegetables*	
6	VITAMIN A RICH FRUITS	ripe mango, cantaloupe, apricot (fresh or dried), ripe papaya, dried peach, and 100% fruit juice made from these + *other locally available vitamin A rich fruits*	
7	OTHER FRUITS	other fruits, including wild fruits and 100% fruit juice made from these	
8	ORGAN MEAT	liver, kidney, heart or other organ meats or blood-based foods	
9	FLESH MEATS	beef, pork, lamb, goat, rabbit, game, chicken, duck, other birds, insects	
10	EGGS	eggs from chicken, duck, guinea fowl or any other egg	
11	FISH AND SEAFOOD	fresh or dried fish or shellfish	
12	LEGUMES, NUTS AND SEEDS	dried beans, dried peas, lentils, nuts, seeds or foods made from these (e.g. hummus, peanut butter)	
13	MILK AND MILK PRODUCTS	milk, cheese, yogurt or other milk products	
14	OILS AND FATS	oil, fats or butter added to food or used for cooking	
15	SWEETS	sugar, honey, sweetened soda or sweetened juice drinks, sugary foods such as chocolates, candies, cookies and cakes	
16	SPICES, CONDIMENTS, BEVERAGES	spices (black pepper, salt), condiments (soy sauce, hot sauce), coffee, tea, alcoholic beverages	
Total			

Completed by-

Name: Signature & Date:

12.8. Appendix 8- Dietary Counselling Sessions

A. Dietary Counselling Sessions For Parents/LARs

THEME	ACTION POINTS	
	A. Topics for Dietary Education (Detailed description are mentioned in the respective NIN Dietary guidelines)	**B. Dietary Advices**
SESSION 1		
Eat variety of foods to ensure a balanced diet (based on NIN Dietary Guideline No 1)	• Why do we need nutritionally adequate foods? • What is a balanced diet? • What are food groups? • What are nutrient requirements and recommended dietary allowances (RDA)?	• Choose energy-rich, body building and protective foods (milk, vegetables and fruits) for the children in school going age group. • Use a combination of whole grains, grams and greens. Include jiggery or sugar and cooking oils to bridge the calorie or energy gap. • Prefer fresh, locally available vegetables and fruits in plenty. • Include in the diets, foods of animal origin such as milk, eggs and meat, particularly for pregnant and lactating women and children. • Adults should choose low-fat, protein-rich foods such as lean meat, fish, pulses and low-fat milk. • Develop healthy eating habits and exercise regularly and move as much as you can to avoid sedentary lifestyle.

Ensure adequate and appropriate diets for children and adolescents both in health and sickness (based on NIN Dietary Guideline No 5)	• Why do children require more food? • How do infections in children leads to malnutrition? • How should a child be fed during infections? • What should be done during diarrhea • How important is the problem of lactose intolerance?	During illness • Never starve the child. • Feed energy-rich cereals-pulse diet with milk and mashed vegetables. • Feed small quantities at frequent intervals. • Give plenty of fluids during illness. • Use oral rehydration solution to prevent and correct dehydration during diarrhea episodes
Eat plenty of vegetables and fruits (based on NIN Dietary Guideline No 6)	• Why should we eat vegetables/fruits? • What functions do these nutrients and special factors in vegetables/fruits perform in our body? • Which vegetables and fruits should be consumed? • How to prevent cooking losses? • How do we get these foods? • How to accommodate more servings of vegetables and fruits in a day?	• Eat as much of other vegetables as possible daily. • Eat vegetables/ fruits in all your meals in various forms (curry, soups, mixed with curd, added to pulse preparations and rice). • Consume raw and fresh vegetables as salads. • Grow the family's requirements of vegetables in the kitchen garden if possible. • Green leafy vegetables, when properly cleaned and cooked are safe even for infants. • Let different varieties of vegetables and fruits add color to your plate and vitality to your life. • Beta-carotene rich foods like dark green, yellow and orange colored vegetables and fruits (GLVs, carrots, papaya and mangoes) protect from vitamin A deficiency.

Avoid overeating to prevent overweight and obesity (based on NIN Dietary Guideline No 8)	• What is obesity? • What is desirable body weight or Body mass Index (BMI)? • Central obesity • Why should we avoid obesity? • What causes obesity? • How to reduce body weight?	• Slow and steady reduction in body weight is advisable. • Severe fasting may lead to health hazards. • Achieve energy balance and appropriate weight for height. • Encourage regular physical activity. • Eat small meals regularly at frequent intervals. • Cut down sugar, salt, fatty foods, refined foods, soft drinks and alcohol. • Eat complex carbohydrates, low glycemic foods and fibre rich diets. • Increase consumption of fruits and vegetables, legumes, whole grains and nuts. • Limit fat intake and shift from saturated to unsaturated fats. • Avoid trans-fatty rich foods (vanaspati, bakery products and sweets). • Use low- fat milk.

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SESSION 2		
Ensure the use of safe and clean foods (based on NIN Dietary Guideline No 11)	• What makes food unsafe? • How do we select safe food? • What are the best practices of storage? • Why do food borne diseases occur? • How should perishable foods be handled? • What about personal hygiene? • What are the common adulterants? • How to minimise effects of pesticide residues?	• Buy food items from reliable sources after careful examination. • Wash vegetables and fruits thoroughly before use. • Store the raw and cooked foods properly and prevent microbial, rodent and insect invasion. • Refrigerate perishable food items. • Maintain good personal hygiene and keep the cooking and food storage areas clean and safe. • Always use thoroughly cleaned utensils for cooking/ eating.
Adopt right pre-cooking processes and appropriate cooking methods (based on NIN Dietary Guideline No 12)	• What are common Indian food beliefs, fads and taboos? • What are the effects of the pre-cooking processes? • What are the effects of washing and cutting? • What are the effects of cooking? • Microwave Cooking	• Do not wash food grains repeatedly before cooking. • Do not wash vegetables after cutting. • Do not soak the cut vegetables in water for long periods. • Do not discard the excess water left over after cooking. Use only sufficient water for cooking. • Cook foods in vessels covered with lids. • Prefer pressure/steam cooking to deep frying/roasting. • Encourage consumption of sprouted/fermented foods. • Avoid use of baking soda while cooking pulses and vegetables. • Do not reheat the left over oil repeatedly.

Drink plenty of water and take beverages in moderation (based on NIN Dietary Guideline No 13)	• Why do we need water? • When is water considered safe and wholesome? • How is water rendered safe? • How nutritious is milk? • What is lactose intolerance? • What are soft drinks? • What about tea and coffee? • Tender coconut water • Alcohol	• Drink enough of safe and wholesome water to meet daily fluid requirements. • Drink boiled water, when safety of the water is in doubt. • Consume at least 250 ml of boiled or pasteurised milk per day. • Drink natural and fresh fruit juices instead of carbonated beverages. • Prefer tea over coffee. • Avoid alcohol. Those who drink should limit its intake.
Minimize the use of processed foods rich in salt, sugar and fats (based on NIN Dietary Guideline No 14)	• What are processed foods? • Do we need processed foods? • Do processed foods contribute to nutrient intake? • What is the difference between instant foods, fast foods, street foods and unhealthy (junk) foods? • Why should we restrict intake of unhealthy processed foods? • Why should we moderate intake of sugar?	• Prefer traditional, homemade foods. • Avoid replacing meals with snack foods. • Limit consumption of sugar and unhealthy processed foods which provide only (empty) calories. • Prefer fortified processed foods. • Always read food labels (given on containers) regarding content of nutrients, shelf-life and the additives present.

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B. Dietary Counselling Sessions For Children

THEME	**ACTION POINTS**	
	A. Topics for Dietary Education (Detailed description are mentioned in the respective NIN Dietary guidelines)	**B. Dietary Advices**
SESSION 1		
Eat variety of foods to ensure a balanced diet (based on NIN Dietary Guideline No 1)	• Why do we need nutritionally adequate foods? • What is a balanced diet? • What are food groups?	• Choose energy-rich, body building and protective foods (milk, vegetables and fruits). • Use a combination of whole grains, grams and greens. • Include jiggery or sugar and cooking oils to bridge the calorie or energy gap. • Prefer fresh, locally available vegetables and fruits in plenty. • Include in the diets, foods of animal origin such as milk, eggs and meat, particularly for pregnant and lactating women and children. • Adults should choose low-fat, protein-rich foods such as lean meat, fish, pulses and low-fat milk. • Develop healthy eating habits and exercise regularly and move as much as you can to avoid sedentary lifestyle.

Eat plenty of vegetables and fruits (based on NIN Dietary Guideline No 6)	• Why should we eat vegetables/fruits? • What functions do these nutrients and special factors in vegetables/fruits perform in our body? • Which vegetables and fruits should be consumed? • How to prevent cooking losses? • How do we get these foods? • How to accommodate more servings of vegetables and fruits in a day?	• Eat as much of other vegetables as possible daily. • Eat vegetables/ fruits in all your meals in various forms (curry, soups, mixed with curd, added to pulse preparations and rice). • Consume raw and fresh vegetables as salads. • Grow the family's requirements of vegetables in the kitchen garden if possible. • Green leafy vegetables, when properly cleaned and cooked are safe even for infants. • Let different varieties of vegetables and fruits add color to your plate and vitality to your life. • Beta-carotene rich foods like dark green, yellow and orange colored vegetables and fruits (GLVs, carrots, papaya and mangoes) protect from vitamin A deficiency.
Ensure the use of safe and clean foods (based on NIN Dietary Guideline No 11)	• What makes food unsafe? • How do we select safe food? • What are the best practices of storage? • Why do food borne diseases occur? • How should perishable foods be handled? • What about personal hygiene? • What are the common adulterants? • How to minimise effects of pesticide residues?	• Buy food items from reliable sources after careful examination. • Wash vegetables and fruits thoroughly before use. • Store the raw and cooked foods properly and prevent microbial, rodent and insect invasion. • Refrigerate perishable food items. • Maintain good personal hygiene and keep the cooking and food storage areas clean and safe. • Always use thoroughly cleaned utensils for cooking/ eating.

Completed by-

Name: Signature & Date:

SESSION 2		
Drink plenty of water and take beverages in moderation (based on NIN Dietary Guideline No 13)	• Why do we need water? • When is water considered safe and wholesome? • How is water rendered safe? • How nutritious is milk? • What is lactose intolerance? • What are soft drinks? • What about tea and coffee? • Tender coconut water • Alcohol	• Drink enough of safe and wholesome water to meet daily fluid requirements. • Drink boiled water, when safety of the water is in doubt. • Consume at least 250 ml of boiled or pasteurised milk per day. • Drink natural and fresh fruit juices instead of carbonated beverages. • Prefer tea over coffee. • Avoid alcohol. Those who drink should limit its intake.
Minimise the use of processed foods rich in salt, sugar and fats (based on NIN Dietary Guideline No 14)	• What are processed foods? • Do we need processed foods? • Do processed foods contribute to nutrient intake? • What is the difference between instant foods, fast foods, street foods and unhealthy (junk) foods? • Why should we restrict intake of unhealthy processed foods? • Why should we moderate intake of sugar?	• Prefer traditional, homemade foods. • Avoid replacing meals with snack foods. • Limit consumption of sugar and unhealthy processed foods which provide only (empty) calories. • Prefer fortified processed foods. • Always read food labels (given on containers) regarding content of nutrients, shelf-life and the additives present.

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06-Oct-2017 08:52:08	PPD
Justification	Approved

Date	Signed By
08-Oct-2017 21:17:46	PPD
Justification	Approved

Date	Signed By
10-Oct-2017 05:30:50	PPD
Justification	Clinical Operations Approval

Date	Signed By
10-Oct-2017 06:16:38	PPD
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Justification	

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Justification	