Clinical Study Protocol **NCT06122870**

***Protocol Title*:** Double-blind, Placebo-Controlled Trial Assessing the Efficacy and Safety of CampETEC Hyperimmune Bovine Colostrum (HBC) for the Prevention of Campylobacter-Mediated Diarrheal Diseases

***Protocol Version/Date*:** Version 1.1/ 12 September 2023

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***CIR Number*:** 360

Sponsor Investigator
David Sack, MD
Department of International Health
Johns Hopkins Bloomberg School of Public Health
615 N Wolfe St / E5537
Baltimore, MD 21205-5748
Telephone: 443-287-8795
Email: dsack1@jhu.edu

Principal Investigator:
Kawsar Talaat, MD
Center for Immunization Research (CIR)
Department of International Health
Johns Hopkins University (JHU)
Bloomberg School of Public Health (SPH)
624 N. Broadway, HH, Room 205
Baltimore, MD 21205

Associate Investigators"
Subhra Chakraborty, PHD
DIH, JHU, SPH

Rediet Tekalign MD, MPH
CIR, JHU, SPH

Barbara DeNearing, BSN, RN, CCRC
CIR, JHU, SPH

Courtney Swisher BSN, RN, CPEN
CIR, JHU, SPH

Brittany Feijoo, MSN, FNP-BC
CIR, JHU, SPH

Kamal Dhanjani, MPAS, PA-C, FCCM
CIR, JHU, SPH

A Louis Bourgeois, PhD
CIR, JHU, SPH

Daniel Selig, MD
Walter Reed Army Institute of Research (WRAIR)

Frederic Poly, PhD
Head, Operationally Relevant Infections Department (ORI)
Directorate for DoD Infectious Diseases (DDID)
Naval Medical Research Command (NMRC)

Chad Porter, PhD, MPH
Head, Translational and Clinical Research Department (TraCR)
DDID, NMRC

Samuel Walther, DO
TraCR, NMRC

Sandra Isidean, PhD, MPH
TraCR, NMRC

	Kayla Testa, MPH TraCR, NMRC
Research Monitor:	Nekhonti Adams, MD Director, Clinical Trials Center Translational and Clinical Research Department (TraCR) DDID, NMRC
Data Management:	The Emmes Company, LLC 401 N. Washington Street, Suite 700 Rockville, MD 20850 Telephone: 301-251-1161 (Administrative Coordinator)
Study Sites:	Center for Immunization Research (CIR) Isolation Unit 301 Building 301 Mason Lord Drive Suite 4300 Baltimore, MD 21224 CIR Outpatient Clinic 624 N Broadway, Hampton House Rm.117 Baltimore, MD 21205 Center for Immunization Research Annex 1101 North Point Blvd Suite 101 103 112 Baltimore, MD 21224
Laboratories:	Quest Diagnostics Incorporated, Baltimore, MD 21227 1901 Sulphur Spring Rd. Baltimore, MD 21227 Johns Hopkins Hospital 600 N Wolfe Street / Meyer B-130 Baltimore, MD 21287 — 7070 Johns Hopkins Bayview Medical Center 4940 Eastern Ave Baltimore, MD 21224
Immunology Laboratories:	Dilara Islam, PhD ORI, DDID, NMRC Phone: 301-319-9094 Email: dilara.islam.ctr@health.mil
Research Laboratories:	Johns Hopkins University School of Public Heath GDEC Lab 615 N. Wolfe Street Baltimore, MD 21205 Johns Hopkins Biological Repository Johns Hopkins Bloomberg School of Public Health Room W6620 / 615 N. Wolfe Street Baltimore, MD 21205 Telephone: 410-955-7203 Email: JHSPH.jhbrlab@jhu.edu
Institutional Review Board:	JHSPH IRB Office 615 N. Wolfe Street Suite E1100 Baltimore, MD 21205 Phone: 410-955-3193 Toll-Free: 1-888-262-3242 Fax: 410-502-0584 Email: JHSPH.irboffice@jhu.edu

Investigator's Agreement

Double Blind, Placebo-Controlled Trial Assessing the Efficacy and Safety of CampETEC Hyperimmune Bovine Colostrum (HBC) for the Prevention of Campylobacteriosis

"I have read this protocol and agree to conduct the study as outlined herein in accordance with International Conference on Harmonization Good Clinical Practice Guideline, and FDA and DoD Regulations."

Kawsar R. Talaat, M.D. Principal Investigator	Date

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALS	Antibodies from lymphocyte supernatant
ASC	Antibody secreting cell
BSIgG	Bovine serum-derived immunoglobulin G
CBC	Complete Blood Count
CF	ETEC colonization factor
CFA	ETEC colonization factor antigen
CFA+BS	Colonization factor antigen agar plates with bile salts
CfaB	Repeating subunit of CFA/I
CfaE	The tip-localized adhesin subunit of CFA/I
CfaEB	Fusion of CfaE and CfaB
CFU	Colony forming unit
cGMP	Current good manufacturing practice
CHIM	Controlled Human Infection Model
CLIA	Clinical Laboratory Improvement Act
CIR	Center for Immunization Research
CMI	Cell mediated immunity
CPS	Capsule polysaccharide
CPS-CfaEB	Conjugate vaccine composed of *C. jejuni* CPS conjugated to CfaEB
CWC	Campylobacter whole cell
CRP	C-Reactive Protein
CRM197	Non-toxic mutant of diphtheria toxin
DoD	Department of Defense
eCRF	Electronic Case Report Form
EDD	Enteric Disease Department
ESR	Erythrocyte Sedimentation Rate
ETEC	Enterotoxigenic *Escherichia coli*
ELISA	Enzyme-linked immunosorbent assay
FBD	Functional Bowel Disorder
FQ	Fluoroquinolones
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GE	Glycine extract
G CSF/Gm-CSF	Granulocyte colony stimulating factor/ Granulocyte-macrophage colony stimulating factor

GMP	Good Manufacturing Practice
HBC	Hyperimmune bovine colostrum
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HSRRB	Human Subjects Research Review Board (Army Surgeon General)
IBS	Irritable Bowel Syndrome
IBD	Inflammatory Bowel Disease
IFN	Interferon
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IL	Interleukin
IP	Investigational Product (CampETEC HBC)
IRB	Institutional Review Board
IVF	Intravenous fluids
JHBSPH	Johns Hopkins Bloomberg School of Public Health
JHU	Johns Hopkins University
LMIC	Low- and middle-income country
LPS	Lipopolysaccharides
LT	Heat-labile enterotoxin
MCB	Master Cell bank
MCP	Monocyte chemoattractant protein
NMRC	Naval Medical Research Command
MH	Mueller-Hinton agar
ORS	Oral Rehydration solution
PBMC	Peripheral blood mononuclear cells
PE	Protective Efficacy
PI	Principal Investigator
PSG	Protocol specific guideline
PVT	Psychomotor Vigilance Testing
QA	Quality assurance
ReA	Reactive Arthritis
SAE	Serious adverse event
SD	Study day
SOP	Standard Operating Procedure
SSP	Study Specific Procedure
ST	Heat stable enterotoxin

TD	Travelers’ diarrhea
TLUS	Time to Last Unformed Stool
TNF	Tumor necrosis factor
USP	United States Pharmacopeia
WBC	White blood cell
WIRB	Western Institutional Review Board
WRAIR	Walter Reed Army Institute of Research

CLINICAL PROTOCOL SYNOPSIS

<table>
<tr><td>Protocol Title</td><td>Double-blind, Placebo-Controlled Trial Assessing the Efficacy and Safety of CampETEC Hyperimmune Bovine Colostrum (HBC) for the Prevention of Campylobacter-Mediated Diarrheal Diseases</td></tr>
<tr><td>IND Number</td><td>28504</td></tr>
<tr><td>Investigational Products</td><td>1. CampETEC Hyperimmune Bovine Colostrum (HBC)
2. C. jejuni CG8421 challenge strain</td></tr>
<tr><td>Sponsor</td><td>David Sack, MD</td></tr>
<tr><td>Manufacturers</td><td><u>CampETEC HBC</u>
Immuron Limited
Address: Unit 10, 25 - 37 Chapman Street,
Blackburn North, VIC 3130, Australia

<u>C. jejuni strain CG8421</u>
Charles River Malvern
358 Technology Drive
Malvern, PA 19355</td></tr>
<tr><td>Principal Investigator</td><td>Kawsar Talaat, MD</td></tr>
<tr><td>Research Monitor</td><td>Nekhonti Adams, MD</td></tr>
<tr><td>Study Site</td><td>Center for Immunization Research (CIR) Isolation Unit
301 Building
301 Mason Lord Drive Suite 4300
Baltimore, MD 21224

CIR Outpatient Clinic
624 N. Broadway, Hampton House Rm. 117
Baltimore, MD 21205

Center for Immunization Research Annex
1101 North Point Blvd Suite 101 103 112
Baltimore, MD 21224</td></tr>
<tr><td>Laboratories</td><td>Quest Diagnostics Incorporated, Baltimore, MD 21227
Johns Hopkins Hospital, Baltimore, MD 21287
Johns Hopkins University School of Public Health, Baltimore, MD 21205
Johns Hopkins Biological Repository, Baltimore, MD 21205
Naval Medical Research Command, Silver Spring, MD 20910</td></tr>
<tr><td>Study Objectives</td><td>The primary objectives of the study are as follows:
1. To estimate protective efficacy (PE) of CampETEC HBC against campylobacteriosis following challenge with C. jejuni strain CG8421
2. To assess the safety and tolerability of CampETEC HBC

The secondary objectives of this research are to assess the ability of CampETEC HBC to prevent or reduce a variety of secondary clinical endpoints.
The exploratory objectives are to measure mucosal and systemic immune responses to the challenge organism, and to obtain and archive samples for future immunologic, proteomic, microbiome, and/or systems biology efforts. Additionally, we will assess the utility of a novel Campylobacter disease scoring metric, and may also assess the role of sleep on disease risk as well as the effect of disease on cognitive assessments.</td></tr>
<tr><td>Study Design</td><td>This study is designed to evaluate the ability of a hyperimmune bovine colostrum-derived IgG product to confer passive protection against C. jejuni in the controlled human infection model (CHIM).
This study is a randomized (1:1), double-blind, placebo-controlled clinical trial in which up to 30 participants will receive the investigational product (IP) or placebo three times daily following meals beginning 2 days prior to experimental challenge with C. jejuni strain CG8421. The placebo is a commercially sourced high protein milk powder called ProMilk 85. Participants will be assigned to groups as per the table below.
<table>
<tr><td>Product</td><td>N</td><td>Dose (approximate)</td></tr>
<tr><td>CampETEC HBC</td><td>15</td><td>1.0 g three times daily (tid)</td></tr>
<tr><td>Placebo</td><td>15</td><td>1.0 g tid</td></tr>
</table>
The test article/placebo will be administered for a total of 8 days, or until antibiotic treatment has been initiated. Participants will be assessed daily for adverse events and all stools will be collected to assess for the primary endpoint of campylobacteriosis post-inoculation. Any participant passing a grade 3-5 stool will be encouraged to start drinking oral rehydration</td></tr>
</table>

	solution (ORS) (an oral glucose/electrolyte solution to prevent dehydration) or Gatorade (or a similar rehydration drink) at a rate equal to their stool output. Intravenous (IV) rehydration will be provided if pre-specified criteria are met. All participants will be treated with ciprofloxacin (500 mg by mouth twice daily for 5 days) and azithromycin (500 mg by mouth daily for 5 days) six days after ingesting the challenge strain unless early treatment criteria are met. Alternate antibiotic treatment to which the strain is susceptible may also be considered as clinically appropriate. Participants will be discharged from the inpatient facility when clinical symptoms are resolved or resolving, two doses of antibiotics are taken, AND two consecutive stool cultures are negative for *C. jejuni*. All participants will receive *C. jejuni* strain CG8421 administered one time at a target dose of $5x10^5$ colony-forming units (CFU) diluted in 30 mL sodium bicarbonate buffer following a 90 minute fast.
Primary and Secondary Endpoints	The primary efficacy outcome is campylobacteriosis, defined as a clinical illness meeting at least one of the following patterns starting within 144 hours of challenge: • Moderate diarrhea (4 to 5 loose/liquid stools or 401-800 grams in any 24 hour period) OR • Severe diarrhea (≥ 6 loose/liquid stools or > 800 grams in any 24 hour period) OR • Fever (present on at least 2 occasions, at least 20 minutes apart) without diarrhea, plus an associated symptom (nausea, vomiting, abdominal cramps, tenesmus, or dysentery (gross blood in ≥ 2 grade 3 – 5 stools with in any 24 hour period); with consideration of potential alternative diagnosis per clinical investigator based on illness time course and associated symptoms. The primary safety and tolerability outcome is the presence of CampETEC HBC-associated adverse events during the study period. Secondary efficacy endpoints are chosen to support the primary endpoint in determining the protective efficacy of the CampETEC product. They further quantify and qualify the degree to which a participant experiences Campylobacter-attributable disease. • Evaluate the efficacy of CampETEC in reducing various clinical and microbiological outcomes (e.g. disease severity, fever, dysentery, stool frequency, shedding).
Exploratory Endpoints	Exploratory endpoints include microbiology, immunogenicity, clinical and cognitive. • Microbiology: Intestinal colonization by the challenge strain will be assessed by monitoring fecal shedding patterns by qualitative culture. Quantitative cultures for the challenge strain will be performed on selected inpatient days. • Immunogenicity: Evaluate the natural immune response to *C. jejuni* infections in humans. • Blood and stool samples to detect an immune response to the infection may include assays using the *Campylobacter* glycine extracts (GE) antigen.). o Systemic immune response: Assays to determine *Campylobacter* antigen-specific (GE) serum IgA and IgG responses will be performed. • Stool collected from the participants will be used to assess for *Campylobacter* antigen-specific (GE) fecal IgA and total fecal IgA responses. • Clinical Response: We will utilize a new *Campylobacter* disease scoring metric to assess its performance in this trial. • Functional Bowel Symptom Development: A functional bowel survey based on Rome criteria will be used to assess the prevalence of baseline bowel symptoms as well as the development of such symptoms at 6 months after challenge. Incidence of functional bowel symptoms will be compared among those who develop campylobacteriosis after challenge relative to those who may be protected from illness and against the expected incidence in the normal population. • Cognitive evaluations: Exploratory evaluations of the cognitive impacts of acute diarrhea may be performed with the use psychomotor vigilance testing (PVT). Participant samples may also be collected for potential future use, to include the following studies: antibody in lymphocyte supernatant (ALS), memory B cells, flow cytometry, fecal microbiota, and serum and fecal proteomics.
Study Duration	Volunteers will complete 1-3 screening visits that may occur up to 120 days prior to enrollment under a separate IRB approved screening protocol. Consenting and eligible volunteers will spend approximately 13 days on the inpatient isolation unit. They will be asked to return for 5-6 outpatient follow-up visits at 15, 29, 42, 57, and 85 days post challenge and complete a telephone assessment 6 months post-challenge. A visit at day 113 will be added if there is any recrudescence at day 85. Additional outpatient follow-up visits may be required if any participant has a recrudescent infection after completing antibiotic treatment. The total planned participation for an individual volunteer is about 9 months.

	Screening, study intervention, CHIM, follow-up, immunology studies, analysis, and reporting after all volunteer contact is complete is anticipated to take 1.5 to 2 years.
Eligibility Criteria	Inclusion Criteria: 1. Adult between 18 and 50 years of age, inclusive. 2. General good health, without significant medical illness, abnormal physical examination findings, or clinical laboratory abnormalities, as determined by principal investigator (PI) or PI in consultation with the research monitor and sponsor. 3. Demonstrate comprehension of the protocol procedures, requirements, and CHIM by passing a written examination (passing grade ≥ 70%). 4. Willing to participate, as evidenced by signing the informed consent document. 5. Available for all planned follow-up visits. 6. Negative serum pregnancy test at screening and negative serum and/or urine pregnancy test on the day of admittance to the inpatient phase for participants of childbearing potential. Participants of childbearing potential must agree to use an efficacious hormonal or barrier method of birth control during the study. Abstinence from intercourse with a male partner is acceptable. Participants who no longer have childbearing potential must have this documented (e.g., tubal ligation or hysterectomy). Exclusion criteria: 1. Presence of a significant medical condition (e.g., psychiatric conditions, such as significant anxiety, depression, or somatization disorder; gastrointestinal disease, such as peptic ulcer, symptoms or evidence of active gastritis/dyspepsia, gastroesophageal reflux disease, inflammatory bowel disease, irritable bowel syndrome (as suggested by the functional bowel disorder survey or medical diagnosis); alcohol or illicit drug abuse/dependency; or laboratory abnormalities that in the opinion of the investigator preclude participation in the study. Significant medical conditions include evidence of cardiac, pulmonary, endocrine, neurologic or renal disease that is uncontrolled or poorly controlled, any diabetes mellitus, and other such illnesses that can put a volunteer at increased risk. Exclusionary laboratory abnormalities include any abnormality that is grade 2 or above. 2. Immunosuppressive illness or evidence of IgA deficiency (serum IgA < 7 mg/dL or below the limit of detection of assay), or any autoimmune disease. 3. Positive serology results for HIV, HBsAg, or HCV antibodies, and confirmatory tests if appropriate. 4. Positive urine toxicology screen for amphetamines, barbiturates, benzodiazepines, cocaine metabolite, methadone metabolite, opiates, oxycodone, or phencyclidine. 5. Significant abnormalities in screening laboratory hematology or serum chemistry, as determined by PI or PI in consultation with the research monitor and sponsor. 6. Evidence of abnormal ECG findings per PI (e.g., QT prolongation) 7. Use of any medication known to affect immune function (e.g., regular systemic corticosteroids, monoclonal antibodies that target key aspects of the immune system (such as rituximab or TNF blockers); others [topical, intranasal and inhaled steroids will be permitted]) within 30 days preceding receipt of the investigational product or planned to be used during the active study period. 8. Nursing or lactating on the day of admittance to the inpatient unit. 9. Inability to tolerate 150 mL sodium bicarbonate buffer (based on requirement for frequent dosing). 10. Recent vaccination (including licensed vaccines) or receipt of an investigational product (within 30 days before challenge through 30 days following the last challenge dose). 11. Prior history of *C. difficile* infection 12. History of diarrhea in the 2 weeks prior to planned inpatient phase. 13. Fewer than 3 stools per week or more than 3 stools per day as the usual frequency, or loose or liquid stools other than on an occasional basis. 14. Regular use of laxatives or any agent that increases gastric pH (regular defined as at least weekly). 15. Use of proton pump inhibitors, H2 blockers, or antacids within 48 hours of dosing. 16. A fever (≥ 38.0°C) in the 2 weeks prior to time of challenge. 17. Use of antibiotics during the 7 days before bacterial dosing or receipt of more than 2 courses of antibiotics over the two months prior to dosing. 18. Blood donation within 30 days prior to the planned receipt of this IP. 19. Lactose intolerance or allergy to milk or milk products. 20. Personal or documented family history of Guillain-Barré syndrome or neuromuscular disease; or an inflammatory arthritis such as reactive arthritis, ankylosing spondylitis, or rheumatoid arthritis. 21. Evidence of inflammatory arthritis on exam. 22. HLA-B27 positive.

	23. Allergy or prior intolerance to two or more of the following: fluoroquinolones, azithromycin, augmentin or cephalosporins 24. Have household contacts who are < 2 years old or > 80 years old or infirm or immunocompromised. 25. Employment as a healthcare worker with direct patient care, in a daycare center (for children or the elderly), or direct food handler; includes individuals who work directly with food in commercial establishments. 26. History of microbiologically confirmed *Campylobacter* infection in last 3 years. 27. Serological immunological evidence of prior *Campylobacter* exposure defined as *Campylobacter* antigen-specific (GE)specific anti-glycine extract serum IgA endpoint titer > 1:4,000. 28. Occupation involving handling of *Campylobacter* currently, or in the past 3 years. 29. Symptoms consistent with travelers' diarrhea concurrent with travel to countries where *Campylobacter, Cholera, Salmonella, Shigella, Typhoid or ETEC* infection are endemic (most of the developing world) within 3 years prior to dosing, OR planned travel to endemic countries during the length of the study. 30. Vaccination for or ingestion of *Campylobacter, Cholera, Salmonella, Shigella, Typhoid, or ETEC* within 5 years prior to dosing. 31. Other dietary or environmental exposures that may place the participant at high risk for prior *Campylobacter* exposure (to be determined on a case-by-case basis by the PI).
CampETEC Dose Preparation	Sachets of CampETEC HBC (and placebo) will be stored at 2-8°C. Individual doses will be prepared by reconstituting in 150 mL water containing 2 g sodium bicarbonate for ingestion by a single individual. Each volunteer will receive either the CampETEC or placebo 3 times a day on specified study days. Preparation procedures will be detailed in the MOP.
***C. jejuni* Challenge Strain Preparation**	Vials from the master cell bank will be thawed at room temperature. One hundred microliters of the master cell bank lot will be spread onto an appropriate number of Mueller-Hinton agar plates for confluent growth and incubated overnight (21±1 hours) at 42°C under microaerobic conditions. After overnight growth, *C. jejuni* identity will be confirmed by Gram stain, oxidase testing, and confirmation of darting motility. After confirmation, bacterial biomass will be harvested by suspension in sterile PBS and adjusted to the appropriate optical density to achieve the target inoculum. Challenge inoculum will be verified by enumeration of viable counts and purity will be determined by plating and incubating according to study-specific procedures.
Clinical Evaluation and Management of Recrudescence	In the event of a recrudescence, participants will be assessed as soon as possible with a medical interview and physical assessments. Antibiotic treatment will be initiated (same dosage as initial regimen). The *C. jejuni* isolate will be tested to ensure continued antibiotic susceptibility. The isolate will also be tested to verify that it is strain CG8421. Repeat stool collection will occur with testing for stool microbiology, and expanded to include routine *C. difficile*, stool bacteriology, and parasitology, if appropriate. The participant may be tested for evidence of immunocompromise; including possible hypogammaglobulinemia testing and a repeat HIV test. The participant will be followed for a total of 6 months from the date of documented infection recurrence. The date of the stool from which the recrudescence was identified will be recrudescence day 1 for follow-up purposes. Follow-up will include medical interview and physical assessment on recrudescence day 15 along with repeat stool collection for microbiology. On recrudescence days 29, 42, 57, and 85, the participant will undergo a medical interview and physical assessment, along with stool collection for microbiology; on recrudescence days 57 and 85, stool may also be collected for exploratory endpoints. Follow-up will be completed with a telephone interview on day 181 (± 30 days) to inquire about new-onset serious health events. In the event of any recrudescence on day 85 any volunteer who has not previously recrudesced will be asked to return on day 113 for an additional visit.
Sample Size Estimate/Analysis	The null hypothesis is that the proportion of participants with campylobacteriosis will be the same in participants receiving CampETEC HBC compared to those receiving placebo. A Fisher's Exact Test with a 5% two-sided significance level will have 79% power to detect the difference between a group 1 proportion, π_1, of 0.68 and a group 2 proportion, π_2, of 0.136 (this is precisely 80% efficacy) when the sample size in each group is 15.

Table 1: Time and Events Schedule

	Screening[a] (1-3 visits)		**Test Article Dosing and Challenge Phase (Inpatient)**												**F/U (Outpatient)**						
Study Event	**-120 - -4**		**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10[b]**	**15**	**29**	**42**	**57**	**85**	**113[c]**	**181[d]**
Compliance Range (study day)	-120 to -4	-30 to -4	--	--	--	--	--	--	--	--	--	--	--	--		±2	±2	±2	±2	±2	±2	±30
Outpatient	X	X														X	X	X	X	X[n]	(X)	
Inpatient stay			X	X	X	X	X	X	X	X	X	X	X	X	X							
Comprehension assessment/consenting	(X)	X																				
Medical interview	(X)	X																				
Complete physical exam[e]	(X)	X	X																			
Interim history				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Focused physical exam			X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	
Assess AEs				X	X	X	X	X	X	X	X	X	X	X	(X)	X	X	X	X	X		
Assess AESIs[f] & SAEs						X	X	X	X	X	X	X	X	X	(X)	X	X	X	X	X	X	X
Assess medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Campylobacter prior exposure test	X	(X)																				
Vital signs[g]	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serology (HIV, HbsAg, HCV), IgA level, HLA-B27, and ABO blood typing	(X)	X																				
COVID-19 testing[h]			X																			
CBC with differential	(X)	X	X													X						
Serum chemistry[i]	(X)	X	X													X						
Serum pregnancy test (people of child-bearing potential)	(X)	X	X																			
Drug screen (urine)[j]		X																				
ECG		X																				
Urine hCG				(X)		X											X					
Functional bowel disorder survey	(X)	X																				X
CampETEC HBC				X	X	X	X	X	X	X	X											

	Screening[a] (1-3 visits)		Test Article Dosing and Challenge Phase (Inpatient)												F/U (Outpatient)						
Study Event	**-120 - -4**		**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10[b]**	**15**	**29**	**42**	**57**	**85**	**113[c]**	**181[d]**
Compliance Range (study day)	-120 to -4	-30 to -4	--	--	--	--	--	--	--	--	--	--	--	--		±2	±2	±2	±2	±2	±2	±30
Challenge						X																
Start antibiotic therapy[k]												X										
Cognitive assessment[l]			X	X	X	X	X	X	X	X	X	X	X	X	(X)							
Stool weighing/grading				X	X	X	X	X	X	X	X	X	X	X	X							
Stool bacteriology (*C. jejuni* detection)[m]						(X)	X	X	X	X	X	X	X	X	(X)	X	X	X	X	X	X	
Stool collection for exploratory objectives			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	
Serum for exploratory objectives			X				X		X				X			X	X		X	X		
PBMCs for exploratory objectives			(X)										X				X			X		
Fingerstick for whole blood[n]			X				X		X				X				X					
Discharge from inpatient phase															X							
Telephone follow-up																						X
CPT (#, mL)-research			8, 64										8, 64				8, 64			8, 64		
SST (#, mL)- research			1, 10				1, 10		1, 10				1, 10			1, 10	1, 10		1, 10	1, 10		
Other screening blood volume[o] (approximate)	(X)	(X)	(10)								0					10						
Approximate total Blood volume (mL)[p]	10	60	84	0	0	0	10	0	10	0	0	0	74	0	0	20	74	0	10	74	0	0

Notes: (X) denotes optional event or procedure. Study completion is defined as a participant completing all clinic visits.

[a] Screening may consist of 1 to 3 visits. If within day -30 window, all screening activities may take place at one visit. After screening, participant continuing eligibility must be confirmed by reassessing relevant inclusion and exclusion criteria prior to first dose of IP, on either day of admission or day -2.

[b] Participants may be discharged from the inpatient phase of the study when they feel well enough, clinical symptoms have resolved or are resolving, have completed at least two doses of antibiotics, and have 2 consecutive negative stool cultures. Participants will be required to complete their antibiotics as outpatients. Participants who meet criteria for discharge will no longer have daily procedures completed. If eligible for early discharge prior to day 8, participants will be required to return to center on Days 8 for collection of samples, vital signs, interim history, AEs and SAEs. If GI symptoms they will have a focused PE. If a participant discharges prior to day 8 they will return on day 8 and have procedures as above.

[c] A visit on day 113 will occur with the collection of stool specimens for *C. jejuni* and exploratory assays for previously non-recrudesced participants only if there are one or more recrudescent participants on day 85.

[d] D 181 (+/- 30 days) phone call to inquire about new-onset serious health events or hospitalizations.

[e] Physical examination will include: HEENT (Head; Ears; Eyes; Nose; Throat), skin, respiratory (lung), cardiovascular (heart), abdomen, neurological and musculoskeletal systems, and will be done at screening and on admission. During the inpatient period, a symptom-focused physical examination will be completed.

[f] AESI include new diagnosis of GBS, ankylosing spondylitis, reactive arthritis, any autoimmune disease after challenge, IBD, IBS

[g] If a VS needs to be repeated, standard practice will be to repeat the VS within approximately 20 minutes of the original reading. Only the VS that needs to be repeated will be repeated. Both the original and repeat measurements will be recorded in the study source documents; however, only the repeat measurement will be recorded in the CRF field for that measurement if needed.

The following VS are obtained and documented in the source documents:

- During the screening visit
- At least 3 times daily during inpatient period

- Before and after challenge
- At each in-person outpatient visit

A grade 1 bradycardia, or other grade 1 abnormalities will not be considered to be exclusionary at screening, unless judged to be clinically significant by the PI. Clinically relevant and concurrent medical conditions or surgical procedures will be recorded as medical history if the onset is prior to administration of IP. This includes pre-existing lab abnormalities, VS abnormalities, and symptoms associated with menses (e.g., cramps, headaches, etc.). Grade 2 abnormalities recorded after screening but prior to challenge administration will be determined on a case-by-case basis at PI discretion. Clinically significant abnormalities not on the toxicology table can be recorded on the MH if deemed necessary by the PI.

The following VS will be captured in the electronic CRF:

- Screening
- Admission
- Before and after challenge
- At discharge
- At outpatient visit days 15, 29, 42, 57 and 85
- In addition, any abnormal VS deemed to be clinically significant or clinically relevant may also be entered into the eCRF.

[h] COVID-19 testing will be completed on presentation for admission

[I] Serum chemistry CMP will include at a minimum: serum transaminases (ALT), Na, K+, BUN creatinine, random glucose. Follow-up samples may be taken if clinically significant abnormalities are seen. Clinically relevant laboratory abnormalities will be recorded as medical history if obtained before receipt of first IP.

[j] Urine drug screen will test for the presence of amphetamine, barbiturates, opiates, phencyclidine, cocaine, benzodiazepine, and methadone at screening and at the discretion of the study clinician. In addition, the study clinician may ask for a sample to test for the presence of antibiotics.

[k] Participants may begin antibiotic treatment early if one or more criteria are met.

[l] Exploratory cognitive assessments may be performed on individuals during the inpatient phase (thrice daily) using PVT evaluation.

[m] Stool sample for bacteriology will begin the day after challenge, or prior to institution of early antibiotic therapy (whichever is sooner). If a stool sample is not obtained before 1300 hours, a rectal swab will be obtained. Swabs will be used only for bacteriology. Stool samples will be collected for assays as specified in the laboratory study event schedule and as per written SSPs.

[n] Whole blood from finger pricks will be collected on filter paper, dried, and stored at -80°C for exploratory objectives.

[o] Additional blood samples may be collected on a case-by-case basis at the investigator's discretion in the event of clinically significant abnormalities.

[p] Blood for immunology endpoints will be collected as specified in the laboratory study event schedule and as per written SSPs. Blood volumes do not include fingerstick amount. Approximate total blood volume to be collected is <500 mL in 6 months.

1.0 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Diarrheal Disease

Gastrointestinal infections cause significant morbidity in the form of acute diarrheal illness in the United States (US) [1] and among travelers to low- and middle-income countries (LMICs) [2]. Among infants, young children, and vulnerable populations in resource-limited countries, the acute morbidity and mortality stemming from infectious diarrhea are particularly meaningful [3]. Nearly 500,000 deaths occurred among children aged ≤5 years in 2016 alone [3]. Although the number of pediatric deaths due to diarrhea has decreased over the last several decades, morbidity remains unchanged. In addition to the acute illness, diarrhea can lead to the development of wasting and stunting in the most vulnerable children, causing long-term chronic disease and cognitive limitation [3].

Diarrhea continues to be the most frequent health problem among travelers with destinations in lower and middle-income regions [4]. Deployed US military personnel, essentially representing a long-term traveler population, are particularly affected given their population dynamics and the context in which they seek care and treatment [5]. Diarrhea is the leading infectious disease threat to the overall health and preparedness of deployed US armed forces, with diarrheagenic *E. coli*, Campylobacter spp., and Shigella spp. among the most commonly reported etiologies [2, 6]. Diarrheal illness threatens operational capability through lost duty days and mission degradation and has had historically devastating effects on military units in almost all identifiable military campaigns [5, 7]. Research outlining the impacts of TD on military deployments continues to accumulate alongside a burgeoning evidence base of the chronic health consequences of the illness [8-10]. Corollaries to this deployment health threat collectively include the direct costs of acute diarrheal illness, secondary costs and risks associated with diminished service capabilities, and potential for long-term costs of post-infectious care and treatment [11].

Diarrheal disease is primarily managed by oral rehydration and antibiotic treatment; however, antibiotics are not recommended for prophylaxis due to risks of side-effects from prolonged use and increasing levels of antibiotic resistance globally [12, 13]. Until vaccines become available, there is an urgent need for the development of effective primary prevention modalities that are suitable for use in different contingencies.

1.1.1 Campylobacter

Campylobacter is a leading cause of foodborne disease in the US, is associated with 7.5 million disability adjusted life years globally [23] and is a pathogen of concern in pediatric populations in LMICs and adult travelers to those same regions [1, 2, 24]. Campylobacteriosis disproportionately affects poor and marginalized populations of the developing world and is particularly hazardous to the health and viability of infants in this region. The global diarrhea burden caused by Campylobacter spp. is estimated to include 88 million episodes in children aged ≤5 years, resulting in roughly 41,000 deaths [3]. Among all age groups, the estimates of episodes and deaths are roughly 172 million and 75,000, respectively [3]. In the US, Campylobacter causes more than 1.5 million illnesses each year mostly due to the handling and consumption of raw or undercooked poultry [1, 25]. For travelers, Campylobacter causes a severe form of TD, often associated with longer illness duration, increased number of unformed stools, and a high frequency of other symptoms (abdominal pain, nausea, vomiting, and fever) in comparison with other TD etiologies [2]. In addition, Campylobacter infection is associated with several important sequelae, including Guillain-Barré syndrome (GBS), reactive arthritis, irritable bowel syndrome, and, to a lesser extent, inflammatory bowel disease [8]. Until recently, campylobacteriosis has been viewed as a self-limiting illness that is ameliorated by antibiotic treatment; however, resistance of Campylobacter to antibiotics, particularly fluoroquinolones, has become a concern [26]. Thus, alternative measures to control infection are needed.

C. jejuni lacks virulence factors analogous to those of better-characterized pathogens [27]. However, the *C. jejuni* CPS was recently identified and is now recognized as a major virulence factor and the focus of vaccine development efforts [28, 29]. A total of 47 *C. jejuni* capsule types have been described and through structure homology can be collapsed into 35 groups [30]. Based on scant epidemiological data from developing countries, it appears that a limited number of *C. jejuni* capsule types are responsible for the majority of the disease [31].

1.2 Rationale for a Campylobacter-ETEC Hyperimmune Bovine Colostrum (CampETEC HBC)

Vaccines have been repeatedly demonstrated to be a cost-effective means of primary disease prevention; however, vaccine development is a long and costly process and there are currently no licensed vaccines available for ETEC or *C. jejuni*. As such, alternative options with a less prolonged and costly footprint for development are needed. One modality that has shown considerable promise in diarrhea prevention is passive, oral administration of HBC, hyperimmune bovine colostrum. Briefly, cows immunized with antigens derived from viral, bacterial, or parasitic enteropathogens, produce high levels of antigen-specific IgG in their colostrum. Manufacturing processes to make concentrates of these products that are highly enriched for IgG are well-developed, reliable, and effective. In a number of clinical trials, HBC as well as bovine serum IgG (BSIgG), with specific activity against enteropathogens like ETEC, Shigella, and rotavirus, have shown to prevent diarrheal disease in CHIMs [32-37]. While there is no bovine immunoglobulin antidiarrheal product licensed in the US for human use, there are comparable veterinary products [38] as well as commercially available as a dietary supplement. Using this platform, we are advancing an ETEC-*C. jejuni*-based hyperimmune bovine colostrum (HBC) using immunizing antigens for cows developed from ongoing human vaccine development efforts.

1.2.1 *C. jejuni* HS23/36 Capsule

As noted above, the *C. jejuni* capsule is a major virulence determinant for Campylobacter-mediated disease. Mutants deficient in capsule production exhibit decreased adherence and binding in vitro [43], complement resistance [44], and exhibit reduced colonization in the ferret model of disease [43]. NMRC is currently developing a *C. jejuni* CPS conjugate vaccine for the prevention of campylobacteriosis in US military troops [45]. The prototype vaccine is composed of HS23/36 CPS type conjugated to CRM_{197}.

When parenterally administered to *Aotus nancymaae*, the vaccine demonstrated 100% protection against disease following challenge with a *C. jejuni* strain expressing the HS23/36 CPS type [45].

1.2.2 ETEC CfaEB

As part of an active ETEC vaccine development program, investigators at NMRC developed a recombinant fusion protein containing the adhesin (CfaE) and pilin (CfaB) subunit proteins of CFA/I as part of one component of a multivalent vaccine approach. In a Phase 1 CHIM study, an HBC concentrate derived from cows immunized with killed ETEC of many different serotypes and a cocktail of enterotoxins yielded 100% protection following challenge with the prototype ETEC strain H10407 (CFA/I; LT/ST; O78:H11) [32]. The central role of exogenous antibodies to CFA/I in such protection was confirmed in a subsequent trial where orally administered HBC made from cows immunized with purified CFA/I conferred 90% protection against H10407 challenge in a placebo controlled volunteer trial [37]. Investigators at NMRC followed that work by demonstrating that HBC made from cows immunized with purified CFA/I as well as CfaE significantly protected volunteers from diarrhea after challenge with ETEC strain H10407 [35].

While antibodies against CfaE are expected to neutralize ETEC adhesion to host cells and protect against infection, CfaE is only a minor component of CFA/I and the majority of antibodies raised against CFA/I are to CfaB. Although CfaB is not thought to participate in the adhesion of ETEC to epithelial cells, oral administration of anti-CFA/I HBC to human volunteers was also protective against ETEC challenge. Thus, anti-CfaB antibodies may also play a role in protection against ETEC infection. In contrast to neutralizing the functionality of the fimbriae, the anti-CfaB antibodies damage the biomechanical properties of the fimbriae by increasing their stiffness and, due to their bivalent binding moiety, tangling two or more fimbriae together [39]. Given the lack of sufficient antibody response to CfaE in immunizations with CFA/I, we designed a stable, recombinant fusion that consists of donor strand complemented CfaB fused to the C-terminus of CfaE, resulting in a CfaE-CfaB fusion (CfaEB) using donor strand complementation as previously described [40]. In mice, intradermal immunization with an attenuated mutant of the heat-labile enterotoxin led to robust immune responses against both CFA/I and to CfaE [41, 42].

1.2.3 Campylobacter-ETEC CPS-CfaEB

Based on these data, a research grade formulation of the CPS-CfaEB conjugate was recently evaluated for immunogenicity in mice and demonstrated an ability to induce robust immune responses against both the *C. jejuni* and ETEC components [46]. A similar construct has been utilized to immunize cows, and colostrum from the immunized cows has been collected and will be processed to assess whether antibodies directed to this conjugate bi-pathogen vaccine are able to prevent ETEC- and Campylobacter-attributable illness in two separate controlled human infection model (CHIM) studies.

1.3 Previous Clinical Studies Using Bovine-Derived Immunoprophylactics

While the CampETEC product has not been administered to humans previously, concentrates of immunoglobulin from bovine milk, colostrum, or serum have been evaluated in several human clinical trials in hundreds of volunteers, and these products have been very well-tolerated. The products have been investigated as both a prophylactic and treatment for infectious diseases caused by organisms like diarrheagenic *E. coli* [35-37, 47-52], rotavirus [34, 53-55], Shigella [33], *V. cholerae* [56], *Cryptosporidium parvum* [57-60], *Clostridium difficile* [61, 62], and *Helicobacter pylori* [63]. Depending on the target disease and population, the products have been tested for safety and efficacy in healthy adults, immunocompromised adults and children, and healthy children or children hospitalized with diarrhea.

1.4 *C. jejuni* CG8421 Controlled Human Infection Model

The *C. jejuni* CG8421 strain was isolated from a 29-year-old male US soldier deployed in Thailand and is sensitive to nalidixic acid, ciprofloxacin, and azithromycin, with resistance to tetracycline. The strain has been characterized in detail and was determined to lack ganglioside mimicry [64, 65]. Clinical evaluation of *C. jejuni* strain CG8421 has been undertaken in healthy adult participants at doses ranging from 1 x 10^4 CFU to 1 x 10^6 CFU, with an acceptable safety profile [66-68]. After an initial dose-ranging study [66], the strain was subsequently utilized to assess the efficacy of a prototype vaccine, ACE393; however, doses administered fell below the target dose of 5 x 10^5 CFU, which yielded lower placebo attack rates than anticipated (71%) (B. Kirkpatrick, personal communication; NCT00859716). The strain was used in a subsequent study of homologous protection; however, there were no significant differences were observed in the number or volume of diarrheal stools, incubation time, or duration of the diarrheal episode among those who met the primary outcome [68]. Most recently, 1.7 x 10^5 CFU was given in a randomized, double-blind study testing the prophylactic efficacy of rifaximin, producing an 84.6% attack rate among participants receiving placebo [67]. In the initial dose-finding study, 3 unexpected events of microbial recrudescence of the challenge strain occurred in two participants (8.7%) [66]. All three events occurred after apparent clearance of the *C. jejuni* strain and discharge from the clinical unit, after completing a course of azithromycin treatment. The recrudescent events were treated with additional courses of antibiotics, closely monitored, and evaluated by the clinical team. Subsequent studies with this strain have closely monitored for recrudescent infection, to include extended antibiotic treatment and duration of follow-up. In the most recent study, a higher rate (17.9%) of recrudescence 3-4 weeks post-inoculation was observed [67]. One possible explanation for this higher recrudescence rate is a slight modification of the stool microbiological methods used for Campylobacter culture post-inoculation. Specifically, stool specimens were incubated in thioglycolate broth prior to plating on CVA (cefoperazone, vancomycin, and amphotericin B) solid media. This intermediate incubation in thioglycolate had not been utilized in previous trials but will be utilized for the study described herein.

2.0 OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

1. To estimate protective efficacy of CampETEC HBC against campylobacteriosis following challenge with *C. jejuni* strain CG8421

The primary efficacy outcome is campylobacteriosis, defined as a clinical illness meeting at least one of the following patterns starting within 144 hours of challenge:

- Moderate diarrhea (4 to 5 loose/liquid stools or 401-800 grams) OR
- Severe diarrhea (≥ 6 loose/liquid stools or > 800 grams) OR
- Fever (present on at least 2 occasions, at least 20 minutes apart) without diarrhea, plus an associated symptom (nausea, vomiting, abdominal cramps, tenesmus, or gross blood in ≥ 2 stools); with consideration of potential alternative diagnosis per clinical investigator based on illness time course and associated symptoms.

2. To assess the safety and tolerability of CampETEC HBC

2.2 Secondary Objectives

The secondary objectives of this research are to assess a variety of clinical endpoints to further evaluate the efficacy of CampETEC. Secondary efficacy endpoints are chosen to support the primary endpoint in determining the PE of the CampETEC product. They further quantify and qualify the degree to which a participant experiences *Campylobacter*-attributable diarrhea.

- Secondary endpoints will be to evaluate the efficacy of CampETEC in reducing various clinical and microbiological outcomes (e.g. disease severity, fever, dysentery, stool frequency, shedding).

2.3 Exploratory Objectives

Exploratory objectives are to measure mucosal and systemic immune responses to the challenge organism, and to obtain and archive samples for future immunologic, proteomic, microbiome, and/or systems biology efforts. Additionally, . Additionally, we will assess the utility of a novel *Campylobacter* disease scoring metric, and participants may also be evaluated to assess the role of sleep on disease susceptibility as well as the effect of acute infection on cognition (as assessed by a psychomotor vigilance test).

3.0 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled study designed to investigate whether CampETEC HBC protects adult volunteers from clinical disease upon challenge with *C. jejuni* strain CG8421. Up to 30 participants will be randomized to receive either the investigational product or a placebo followed by challenge with *C. jejuni* strain CG8421.

Table 2 : Description of Study Groups

Test Article	n	Dose Amount (in grams IgG)
CampETEC HBC	15	1.0 g tid
Placebo (ProMilk 85)	15	1.0 g tid

The trial will consist of 1-3 screening visits, approximately 13 inpatient days, 5-6 out-patient follow-up visits, and a follow-up phone call at 6 months post challenge. Participants will be admitted 3 days prior to challenge (SD -3), receive HBC or placebo three times daily starting 2 days prior to challenge (SD -2). The *C. jejuni* strain CG8421 challenge will be administered on Study Day 1. Participants will continue HBC dosing through the end up study day 6 (until antibiotic treatment is initiated on study day 7), or sooner if criteria for early treatment are met.

Each CampETEC HBC unit (1 g of product in a foil packet), will be reconstituted by the research pharmacist in 150 mL water containing 2 g sodium bicarbonate for ingestion by a single individual. Each volunteer will receive either the HBC or placebo 3 times a day, approximately15 minutes post meals for a period of 8 days (from 2 days prior to challenge through study day 7) or until antibiotic treatment is initiated.

Previous CHIM studies utilizing this formulation have been successful, with participants exhibiting minimal complications other than flatulence [1]. A high protein milk product called ProMilk 85 will be commercially sourced and used as a placebo control in the study. The placebo will be repackaged and labeled to mirror the HBC product and should appear similar to the HBC product when reconstituted.

Upon admission to the inpatient unit, clinical monitoring will consist of

- daily medical assessments with adverse event (AE) determination,
- vital signs at least three times daily,
- weighing and grading of all stools,
- stool culture for the challenge study strain (up to 3 samples daily) starting day after challenge, and
- safety laboratory tests–- CBC, chemistry, renal, and hepatic panels.

Antibiotic treatment will be initiated on study day 7 or according to criteria for early antibiotic treatment. Participants will be discharged from the inpatient facility when they feel well enough (clinical symptoms are resolved or resolving), 2 consecutive stool samples culture negative for the challenge strain and at least two doses of antibiotic treatment have been taken. Routine discharge is scheduled for day 10–- when most participants are expected to meet the discharge criteria. Participants may be discharged earlier than day 9 on if they meet criteria per the PIs' discretion. Participants who do not meet the discharge criteria on day 10 will remain on the unit until all criteria have been met. The duration of the active study period is approximately twelve months, encompassing up to 90

days of screening/enrollment, 12 weeks for the inpatient/outpatient phase when data and samples will be collected, 12 weeks for immunology assays, and 3 months for analysis and reporting. Additionally, participants will be contacted approximately 6 months after challenge to assess SAEs, AESIs, and any new chronic illnesses, and to complete the functional bowel disorder survey.

4.0 STUDY POPULATION

The study site will recruit participants from the greater Baltimore, Washington DC and the broader mid-Atlantic and the northeast regions using a wide range of IRB-approved print, digital, video and audio advertisements including (but not limited to) flyers, brochures and recruitment scripts. General advertisements approved under the CIR adult screening protocol in addition to study specific ads approved under this protocol may be used to recruit for this study. Other recruitment methods may include (but are not limited to) the use of third-party marketing and advertising services, social media platforms, websites dedicated to pairing research participants with research studies, electronic medical record recruitment messaging, and reaching out to previous CIR study participants who've agreed to be contacted about upcoming studies.

Participants responding to advertisements may contact the CIR directly by phone, email, or website. If responding to a third-party marketing campaign, they may submit their contact information directly to the website(s) to be contacted by CIR study staff (note: identifiable information obtained on 3rd party platforms is encrypted, stored according to applicable guidelines and regulations and accessible only to authorized CIR staff). Interested individuals will be pre-screened for eligibility using a standard pre-screening questionnaire administered on-line or by CIR staff. Participants who successfully complete the online questionnaire will be contacted by CIR staff to schedule a screening visit. In both cases, some elements of the inclusion/exclusion criteria will be discussed with the participant to determine preliminary eligibility prior to scheduling a screening visit. Telephone and on-line pre-screening and in-person screening visits are conducted under a separate IRB-approved general screening protocol ("Screening of Adult Subjects for Eligibility to Participate in Clinical studies evaluating investigational vaccines, antimicrobial agents, other disease preventive measures or the pathogenesis of infectious agents" CIR 200, JHSPH IRB 00010083). Participants who are eligible after completing the general CIR200 screening may be asked to complete a study-specific screening under this protocol.

4.1 Participant Inclusion Criteria

Inclusion Criteria:

1. Adult between 18 and 50 years of age, inclusive.
2. General good health, without significant medical illness, abnormal physical examination findings, or clinical laboratory abnormalities, as determined by principal investigator (PI) or PI in consultation with the research monitor and sponsor.
3. Demonstrate comprehension of the protocol procedures, requirements, and CHIM by passing a written examination (passing grade ≥ 70%).
4. Willing to participate, as evidenced by signing the informed consent document.
5. Available for all planned follow-up visits.
6. Negative serum pregnancy test at screening and negative serum and/or urine pregnancy test on the day of admittance to the inpatient phase for participants of childbearing potential. Participants of childbearing potential must agree to use an efficacious hormonal or barrier method of birth control during the study. Abstinence from intercourse with a male partner is acceptable. Participants who no longer have childbearing potential must have this documented (e.g., tubal ligation or hysterectomy).

4.2 Participant Exclusion Criteria

1. Presence of a significant medical condition (e.g., psychiatric conditions, such as significant anxiety, depression, or somatization disorder; gastrointestinal disease, such as peptic ulcer, symptoms or evidence of active gastritis/dyspepsia, gastroesophageal reflux disease, inflammatory bowel disease, irritable bowel syndrome (as suggested by the functional bowel disorder survey or medical diagnosis); alcohol or illicit drug abuse/dependency; or laboratory abnormalities that in the opinion of the investigator preclude participation in the study. Significant medical conditions include evidence of cardiac, pulmonary, endocrine, neurologic or renal disease that is uncontrolled or poorly controlled, any diabetes mellitus, and other such illnesses that can put a volunteer at increased risk. Exclusionary laboratory abnormalities include any abnormality that is grade 2 or above.
2. Immunosuppressive illness or evidence of IgA deficiency (serum IgA < 7 mg/dL or below the limit of detection of assay), or any autoimmune disease.
3. Positive serology results for HIV, hBsAg, or HCV antibodies, and confirmatory tests if appropriate.
4. Positive urine toxicology screen for amphetamines, barbiturates, benzodiazepines, cocaine metabolite, methadone metabolite, opiates, oxycodone, or phencyclidine.
5. Significant abnormalities in screening laboratory hematology or serum chemistry, as determined by PI or PI in consultation with the research monitor and sponsor.
6. Evidence of abnormal ECG findings per PI (e.g., QT prolongation)
7. Use of any medication known to affect immune function (e.g., regular systemic corticosteroids, monoclonal antibodies that target key aspects of the immune system (such as rituximab or TNF blockers); others [topical, intranasal and inhaled steroids will be permitted]) within 30 days preceding receipt of the investigational product or planned to be used during the active study period.
8. Nursing or lactating on the day of admittance to the inpatient unit.
9. Inability to tolerate 150 mL sodium bicarbonate buffer (based on requirement for frequent dosing).
10. Recent vaccination (including licensed vaccines) or receipt of an investigational product (within 30 days before challenge through 30 days following the last challenge dose).
11. Prior history of *C. difficile* infection
12. History of diarrhea in the 2 weeks prior to planned inpatient phase.
13. Fewer than 3 stools per week or more than 3 stools per day as the usual frequency, or loose or liquid stools other than on an

occasional basis.

14. Regular use of laxatives or any agent that increases gastric pH (regular defined as at least weekly).
15. Use of proton pump inhibitors, H2 blockers, or antacids within 48 hours of dosing.
16. A fever (≥ 38.0°C) in the 2 weeks prior to time of challenge.
17. Use of antibiotics during the 7 days before bacterial dosing or receipt of more than 2 courses of antibiotics over the two months prior to dosing.
18. Blood donation within 30 days prior to the planned receipt of this IP.
19. Lactose intolerance or allergy to milk or milk products.
20. Personal or documented family history of Guillain-Barré syndrome or neuromuscular disease; or an inflammatory arthritis such as reactive arthritis, ankylosing spondylitis, or rheumatoid arthritis.
21. Evidence of inflammatory arthritis on exam.
22. HLA-B27 positive.
23. Allergy or prior intolerance to two or more of the following: fluoroquinolones, azithromycin, augmentin or cephalosporins
24. Have household contacts who are < 2 years old or > 80 years old or infirm or immunocompromised.
25. Employment as a healthcare worker with direct patient care, in a daycare center (for children or the elderly), or direct food handler; includes individuals who work directly with food in commercial establishments.
26. History of microbiologically confirmed *Campylobacter* infection in last 3 years.
27. Serological immunological evidence of prior *Campylobacter* exposure defined as *Campylobacter* antigen-specific (GE)specific anti-glycine extract serum IgA endpoint titer > 1:4,000.
28. Occupation involving handling of *Campylobacter,* currently or in the past 3 years.
29. Symptoms consistent with travelers' diarrhea concurrent with travel to countries where *Campylobacter, Cholera, Salmonella, Shigella, Typhoid or ETEC* infection are endemic (most of the developing world) within 3 years prior to dosing, OR planned travel to endemic countries during the length of the study.
30. Vaccination for or ingestion of *Campylobacter, Cholera, Salmonella. Shigella, Typhoid or ETEC* within 5 years prior to dosing.
31. Other dietary or environmental exposures that may place the participant at high risk for prior *Campylobacter* exposure (to be determined on a case-by-case basis by the PI).

Vaccination

5.0 STUDY PROCEDURES

5.1 Study-Specific Screening and Consenting

Screening, consenting and eligibility evaluations and procedures will be carried out over about 1 - 3 visits under the general screening protocol and/or this study protocol during the study specific screening and consenting visit. Medical history, laboratory specimens and physical examination may be obtained/completed during general screening or deferred to study specific screening under this protocol. See Section 6.0, Study Schedule for detailed information about screening procedures and assessments.

During study-specific screening, study staff will present study information, employing multiple IRB-approved formats to aid understanding across a wide range of volunteers from different backgrounds. Potential volunteers will be asked to read the informed consent document and complete a multiple choice/short answer comprehension assessment.

Prior to signing the informed consent document, all volunteers must be able to pass a written comprehension assessment with a minimum passing grade of 70%. Incorrect answers will be discussed with volunteers and corresponding parts of the consent reviewed. Participants who are not able to achieve a passing score on the first attempt may retake the comprehension assessment on the same day or may reschedule for another time. Participants who are unable to demonstrate comprehension of essential study information by answering 70% of the questions correctly after two attempts are not be eligible for study enrollment. Informed consent is an ongoing process. Ensuring that consent is voluntary and competent throughout the duration of the trial is a component of every assessment and procedure.

Consent forms will be signed and dated by participants as well as by the PI or designated study staff prior to completing any study assessments or procedures. As part of the consent interview, participants will also be asked to read and sign additional IRB-approved forms. Participants will receive a signed copy of the Informed Consent document as well as other signed documents and encouraged to keep them with their other health records. Screening, consenting and eligibility evaluations/procedures will be carried out over 1 - 3 visits under the general CIR200 screening protocol and/or this study protocol during the study specific screening and consenting visit. See Section 6.0, Study Schedule for detailed information about screening procedures and assessments.

Based on current COVID-19 illness in the community and CDC and JHU guidelines, volunteers may be asked to come to the center or obtain a COVID-19 test 1-5 days prior to admission or they may be contacted and asked about COVID-19 symptoms. All volunteers will be COVID-19 tested on admission to the unit. Any volunteer who tests positive for COVID-19 will not be eligible for that admission.

During screening, participants will be asked to complete a Functional Bowel Disorder Survey to screen for GI dysfunction and establish a baseline of general GI health for subsequent surveys (may be administered by study staff or self-administered).

More volunteers may be consented for study participation than can be enrolled, to allow for alternates to replace anyone who does not report for admission or is deemed ineligible prior to receiving the investigational product. Up to two alternates may be admitted on Day -3, complete Day -3 continuing eligibility review and remain on the unit overnight until the first dose of IP is given. Volunteers designated as alternates will replace participants who become ineligible during continuing eligibility review or decide not to participate after admission but prior to receipt of IP. Alternates not replacing a participant will be discharged on Day -2 prior to IP administration and no further follow up will be done. Enrolled participants who do not complete the study will not be replaced.

5.2 Randomization

Should more than the requisite number of participants remain eligible and interested in participating in the study, participants will be selected using a random number generator stratified by gender to ensure appropriate room allocation.

Consenting, eligible participants will be randomized in a 1:1 ratio to receive either the test article or placebo. The randomization scheme will utilize block sizes as described in the MOP to ensure comparable numbers of HBC and placebo recipients.

The randomization procedure will be described in the MOP. A study statistician will write code and the seed(s) for the random number generator will be documented. When a participant is randomized, the statistician will conduct and document quality control (QC) of the randomization plan, treatment table and all other related documents using the statistical considerations. Once the treatment table has been finalized, the person performing product formulation will be provided a list of the coded treatment numbers with their corresponding unblinded treatment assignments, as well as the sealed back-up manual randomization list. In the event a randomized participant is no longer eligible prior to receiving the IP, one of the alternates will replace that participant (as available).

5.3 Study Identification Number

Once study specific consent has been obtained participants will be assigned a study number. Participants will receive the test article/placebo in containers bearing their assigned study number. This number will be linked to the randomization code list securely maintained throughout the clinical phase of the study by the designated NMRC staff and the JHU research pharmacist. Study numbers will also identify all samples for laboratory analyses.

5.4 Blinding

Investigators and participants will remain blinded to group assignments until completion of the clinical phase of the trial and validation of the clinical and immunological data. Each sachet will be labeled with an open label. The research pharmacist will use the randomization list to prepare the IP product for dosing. All mixing and administration of the test article/placebo will be performed per formulation and product administration study specific procedures. Administration will occur in a separate room from where the doses are formulated. Participants will receive the test article/placebo in containers bearing their assigned study numbers which are linked to the randomization code list securely maintained by unblinded members of the research team throughout the clinical phase of the study.

In the event of emergency, the site Investigator may require that the blind be broken for the participant experiencing the emergency, when knowledge of the participant's treatment assignment may influence the participant's clinical care. Emergency unblinding can occur by using the randomized list of participant investigational product assignment that will be kept in a sealed envelope under lock and key at the clinical site. Every effort will be made not to unblind the participant unless it is considered necessary for the welfare of the participant. Prior to unblinding, the site Investigator is encouraged (to the extent possible, without jeopardizing the participant's health) to contact the Sponsor (or designee) to discuss the decision to break the blind. The PI will be expected to provide a rationale for the necessity of unblinding based on the expectation that knowledge of the participant's treatment assignment will have a meaningful impact on the participant's medical care in the short term. If a participant's treatment assignment is unblinded, the participant will remain in the study and continue with protocol-defined study visits, but not receive additional investigational product. The decision to unblind will be communicated to any regulatory bodies (e.g., institutional review boards [IRBs]) as required.

5.5 Clinical Evaluations

5.5.1 Monitoring During Inpatient Phase

The Center for Immunization Research's (CIR) inpatient facility at the Johns Hopkins Bayview Medical Center is a self-contained unit, suited for conducting inpatient studies. Participants will remain at the inpatient facility under clinical observation by study staff at all times. During each day of the inpatient period, volunteers will be evaluated by a study physician, nurse practitioner, or physician assistant. The study providers will conduct daily medical assessments with AE determination. Participants will be monitored for solicited signs and symptoms listed in section 8.4.1.2 and/or an abnormal abdominal exam. Vital signs will be assessed at least three times daily – more often if participant is ill. Volunteers will collect all the stool they produce from study day -22 until 2 consecutive stool samples test negative for the challenge strain. All stools will be weighed, graded and evaluated for blood. Stool cultures or rectal swabs for the challenge study strain will be done at least once daily starting on Study Day 2 (or study day 1 if volunteer develops grade 3-5 stools and might be started on early antibiotic treatment). If a participant is unable to provide a stool sample by 1300 hours, they will be asked to obtain a sample using a rectal swab. Safety laboratory tests are also planned. In cases of moderate to severe diarrhea, postural blood pressure (BP) and pulse may be assessed as tolerated, to support clinical management decisions according to the judgment of the PI/study providers. Participants will be examined for other signs and symptoms of dehydration, including thirst, dizziness on standing, decreased skin turgor, lightheadedness and dryness of mucous membranes.

5.5.1.1 Rehydration Procedures

Participants passing grade 3-5 stools post-challenge will be offered ORS and electrolyte drinks to prevent dehydration, at the same volume as their stool output. ORS/electrolyte drinks will not be considered a concomitant medication, while IV fluids will. Treatment for severe nausea or vomiting may be needed. Participants who experience severe nausea or vomiting may be given ondansetron (Zofran) ODT or ondansetron IV.

A participant may be given IV fluids at the PI or designee's discretion, for the following reasons:

- Participant experiences abrupt onset of diarrhea, defined as passage of an initial grade 3-5 stool of > 300 grams or passage of > 400 grams of grade 3-5 stools within 2 hours.
- Participant becomes hypovolemic as defined below.
- It is determined necessary by a study clinician, i.e., the participant has diarrhea with nausea/vomiting and is unable to drink enough to replace their output, or other reason.

Hypovolemia is a significant decrease in blood volume, characterized by:

- Hypotension, characterized by a confirmed systolic blood pressure (BP) < 90 mmHg and associated symptoms
- *Or orthostatic hypotension defined as* a confirmed postural change in BP or pulse. Postural vital signs will be measured lying supine and again after 2 minutes of standing, if tolerated by participant. The following will be considered a significant change: decrease in systolic BP of > 20 mmHg, or diastolic BP of > 10 mmHg or increase in pulse of > 30 beats/min

5.5.1.2 Routine Discharge

Routine discharge is scheduled for study day 10. Two consecutive negative stool cultures for the challenge strain are required before discharge (can be collected on the same study day). If the participant has not completed antibiotics, then the remaining doses of antibiotic will be given to the participant, along with education on self-administration. Vital signs will be collected and a focused physical exam will be done.

5.5.1.3 Early Discharge

Early discharge is permitted in cases where early antibiotic treatment has been initiated and the participant has otherwise met discharge criteria, including:

- 2 consecutive stool cultures negative for the challenge strain,
- 2 doses of both antibiotic taken, and
- resolved or resolving clinical symptoms.

Participants who meet early discharge criteria will be given the option to leave the unit and return for Day 8 as an outpatient or to remain on the unit as a boarder. Once a participant is eligible for discharge, they will only undergo the procedures required for Day 8 and outpatient visits,, rather than the usual daily procedures. Concomitant medications will still be administered by study staff to any boarders. Participants who are discharged and leave the unit before Study Day 8 will be provided with any remaining doses of antibiotic and will return on day 8 and provide the requisite samples (stool, blood) and undergo required procedures as delineated in Table 1.

5.5.2 Monitoring During Outpatient Phase

The participants will return to the CIR for outpatient visits on Study Days 15, 29, 42, 57, and 85. There is a phone call visit on Study Day 181. Some or all of the following procedures may be conducted, as outlined in Table 1: Time and Events Schedule.

- Interim medical history
- Review of any new or change in AEs through day 85
- Physical assessment, (only if participant with GI symptoms, SAE or AESI, as indicated)
- Assessment AEs (through day 85), AESIs, and/or SAEs (through day 181)
- Vital signs (heart rate, blood pressure, and oral temperature)
- Serum sample for immunological testing (per schedule of events)
- A stool sample for assessment of eradication of the challenge strain of *C. jejuni,* if the patient cannot produce a stool sample they should reschedule to a different day within the allocated window (e.g. ±2), as a last resort a rectal swab could be obtained
- A stool sample for exploratory endpoints when required
- Serology for assessment of anti-*C. jejuni* specific serum immune responses when required
- Review of any new or change in concomitant medications (through day 57)
- Functional Bowel Survey on day 181

5.6 Concomitant Medications/Treatments

Only concomitant medications approved by the study physician will be administered during the study. Participants needing to take unapproved or excluded medications will not be eligible for enrollment. Participants taking a permitted medication (i.e., birth control pills) prior to enrollment will be allowed to continue. Prescription medications brought onto the unit must be in in the original packaging, will be stored in a locked drawer in the nurse's station and will be dispensed by a study clinician to the volunteer as prescribed. Any medication ordered during the trial (i.e., Acetaminophen, Ibuprofen, Azithromycin, or alternative, anti-emetics) as well as ongoing medications will be documented in the participant's study chart and on the appropriate page of the eCRFs.

5.6.1 Antibiotic Treatment

Antibiotic treatment after challenge will be administered according to criteria for early antibiotic treatment, or on Study Day 7 if early treatment criteria are not met. All participants will be treated with azithromycin (500 mg by mouth once daily for 5 days) concurrently with ciprofloxacin (500 mg by mouth BID for 5 days) Alternate antibiotic treatment to which the strain is susceptible may also be considered, as clinically appropriate. If the study physician determines that IV antibiotics are required, then these will be supplied through Bayview pharmacy.

5.6.2 Criteria for Early Antibiotic Treatment

Early antibiotic treatment after challenge may commence when any of the following criteria are identified and a study physician considers it to be warranted, (once antibiotics are started the participant will no longer take the HBC/placebo IP):

- When participant meets the primary endpoint (clinical definition of campylobacteriosis)
- Confirmed oral temperature ≥ 39°C (after volunteer has not had anything to drink for about 20 minutes)
- Any other reason warranting early treatment in the physician's opinion

Administration of IV antibiotic treatment may be performed if warranted by the investigators.

5.6.3 Unscheduled Visit

If an unscheduled visit occurs, a member of the clinical study team will interview and evaluate the subject to determine the cause of the visit and provide care as needed and information documented in the source data. Adverse events and concomitant medications may be reviewed as indicated. Clinical laboratory tests and physical examination may be done as indicated.

5.7 Laboratory Evaluations

5.7.1 Specimen Preparation, Handling, and Shipping

Research microbiology, including the preparation of live inoculum and culturing of specimens, will be carried out in the laboratory of the CIR in the JHSPH. Immunologic assays will be carried out at the Operationally Relevant Infections Department (ORI) at NMRC. Samples collected under this protocol will be used to conduct protocol-related safety, microbiologic, and immunogenicity evaluations. Samples for immunogenicity will be collected at the CIR and maintained at the CIR or core lab until transport to NMRC at a mutually agreed upon time. Storage at NMRC of these biological samples will be handled according to appropriate procedures. Any future research use of these biological samples will require IRB approval. Participants will be asked to consent for the future use of their specimens as part of consenting to participate in this study.

5.7.2 Laboratory Evaluations

Standard clinical laboratory tests for the purpose of inclusion and exclusion of potential participants and for safety monitoring will be carried out at JHH, JH Bayview Medical Center, or Quest Diagnostics in Baltimore City. Microbiology tests will be done in the CIR bacteriology laboratory. It is possible that isolates may be sent to the JHH microbiology lab for further testing. Study-related samples will be collected, processed, stored, shipped, and labeled according to the relevant MOP/SSPs. The maximum volume of blood to be drawn over any 3 month period of the trial is less than 500 mL, which healthy adults should regenerate within this period and which should not compromise the health of trial participants.

5.8 Outcome Measures

5.8.1 Clinical

The primary safety and tolerability outcome is the presence of CampETEC HBC-associated adverse events during the study period.

The primary efficacy outcome is campylobacteriosis, defined as a clinical illness meeting at least one of the following patterns starting within 144 hours of challenge:

- Moderate diarrhea (4 to 5 loose/liquid stools or 401-800 grams in any 24 hour period) OR
- Severe diarrhea (≥ 6 loose/liquid stools or > 800 grams in any 24 hour period) OR
- Fever (present on at least 2 occasions, at least 20 minutes apart) without diarrhea, plus an associated symptom (nausea, vomiting, abdominal cramps, tenesmus, or dysentery (gross blood in ≥ 2 grade 3 – 5 stools with in any 24 hour period); with consideration of potential alternative diagnosis per clinical investigator based on illness time course and associated symptoms.

Stool will be graded based on a standard stool grading scale as follows:

Grade 1 = Firm, formed (normal)

Grade 2 = Soft, but still formed (normal)

Grade 3 = Thick liquid (diarrheal)

Grade 4 = Opaque, thin liquid (diarrheal)

Grade 5 = Clear or translucent, watery (diarrheal)

Secondary efficacy endpoints are chosen to support the primary endpoint of determining the protective efficacy of the CampETEC HBC product. They further quantify and qualify the degree to which a participant experiences diarrhea.

Additional comparisons between the placebo and test article groups as per secondary objectives Section 2.2.

5.8.2 Exploratory Immunological Analysis

Blood and stools will be collected per the Time and Events Schedule (Table 1) to assess for Campylobacter challenge antigen-specific serum IgA and IgG responses. The blood collected at the clinical unit will be transferred to the NMRC laboratory and assayed for IgG and IgA antibody titers against *Campylobacter* antigen (GE). Stools will be collected and transferred to the NMRC ORI laboratory for extraction to determine total IgA content and GE-specific fecal IgA responses. The antibody titer ascribed to each sample will be reported as reciprocal endpoint titer. Qualitative (responder rates) and quantitative assessments (log-transformed values) may be made, in addition to evaluation of the kinetics of the immune response. Median increases (fold-rises) of anti-GE antibody titers and seroconversion rates will be calculated. Exploratory immunological assays may include immunologic responses to other relevant Campylobacter antigens, antibody in lymphocyte supernatant (ALS) responses, memory B cell evaluation, flow cytometric assays, fecal inflammatory marker assays, and systems biological assays (proteomics, phosphoproteomics) as outlined in the Time and Events Schedule.

5.8.3 Microbiological

Study Day 1 post challenge though Study Day 9, or through day of discharge eligibility (if sooner) and at Days 15 (±2), 29 (±2), 42 (±2), 57 (±2) and 85 (±2), intestinal colonization by the challenge strain will be assessed by monitoring fecal shedding patterns by qualitative culture. In the event of a recrudescence on day 85, participants with no prior recrudescence will be asked to return for a follow-up visit on day 113 (±2) to provide a stool sample for monitoring of fecal shedding by qualitative culture. Stool and/or rectal swab samples (at least 1 per participant per day starting on Study Day 2) will be screened for the presence of the *C. jejuni* strain CG8421 challenge strain. A sample from Day 1, after Challenge may be processed if the participant meets treatment criteria on Study Day 1 or 2. Samples will be collected, processed and shipped as per the MOP and lab SSPs, for qualitative cultures. Quantitative cultures for the challenge strain may be performed on selected inpatient days. Additional culture-independent methods may be used to quantitate *C. jejuni* strain CG8421 shedding.

5.8.4 5.8.4 Exploratory

5.8.4.1 Functional Bowel Symptom Development

An IRB-approved functional bowel disorder survey will be used to assess the prevalence of baseline bowel symptoms, as well as the development of such symptoms at about 6 months after challenge. Incidence of functional bowel symptoms will be compared among those who develop the primary endpoint after challenge relative to those who do not, and against the expected incidence in the normal population.

5.8.4.2 Microbiota

An assessment of changes in microbiota may be performed employing 16s ribosomal RNA sequencing and/or shotgun metagenomics, which assess the entire microbial community present in the collected stool sample. Human gut microbiota is stable in a given host, but highly variable amongst individuals. For this reason, stool from each individual participant will be collected prior to infection to establish their specific baseline gut microbiota composition.

Gut microbiota changes of individual participants may be evaluated following *Campylobacter* challenge and compared to their "normal" gut microbiota composition (prior to infection). This survey will identify gut microbiota dysbiosis during the development of illness and following CampETEC HBC and antibiotic treatments.

5.8.4.3 Proteomics (Serum & Fecal)

Stool and serum may be used to evaluate a panel of exploratory biomarkers which may be acutely and persistently modified in individuals who are exposed and may or may not develop diarrhea. These specimens will be collected and archived for future use with additional funding being sought. Biomarker domains to be evaluated include:

Barrier Dysfunction & Dysbiosis: Fecal samples may be assayed for fecal α1-antitrypsin, a marker of protein leakage into the intestinal tract. In addition, to measure changes in barrier function and response, serum may be collected to test for changes in immunodominant antigens of the microbiota that stimulate T cells and have been shown to be associated with inflammatory bowel diseases. Seroreactivity to these flagellins is found in multiple experimental models of colitis in mice. The protein-based microarray includes 45 select antigens. Blood samples may be taken for a Limulus amebocyte lysate (LAL) assay.

Inflammatory dysregulation: Samples may be analyzed for biomarker antigens through the use of multiplex technology (e.g. MSD, Luminex). Selected biomarkers may be chosen based upon an assessment for Th1, Th2, anti-inflammatory, pro-inflammatory and Th17 responses. These cytokines will include but not be limited to, IL-1beta, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL17, G-CSF, GM-CSF, IFNg, MCP-1, MIP1b, TNFa, IL-22, IL-23 and IL-33.

Intestinal Inflammation & Repair: Serum samples may also be tested for changes in levels of leptin (and IL-8), and fecal samples will be obtained to evaluate REG1, calprotectin, neopterin, and myeloperoxidase.

5.8.4.4 Cognitive Evaluation and Actigraphy

Exploratory evaluations of the cognitive impact of acute diarrhea (assessed by psychomotor vigilance testing (PVT) may be performed according to the Time and Events Schedule. These outcomes are exploratory in nature and will not be utilized as part of the regulatory, safety, immunogenicity, or efficacy evaluations of the study product. If performed, participants will complete PVT assessments while at the inpatient facility. The PVT is a measure of a participant's ability to respond to an external stimulus over a period of time. Three PVT tests per day would be performed by each participant up until discharge from the inpatient facility or as outlined in the MOP. Comparisons would be made between symptom presence/severity and adjusted for other confounding variables.

5.9 Outcome Adjudication Committee

To ensure an unbiased determination of the efficacy outcomes, an independent outcome adjudication committee, the members of which will be blinded as to the treatment regimens of the participants, will evaluate challenge outcome data after completion of the inpatient phase of the study.

The committee will be comprised of at least 3 individuals, independent of the study sponsor and investigative team, who are experts on diarrheal illness case identification and pathogen diagnosis. The committee will also include a statistician/data analyst who will lead and coordinate the committee but will not have a voting role in deliberations.

The committee voting members will review all potential efficacy-related cases and endpoint data. The committee's responsibilities include,

(1) reviewing and confirming all primary endpoint cases,
(2) reviewing all protocol-specified entry criteria, adherence, and compliance issues to ascertain classification in the per-protocol and other study populations; and
(3) providing guidance regarding secondary and other endpoint classifications, to include agreement on objective criteria for classification of endpoints.

Specific duties and responsibilities will be outlined by charter prior to the start of the study.

6.0 STUDY SCHEDULE – PROCEDURES BY STUDY DAY

See also Time and Events Schedule (Table 1).

6.1 Screening (Day –120 to Day –5)

The following screening assessments and procedures may be completed under the general screening protocol, CIR200, and/or under this CampETEC protocol over the course of 1 – 3 visits depending on screening visit outcomes.

a. Oral and/or audiovisual presentation of clinical trial design, risks, and study schedule and requirements
b. Read informed consent document(s)
c. Complete written comprehension assessment (minimum of 70% accuracy required for eligibility)
d. One-on-one discussions with principal investigator or designee
e. Informed consent document signed, dated and timed by volunteer and the study team member obtaining consent
f. Review and sign additional IRB-approved forms, which may include, but are not limited to the Alternate Agreement, Inpatient Unit Guidelines, Correct Hand Washing Procedure, HIPAA Medical Record Release Form, HIV Test Counseling and/or COVID Vaccination Form
g. Copies of signed documents given to volunteer
h. Medical history, including height, weight, and any allergies.
i. Vital signs (heart rate, blood pressure, and oral temperature)
j. Pregnancy prevention counseling
k. Physical examination including assessment of HEENT, heart, lungs, abdomen, skin, neurological and musculoskeletal systems
l. Ingestion of 150 mL of sodium bicarbonate buffer to assess volunteer's ability to tolerate consumption
m. Functional Bowel Disorder Survey
n. Begin assessment of inclusion and exclusion criteria
o. PI or designee review and confirm pending eligibility
p. Record demographics - gender, date of birth, race, ethnicity
q. Screening laboratory analyses

(a) Titer (May be done up to 120 days prior to enrollment)
(b) Complete blood count with differential (day -30 – day -4)
(c) Complete Metabolic Panel (CMP) must include but not limited to: Serum transaminase (ALT), Na, K+, BUN, creatinine, random glucose (day -30 – day -4)
(d) IgA level, HLA B27 (Maybe done within 120 days of enrollment)
(e) Pregnancy test (serum and/or urine ß-hCG) for people of childbearing potential (will be repeated on admission and prior to administration of challenge)
(f) Serum HIV antibody and confirmatory test (day-30 to day -4)
(g) Hepatitis B surface antigen (HBsAg) (day-30 to day -4)
(h) Hepatitis C virus ELISA and confirmatory test (day-30 to day-4)
(i) Urine drug screen must include (but is not limited to) testing for the presence of amphetamine, barbiturates, opiates, phencyclidine, cocaine, benzodiazepine, and methadone, at screening and at the discretion of the study clinician. In addition, the study clinician may ask for a sample to test for the presence of antibiotics.
(j) ABO blood typing and Rh status (may be done up to 120 days prior to enrollment)
(k) ECG (day -30 – day -4)

If the initial screening visit is within 30 days of enrollment, all screening activities may be performed at the one visit.

Participants may be notified of their screening laboratory results either in person or over the telephone.. Participants with clinically significant abnormalities (determined by the PI) may be asked to have additional blood drawn. If the abnormal result(s) persists,

participants will be referred to their primary care physician. A copy of the screening laboratory results may be provided to the participant at their request.

6.2 Inpatient Phase (Day –3 to Day 9)

6.2.1 Admission to the Inpatient Unit (Study Day –3)

Up to 34 eligible and consenting adults will be asked to come to the CIR inpatient unit (IPU) for admission on Study Day -3. A maximum of 32 participants will be admitted. More volunteers may be asked to come to the unit for admission than can be enrolled, which allows for some dropout of volunteers due to ineligibility or withdrawal of consent. Up to 30 participants will be randomized and receive the IP and challenge as per Time and Events Schedule. Volunteers who are admitted but not enrolled , will be discharged and will not be followed.

On arrival to the unit, the following procedures will be completed:

a. Based on community COVID-19 rates and CDC and JHU guidelines, volunteers may be COVID-19 tested (either at the CIR or independently) 1-5 days prior to admission. Volunteers will be tested upon arrival to the unit. A positive COVID-19 test will be exclusionary for admission to the unit.
b. Personal items will be inventoried. Items not allowed on the unit will be placed into storage for the duration of the admission
c. Medications brought by volunteers must be properly labelled. The PI or designee must approve all medications. All medications will be stored in the nurses' station and dispensed by qualified study staff.
d. Unit orientation and fire drill
e. Continuing eligibility review
    - Inclusion and exclusion criteria reviewed by PI or designee
    - Medical history and concomitant medications since screening reviewed
    - Blood draw for hematology (complete blood count with differential), serum chemistries (Na, K, creatinine, BUN, glucose, ALT)
    - Complete physical exam
    - Serum and/or urine pregnancy tests (for participants of childbearing potential)
    - Pregnancy risk assessment and pregnancy prevention counseling
f. Vital signs (BP, HR and temperature) recorded
g. Blood will be collected for research, including immunological assays and serology, and a fingerstick blood draw.
h. Stool will be collected as per Time and Events Schedule and the MOP. An initial stool may be collected any time on the day of admission or on Day -2, prior to initiating the CampETEC product. A participant's inability to produce a stool on Day -3 or -2 will not be exclusionary for IP or Challenge.
i. PVT demonstration (if applicable)

6.2.2 Study Days –2 to 6 CampETEC/Placebo Dosing

Participants will be randomized as per Section 5.2 and MOP. Dosing will occur three times a day, approximately 15 minutes (range: 10 – 25 minutes) after breakfast, lunch, and dinner for a period of 8 days (day -2 to day 6) as per MOP. The time meals are completed will be recorded by study staff. Study Day 1 (Challenge Day), is an exception to this order of events (see Section 6.2.3).

If a participant decides not to participate prior to receiving any IP (enrollment), the participant will be discharged from the unit and no further follow up will be required. If a participant is enrolled (receives Camp/ETEC HBC or placebo) and does not continue to be eligible or withdraws consent prior to challenge, they will be discharged from the unit and no further inpatient samples will be collected. If possible, they will complete a study day 6 follow up visit for safety this should include:

- Interim medical history review will be completed
- Assessment of any AEs, AESI, and SAEs related to the investigational product
- A focused physical exam

The following assessments and procedures will comprise the daily routine on study days -2 through 6:

- Vital signs (BP, heart rate, and oral temperature) at least 3 times a day; once in the morning, afternoon, and evening.
- Focused PE, with the assessment and grading of new or evolving solicited and unsolicited AEs.
- All medications will be provided by clinical staff and recorded on an inpatient medication administration record.
- All stools will be collected weighed, graded commencing on study day -2. Failure to produce stool will not be considered a protocol deviation.
- Routine stool bacteriology for *C. jejuni* strain CG8421 detection will begin on study day 2, or prior to initiation of early antibiotic therapy, whichever is sooner.
- Stool will be processed daily per the MOP while inpatient. A minimum of one (maximum of 3) stool samples or rectal swabs will be collected daily for culture. If a volunteer is unable to provide a stool sample, rectal swabs will be obtained (per the MOP). If the participant does not produce a stool or enough stool on any day to obtain all samples, it will not be considered a protocol deviation.
- Stool output and hydration status will be monitored to support clinical decisions post-challenge.
- Blood and stool for immunological assessments will be collected per the Time and Events Schedule.
    - Collection of whole blood on filter paper from fingerpricks as per Time and Events Schedule.

- Urine samples may be obtained on any of the study days, at the discretion of the PI, to assess surreptitious antibiotic use or protocol-restricted drug intake.
- PVT.

6.2.3 Campylobacter Challenge (Day 1)

On the day of *Campylobacter* challenge, participants will be monitored as detailed above for days -2 to 66. All participants will be challenged at the same time.

Urine pregnancy will be collected prior to challenge for people of childbearing potential. Participants of childbearing potential must have a negative pregnancy test prior to challenge.

Table 3: Order of Events on Day of Challenge

Event	Volume (approximate)
1st daily dose of test article/placebo	150 ml
Approximately 90 minute fast	-
Bicarbonate buffer	120 ml
1 minute interval (up to 2 minutes)	-
Bicarbonate buffer + Challenge	30 ml
15-minute interval (range 10 – 25 minutes after challenge)	-
2nd daily dose of test article/placebo	150 ml
Approximately 90 minute fast	-
Lunch	-
Dinner	-
15-minute interval (range 10 – 25 minutes)	-
3rd daily dose of test article/placebo	150 ml

Volunteers will be monitored for post-challenge adverse reactions for at least 30 minutes, then have their vital signs done. No test article/placebo dose is scheduled after lunch, but routine dosing will commence again at dinner.

6.3 Day 7- Antibiotic Treatment

- Daily procedures will be conducted per the Time and Events Schedule (Table 1)
- Initiate antibiotic treatment for all volunteers who have not started treatment earlier - azithromycin 500 mg by mouth once daily for 5 days and ciprofloxacin 500 mg by mouth twice daily for 5 days.
- Assess volunteers for discharge criteria. Participants meeting discharge criteria prior to completing antibiotics may be released with the remaining antibiotic treatment to be taken at home.

6.4 Study Days 8 – 10 Planned Discharge

Volunteers will be eligible for discharge when symptoms are resolved or are resolving, and they have had at least two consecutive stool cultures negative for the challenge strains (can be collected on the same study day) and have received at least 2 doses of both antibiotics. At discharge, participants will be reminded not to donate blood or blood products for one month following the completion of study participation and advised that the American Red Cross will not allow blood donations for 1 year following participation in an investigational research study.

Volunteers will have:

- Focused PE prior to discharge
- Review of solicited and unsolicited AEs
- Receive morning doses of antibiotics (if course is not complete)
- Receive remaining doses of antibiotics and directions for completing the course of treatment at home
- At least one set of vital signs prior to discharge
- Blood sample/fingerstick collection as per Time and Events Schedule

Volunteers who do not meet criteria for discharge will remain on the unit and continue:

- Daily focused PE
- Vital signs at least three times a day
- Receive antibiotics (if not complete)
- Review of solicited and unsolicited AEs
- All stools will be collected, weighed, graded and assessed for blood
- Up to 3 stool samples and/or rectal swabs will be collected for culture daily
- 3 times daily PVT testing (if applicable)
- Stool will be collected for exploratory objectives

6.5 Outpatient Monitoring

6.5.1 Study Day 15 Safety Follow-Up (±2 Days)

- Interim medical history will be obtained
- AEs, AESIs and SAEs will be recorded, including assessment of relatedness to challenge, study procedures and antibiotics and severity grade
- Concomitant medications will be recorded
- Vital signs (BP, HR, and oral temperature)
- Focused PE only if participant has any continuing, or worsening complaints/AEs or new GI symptoms
- Blood for safety (CBC w/differential and comprehensive metabolic panel)
- Serology for assessment of anti-*C. jejuni* specific serum immune responses
- A stool sample from within 8 hours of the visit, for assessment of eradication of the challenge strain of *C. jejuni*. If the participant cannot produce a stool sample within a reasonable amount of time on the unit, a rectal swab may be obtained.
- A stool sample for exploratory endpoints
- A serum sample for immunological testing

6.5.2 Study Day 29 (± 2 Days)

- Interim medical history will be obtained
- AEs, AESIs and SAEs will be recorded, including assessment of relatedness to challenge, study procedures and antibiotics and severity grade
- Concomitant medications will be recorded
- Vital signs (BP, HR, and oral temperature)
- Focused PE only if participant has any continuing, or worsening complaints/AEs or new GI symptoms
- A stool sample from within 8 hours of the visit, for assessment of eradication of the challenge strain of *C. jejuni*. If the patient cannot produce a stool sample they should reschedule to a different day within the allocated window (e.g. ±2), as a last resort a rectal swab could be obtained.
- A stool sample for exploratory endpoints
- Serum for exploratory objectives
- PBMCs for exploratory objectives
- Fingerstick for the collection of whole blood on filter paper
- Urine pregnancy test for participants of childbearing potential

6.5.3 Study Day 42 (± 2 Days)

- Interim medical history will be obtained
- AEs, AESIs and SAEs will be recorded, including assessment of relatedness to challenge, study procedures and antibiotics and severity grade
- Concomitant medications will be recorded
- Vital signs (BP, HR, and oral temperature)
- Focused PE only if participant has any continuing, or worsening complaints/AEs or new GI symptoms
- A stool sample from within 8 hours of the visit, for assessment of eradication of the challenge strain of *C. jejuni.* If the patient cannot produce a stool sample they should reschedule to a different day within the allocated window (e.g. ±2), as a last resort a rectal swab could be obtained
- A stool sample for exploratory endpoints

6.5.4 Study Day 57 (± 2 Days)

- Interim medical history will be obtained
- AEs, AESIs and SAEs will be recorded, including assessment of relatedness to challenge, study procedures and antibiotics and severity grade
- Concomitant medications will be recorded
- Vital signs (BP, HR, and oral temperature)
- Focused PE only if participant has any continuing, or worsening complaints/AEs or new GI symptoms
- A stool sample from within 8 hours of the visit, for assessment of eradication of the challenge strain of *C. jejuni.* If the patient cannot produce a stool sample they should reschedule to a different day within the allocated window (e.g. ±2), as a last resort a rectal swab could be obtained
- A stool sample for exploratory endpoints
- Serum for exploratory objectives

6.5.5 Study Day 85 (± 2 Days)

- Interim medical history will be obtained
- AEs, AESIs and SAEs will be recorded, including assessment of relatedness to challenge, study procedures and antibiotics and severity grade

- Vital signs (BP, HR, and oral temperature)
- Focused PE only if participant has any continuing, or worsening complaints/AEs or new GI symptoms, AEI or SAEs
- A stool sample from within 8 hours of the visit, for assessment of eradication of the challenge strain of *C. jejuni.* If the patient cannot produce a stool sample they should reschedule to a different day within the allocated window (e.g. ±7), as a last resort a rectal swab could be obtained
- A stool sample for fecal IgA and exploratory endpoints
- Serum for exploratory objectives
- PBMCs for exploratory objectives

6.5.6 Study Day 113 (± 2 Days)-

In the event of a recrudescence in any subject on day 85, if there are no recrudescences on day 85 Day 113 will not occur.

- AESIs and SAEs will be recorded, including assessment of relatedness to challenge or antibiotics and severity grade
- Focused PE only if participant has any continuing, or worsening complaints/AEs or new GI symptoms /AESIs/SAEs
- A stool sample from within 8 hours of the visit, for assessment of eradication of the challenge strain of *C. jejuni.* If the patient cannot produce a stool sample they should reschedule to a different day within the allocated window (e.g. ±2), as a last resort a rectal swab could be obtained
- A stool sample for exploratory objectives.

6.5.7 Study Day 181 Telephone Follow-up (± 1 Month)

A phone check will be done to track:

- Assessment of SAEs, AESIs and any new chronic illnesses (specifically GBS, ReA, IBD, or IBS or hospitalizations.
- Completion of Functional Bowel Survey
- Participants with new onset of bowel disorders will be asked to report to the JHU CIR for an in-person follow up visit and counseling with a provider.

6.6 Management plan in the event of *C. jejuni* recrudescence

The participant will be followed for a total of 6 months from the date of documented infection recurrence. The date of production of the stool demonstrating recrudescence will be designated as day R1 for follow-up purposes.

Table 4. Time and Events Schedule for Recrudescence

Study Event	R 3 (+7)	R 15	R29	R 42	R 57	R 85	R 181
Interim History	X	X	X	X	X	X	
Focused physical exam	X	(X)	(X)	(X)	(X)	(X)	
Assess AEs	X	X	X	X	X	X	
Assess AESIs and SAEs	X	X	X	X	X	X	X
Assess concomitant medications	X	X	X	X	X		
Start another round of antibiotic treatment	X						
Vital Signs	X	X	X	X	X	X	
HIV and/or hypogammaglobulinemia	(X)						
Serum chemistry							
Urine hCG	X		X			X	
Functional bowel disorder survey							X
C-diff testing antigen test	X						
Confirm strain micro and PCR	X						
Confirm antibiotic sensitivity	X						
Stool bacteriology (*C. jejuni* detection)		X	X	X	X	X	
Stool for exploratory objectives		X	X	X	X	X	
Approximate Blood Volume	20						0

The participant will be assessed as soon as possible and dual antibiotic treatment with ciprofloxacin and azithromycin for 10 days will be initiated, (same dose as initial regimen, longer duration). R1 will be the day stool was produced. R 3 (+7) will be the day the participant returns and is started on antibiotics. Blood may be drawn to assess for hypogammaglobulinemia and repeat HIV test may be performed. Any volunteer who recrudesces will continue blood draws per the normal schedule, however, the visit times will be adjusted to the recrudescent schedule so that they don't have to make extra visits.

6.7 Early Termination

Participants have the right to withdraw from the study at any time and for any reason without affecting their right to treatment by the investigator (for study-related conditions).

An excessive number of withdrawals can affect the scientific validity of the study, therefore unnecessary withdrawal should be avoided. Should withdrawals occur, efforts will be made to ensure participant safety and continued monitoring as thoroughly as possible. To facilitate this, such participants will be considered "off-treatment" once they complete antibiotics and may be encouraged to continue with outpatient follow-up visits per the PI's discretion. In case of participant withdrawal, for whatever reason, a study status form must be completed, stating the reasons. Withdrawals due to non-attendance must be followed-up to the extent possible to obtain the reason for non-attendance.

A minimum of three attempts to contact the volunteer using the contact information provided by the volunteer will be documented before the volunteer is determined to be lost to follow-up.

Participants who would like to leave the inpatient unit but do not express the desire to withdrawn entirely, after receiving CampETEC/placebo will be considered "off-treatment" once they complete antibiotics and asked to return to the inpatient unit on study day 8 for a brief physical exam and medical history, and blood draw for safety laboratory testing. Participants withdrawing after receiving the challenge, will receive antibiotics for outpatient treatment and will be educated on the importance of complying with treatment. Attempts will be made to follow the participant for safety through study days 29, 42, 57, 85 and for the 6 month telephone call.

7.0 STUDY INTERVENTION/INVESTIGATIONAL PRODUCTS

7.1 Study Products

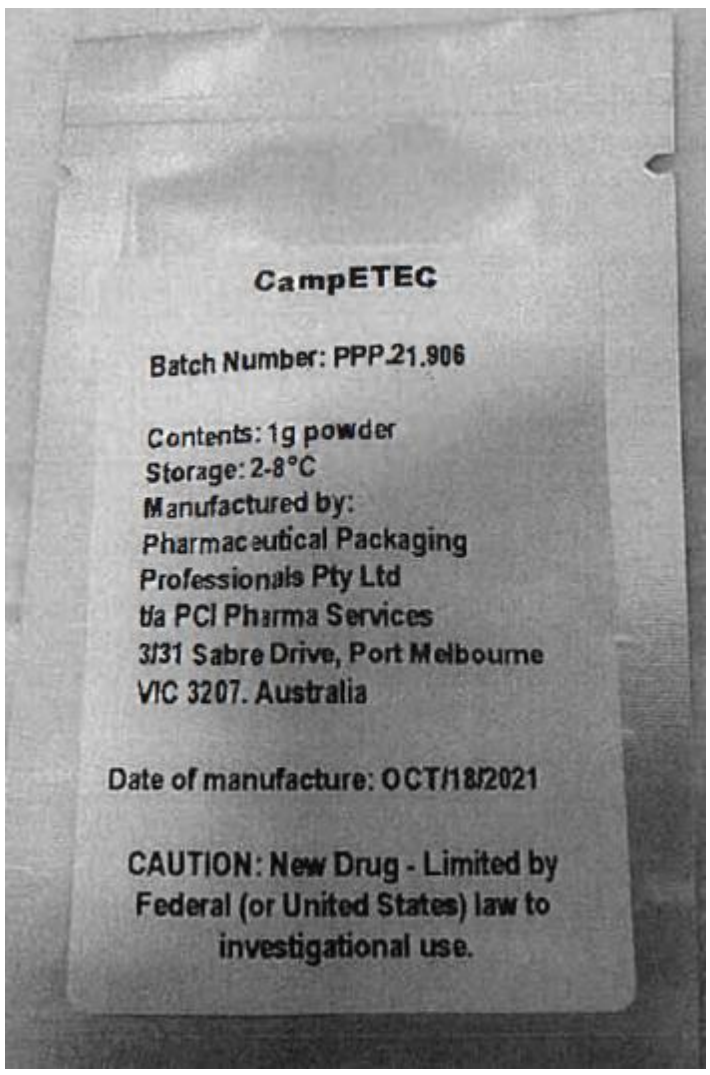
7.1.1 CampETEC

The CampETEC HBC product is a lactose- and fat-reduced, freeze-dried natural product, high in protein and contains no artificial additives or nutrients. The drug substance contains antibodies targeted against the fimbrial subunits of CFA/I expressed by some strains of ETEC and the CPS of *C. jejuni* serotype HS23/36. The drug substance powder is harvested from the first milking of dairy cows that have been immunized with a conjugated vaccine to produce high levels of specific antibodies. The CampETEC drug product contains over 80% proteins, out of which approximately 15% - 35% are antibodies (immunoglobulins) in the dry powder. The main classes of immunoglobulins found in bovine colostrum will be IgG (mainly IgG1) with smaller amounts of IgM and IgA. The colostrum will be assessed for its ability to provide passive protection against *C. jejuni*.

7.1.1.1 Packaging

The dried powder CampETEC was packaged in single-dose sachets. Quality control (QC) tests were performed for the final product.

Figure 1: Label for CampETEC Product



7.1.1.2 Storage

CampETEC sachets will be stored at 2-8°C in the Research Pharmacy.

7.1.1.3 Product Shipping

Prior to the commencement of the study, the IP will be transferred directly to the Research Pharmacy. Any use of the IP will be done under the supervision of the Research Pharmacy, and the Research Pharmacist will maintain the IP accountability log, which tracks the status of all IP received. Any sachets remaining at the end of the study will be returned to NMRC or destroyed per the MOP or pharmacy SOP.

7.1.1.4 Dose Preparation

Each CampETEC or placebo unit (1 g of product in foil packet), will be reconstituted in 150 mL water containing 2 g sodium bicarbonate for ingestion by a single individual. Each volunteer will receive either the CampETEC or placebo 3 times a day on specified study days. Previous CHIM studies utilizing this formulation have been successful, with participants exhibiting minimal complications other than flatulence [35].

The CampETEC preparation and placebo will be administered orally. On Study Day -2,, participants will begin taking the assigned treatment. Each participant will ingest the assigned treatment three times a day, approximately 15 minutes after each meal, except for a variation of dosing schedule on the day of challenge. Participants will continue the thrice daily dosing until for the initiation of antibiotic treatment.

7.1.2 Placebo

A commercially sourced high protein milk powder called ProMilk 85 will be used as a placebo control. The placebo was manufactured by Tantura Milk Industries and repackaged in the same facility and in the same manner, packaging, and has the same labeling as the investigational product. The milk protein concentrate is a food grade product which consists of 85% pure milk protein, 1.3% fat content, 5.3% moisture content, and has a pH of 7.0. The placebo contains no detectable antibiotics or bacterial content. The placebo is an off-white colored, food-grade powder product that should appear similar to the CampETEC product when reconstituted.

7.1.2.1 Packaging

The placebo high protein milk powder is packaged in single-dose sachets. The placebo product is labeled as shown below.

Figure 2: Placebo Label

7.1.2.2 Storage

The placebo will be stored at 2-8°C. in the research pharmacy.

7.2 *C. jejuni* CG8421 Challenge Strain

A human challenge model for studies investigating *C. jejuni* has already been established. It uses the strain *C. jejuni* CG8421. The CG8421 strain mitigates the risk of GBS because it lacks ganglioside mimicry. It has a consistently high attack rate and elicits robust immune responses when even using a low concentration of inoculum ($5x10^5$ CFUs).

When tested previously, clinical disease after CG8421 infection consisted of moderate to large volume diarrhea with symptoms of headache, myalgia, and abdominal cramping. Fever occurred in 9 (39%) participants and was severe (>39°C) in 2 persons (9%). There were no significant clinical differences between patients who received $1x10^6$ and $1x10^5$ CFUs of *C. jejuni,* although participants who received the lower dose had a slightly longer incubation period and a lower total volume of loose stools. There were no serious adverse events related to CG8421 and no hypotension/shock or post-infectious sequelae occurred. After initiation of antibiotics in participants, symptoms resolved, and stool cultures cleared rapidly [66]. In a double blind, randomized study testing the prophylactic efficacy of rifaximin, CG8421 was given at a dose of 1.7 x 10^5 CFU, producing an 84.6% attack rate among participants receiving placebo. Recrudescence was detected in 17.9% of those challenged [67].

The challenge dose that will be used for this study will use 5 x 10^5 CFU of *C. jejuni* CG8421.

7.2.1 Challenge Inoculum

The *C. jejuni* challenge strain underwent cGMP production at Charles River Laboratories (358 Technology Drive, Malvern, PA 19355, 610-640-4550) in October 2006. A Master Cell Bank (MCB) was prepared from the research seed upon release of the strain (refer to Investigator Brochure). The cGMP cell bank was released based on the criteria outlined in Table 5 below.

Table 5 : Release Criteria for C. jejuni cGMP MCB.

Parameter		Methodology	Specification
Viability		Plating on Mueller-Hinton agar, incubation in a jar with *Campylobacter*-specific gas mix at 37ºC for 48 h.	$\geq 10^6$ CFU/vial
Purity		Plating on the appropriate selective agar to include sheep blood and Sabouraud-Dextrose agar. Incubation of plates under aerobic conditions, 37ºC 18-24 h.	No contaminating organisms on agar plates
Identity		16S RNA analysis and *C. jejuni*-specific PCR	*C. jejuni*

7.2.2 Packaging and Labeling

The CG8421 challenge strain is stored as 1 mL aliquots in 2 mL cryostorage tubes (1 mL per tube) held at –80°C ± 10°C in the WRAIR PBF. The cryotubes are labeled as shown below:

Figure 3: Label for C. jejuni stain challenge product

***Campylobacter jejuni* strain CG-99-8421**
CRL # 498006-1
Mfg. Date 07 Oct 06
Vial # xxx of 210
Store at -70 + 10ºC
Prepared by Charles River Laboratories
Malvern PA

7.2.3 Storage and transportation

The vials will be transferred on dry ice from the WRAIR Pilot Bioproduction Facility to Johns Hopkins Bloomberg School of Public Health Research Laboratory, logged in, and stored at -80ºC ± 10ºC in a locked and temperature monitored ultra-low temperature freezer. Any use of these vials will be done under the supervision of JHSPH Research Laboratory personnel and tracked in a strain accountability log. Any vials remaining at the end of the study will be returned to NMRC or disposed by autoclaving.

7.2.4 Preparation, administration and dosage

An appropriate number of master seed vials that have been stored at –80ºC ± 10ºC in Mueller-Hinton broth with 15% glycerol will be thawed at room temperature. One hundred microliters of the master seed lot will be spread onto an appropriate number of Mueller-Hinton agar plates for confluent growth and incubated overnight (22-24 hours) at 42° C under microaerobic conditions achieved using a BBL CampyPak Plus (BD). After overnight growth, *C. jejuni* identity will be confirmed by Gram stain, oxidase testing and confirmation of darting motility. After confirmation, bacterial biomass will be harvested by suspension in sterile PBS (0.01M sodium phosphate, 0.138M sodium chloride, 0.0027M potassium chloride, pH 7.4) and adjusted to the appropriate OD_{600} to achieve the target infectious dose. Challenge inoculum will be verified by enumeration of viable counts on Mueller Hinton agar in duplicate on the sample both the pre- and post-dosing. The mean of the pre- and post-dose CFU will be used for the estimated inoculum size. Purity will be determined by plating the challenge inoculum on sheep blood agar and incubating at 37ºC for 48 hours under aerobic conditions.

C. jejuni CG8421 will be administered with bicarbonate buffer (2 g/dose in a total of 150 mL). Participants will drink 120 mL of buffer, followed approximately 1 minute later by 30 mL of buffer containing CG8421. The CG8421 will be added to the bicarbonate immediately before dosing.

7.3 Accountability Procedures for the Investigational Products

The investigator must ensure that the IP supplies are stored as specified in the protocol and in a secured area, with access limited to authorized study personnel. The investigator has the following responsibility for the products: maintaining inventory; maintaining accurate records of the receipt of IP, including date received, randomization code, manufacture or expiration date, amount received and disposition; holding the amount of product needed; and adequate storage and dispensing of the IP (HBC/placebo).). A record will be maintained that includes the dispensation date, amount of IP dispensed, initials and identification number. The IP must be administered only at the specified institution. Unused product will be shipped to NMRC or destroyed per the MOP.

7.4 Assessment of Participant Compliance with Investigational Products

Members of the study team will witness the ingestion of the test article/placebo on the source document.

8.0 ASSESSMENT OF SAFETY

Assessment of CampETEC product safety is limited to the two days prior to receipt of the challenge dose (day -2 and -1). Unless AEs are temporally related to receipt of CampETEC, AEs that begin post-inoculation will be attributed to the inoculum.

AEs will be summarized and compared between study groups for the periods prior to and after challenge. Summaries of the number and proportion of participants who report a given coded term will be reported. Safety data, including AEs, vital signs, and laboratory tests will be listed by study participant.

During the inpatient period, participants will be monitored for the symptoms of Campylobacter illness listed under 8.4.1.2.

Safety monitoring will be conducted throughout the study; therefore, safety concerns will be identified by continuous review of the data by the PI, clinic staff, clinical monitor, research monitor, and the sponsor.

Study Safety Management: The research monitor and PI will review any safety concerns. A data safety monitoring board (DSMB) is not required for this study.

Research Monitor: The research monitor will function as an independent safety advocate for participants per AR 70-25 and Department of Defense (DoD) Instruction 3216.02. An independent research monitor is required to review all unanticipated problems involving risk to participants or others, SAEs, and all participant deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the research monitor should comment on the outcomes of the event or problem and, in the case of a SAE or death, comment on the relationship to participation in the study. The research monitor should also indicate whether they concur with the details of the report provided by the study investigator. Reports for events determined by either the investigator or research monitor to be probably or definitely related to participation and reports of events resulting in death should be promptly forwarded to the IRBs, ORP HRPO, and USAMRMC Division of Regulated Activities and Compliance.

The research monitor, in accordance with JHBSPH guidelines, will have the following responsibilities:

- Evaluate ongoing safety data and make recommendations in order to ensure participant safety as required
- Be available for consultation by the clinical investigative team through the period of the clinical study in which there is an interaction with human participants
- Be available to review all SAEs and other unanticipated problems involving risk to participants
- Be available to discuss SAEs and significant safety issues
- Provide clinical advice, in accordance with the study protocol, on the clinical management of participants. This advice may include, but is not limited to − Decisions on "borderline" laboratory values and eligibility for enrollment − Confirmation and discussion of treatment decisions for difficult clinical situations
- Must document all clinical decisions including date, time and signature
- Must communicate all decisions to the study PI and other study investigators, which must be stored with participant source documents or study binder.

All safety reports (i.e., serious adverse events, deviations, unanticipated problems involving risk and participant deaths) will be submitted to the JHSPH IRB and NMRC IRB.

8.1 Vital Signs

Vital signs (oral temperature, blood pressure, heart rate) will be obtained throughout the inpatient period and at each study visit after discharge. Respiratory rates will be obtained on a case-by-case basis at the discretion of the study clinician. See Table 6 for applicable AE coding.

Table 6: Reference Ranges and Adverse Event Coding for Vital Signs Parameters

Vital Signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Tachycardia	101–115	116-130	>130	ER visit or hospitalization for arrhythmia
Bradycardia	50-54[a]	45–49	<45	ER visit or hospitalization for arrhythmia
Fever (°C) (°F)	38.0–38.4 100.4–101.1	38.5–38.9 101.2–102.0	39.0-40 102.1- 104	>40 >104
Hypertension (systolic, mm Hg)	141–150	151 - 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic, mm Hg)	91–95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic, mm Hg)[b]	85–89	80 – 84	<80	ER visit or hospitalization for hypotensive shock

[a]Grade 1 bradycardia will not be considered an abnormality for this study unless judged to be clinically significant by the PI or the PI in consultation with the Research Monitor and sponsor.
[b] If a participant has a baseline systolic BP in the 90's then a decrease in BP < 10 without associated clinical symptoms will not be considered an abnormality for this study unless judges to be clinically significant by the PI.

8.2 Physical Examination

A complete physical exam will be conducted during the screening visit and on Day -3 as part of the admission process; a focused physical exam will be conducted prior to receipt of first IP, prior to challenge and daily during participant's inpatient stay. Focused physical exams may occur at outpatient visits with specific attention to the identification of local, systemic or other adverse reactions for participants who have new or continuing gastrointestinal symptoms.

8.3 Laboratory Assessments

Venous blood samples will be collected for chemistry, hematology, and immunological parameters during the screening phase of this study and to provide a baseline sample – see Table 1, Time and Events Schedule. Hematology and chemistry analyses will be performed by commercial laboratory (Quest, Incorporated in Baltimore City or by Johns Hopkins Medical Institutions). Additional specimens may be collected to confirm and evaluate any abnormal values. Additional blood for chemistry and hematology are planned for collection following experimental infection per the time and events schedule. However, samples may be obtained as part of the clinical care of an individual participant. The clinical toxicity grading scale that will be used as a guideline is based on the FDA's Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Subjects enrolled in Preventive Vaccine Clinical Trials and the DAIDS Table for Grading and Severity of Adult and Pediatric Adverse Events.

Final grading determination will be made by the PI based on normal lab values for the specific lab and clinical symptoms. Abnormal laboratory values based on hematology, and clinical chemistry (SGPT/ALT, glucose, creatinine, BUN and electrolytes) after test article dosing will be considered an AE. The investigator will determine severity based on clinical symptoms and using the attached grading scale as a guideline. In the event of a clinically significant abnormal laboratory value, the test will be repeated. If the abnormal value persists, follow-up evaluations will be determined by the PI in consultation with the medical monitor. Additional clinical laboratory evaluations may be performed at other times as required to follow-up a serious or severe adverse event or as deemed

necessary by the investigator. Slightly abnormal laboratory values that remain consistent from the time of screening throughout the study will not be recorded as AEs but will be included in the medical history.

Serologic evidence of chronic HIV-1, HCV, and HBV infections will be obtained during the screening process. Evidence of current infection will make a participant ineligible. Targeted drug screenings are planned for this study at screening and at the discretion of the study clinician.

A serum sample for pregnancy testing will be collected at the screening visit and on Day -3 from participants of childbearing potential. A urine pregnancy test maybe done on day -2 if the serum pregnancy test from Day -3 results are not available. A urine pregnancy test will be collected on Day 1 prior to challenge and day 85 from participants of childbearing potential. A participant will not be enrolled if that have a positive pregnancy test prior to HBC/placebo IP administration. Any participants who become pregnant during the study will be considered "off treatment – safety only" and followed until pregnancy resolution. Procedures to be followed in the event a study participant becomes pregnant during the study period are outlined below.

P**rocedures to be followed in the event of a pregnancy**

- When possible, a safety visit will be completed, this will include:
  - Interim history
  - Focused PE
  - Vital signs
  - Safety Labs- CBC with differentials, CMP, serum pregnancy test if not already completed at day 15 or at PI discretion
- No further research labs will be collected
- Follow up calls will be completed to obtain updates in pregnancy and a final call will be made at the time of resolution. Required IRB and study information will be collected.

Table 7: Reference Ranges and Adverse Event Coding for Clinical Hematology Parameters

Test	**Normal**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (g/dL) (for screening purposes only)	M: LLN = 11.0 F: LLN = 10.5				
Hemoglobin, low		M: 10.0 to 10.9 F:9.5 to 10.4	M: 9.0 to <10.0 F: 8.5 to <9.5	M: 7.0 to <9.0 F: 6.5 to <8.5	M: <7.0 F:<6.5
Eosinophils (cells/mm^3)	15-500	551-1,500	1,501-5,000	> 5,000	ER Visit
Leukocytes (white blood cells) (cells/mm^3)	2,500 to 10,800				
Leukopenia		2,000 to 2,499	1,500 to 1,999	1,000 to 1,499	< 1,000
Leukocytosis		10,801-15,000	15,001-20,000	20,001- 25,000	>25,000
Lymphocytes, low (cells/mm^3)	>650	600 to <650	500 to <600	350 to <500	<350
Neutrophils, low (cells/mm^3)	>1,000	800 to 1,000	600 to 799	400 to 599	<400
Platelets decreased (cells/mm^3)	≥125,000	100,000 to <124,999	50,000 to <100,000	25,000 to <50,000	<25,000

Table 8: Reference Ranges and Adverse Event Coding for Blood Chemistry Parameters

Test	**Normal**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN (elevation)	7-25	26-28	29-31	> 31	Requires dialysis
Creatinine (elevation)	M: 0.7-1.4 F: 0.5-1.1	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to <3.5 x ULN OR Increase of 1.5 < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Glucose, Random (mg/dL)	65 to115				

Hypoglycemia		55 to 64	40 to <55	30 to <40	<30
Hyperglycemia		116 to 160	>160 to 250	>250 to 500	> 500
Potassium (mEq/L; *mmol/L*)	3.4 to 5.6				
Hypokalemia		3.0 to < 3.4	2.5 to <3.0	2.0 to <2.5	<2.0
Hyperkalemia		5.6 to <6.0	6.0 to <6.5	6.5 to <7.0	≥7.0
SGPT/ALT (elevation)	M:9 to 46 F: 6 to 29	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10 x ULN	≥ 10x ULN
Sodium (mEq/L; *mmol/L*)	136 to145				
Hyponatremia		130 to <135	125 to <130	121 to <125	≤120
Hypernatremia		146 to <150	150 to <154	154 to <160	≥ 160

8.4 IND Safety Reporting

The following terms, as defined by 21 CFR 312.32, apply to IND safety reporting.

8.4.1 Adverse Event or Suspected Adverse Reaction

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. This includes an exacerbation or worsening of pre-existing conditions or events, intercurrent illnesses, injuries, or vaccine or drug interaction, or worsening of abnormal clinical laboratory values. Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation do not need to be considered AEs. Discrete episodes or worsening of chronic conditions occurring during a study period will be reported as AEs to assess changes in frequency or severity. Stable, pre-existing conditions and/or elective procedures are not AEs.

AEs will be documented in terms of signs and symptoms observed by the investigator or designee or reported by the participants at each study encounter. Pre-existing conditions or signs and/or symptoms (including any which are not recognized at study entry but are recognized during the study period) present in a participant prior to the start of the study will be recorded in the Medical History form within the participant's source and in the eCRF. AEs occurring after informed consent is obtained, but prior to HBC receipt, will be documented in the Medical History form within the participant's source and in the eCRF.

Hospitalization for elective surgery related to a pre-existing condition which did not increase in severity or frequency following initiation of the study, or for routine clinical procedures (including hospitalization for "social" reasons) that are not the result of an AE is not itself considered an AE, but must be recorded in the AE page of the eCRF. If hospitalization arises from a pre-existing condition, or was planned prior to the first test article dose, it will be recorded in the Medical History form of the eCRF. If planned after the first dose, it will only be recorded in the AE page of the eCRF. In both cases, it will be recorded as `Hospitalization (Not an AE)', and the relationship to test article receipts will be checked "No". Because hospitalization under these circumstances need not be considered an AE, it is therefore also not considered a SAE.

A "suspected" adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. The investigator is responsible for documentation of AEs according to the detailed guidelines set out below. Participants will be instructed to contact the investigator immediately should s/he manifest any signs or symptoms perceived as serious during the study period. Approximately six months after study completion, participants will be contacted by phone to document any intervening medically significant new chronic illnesses or serious health events. These data will be documented in a telephone log and summarized in an annex to the final clinical study report.

All AEs and their grade and relationship to investigational product, challenge, study procedures and antibiotics will be recorded in the participants source document and in the appropriate eCRF. AEs will be tabulated separately for pre-and post-challenge data. The assessment of the safety of the CampETEC IP and control products will be primarily limited to the 2 days prior to receipt of challenge. Following receipt of the challenge inoculum, gastrointestinal and systemic symptoms will likely be attributable to the *C. jejuni* CG8421 challenge strain unless temporally related to receipt of the CampETEC/placebo or antibiotics. AEs occurring after receipt of the challenge inoculum (day 1) will also be assessed as to their relationship with the challenge strain and the antibiotic (if treatment has started).

8.4.1.1 Solicited and Anticipated Adverse Events

A solicited AE is a predetermined event, which may reflect safety concerns related to the IP. Previous clinical studies using much higher quantities of bovine colostrum products than planned for this study, have been orally administered and well tolerated (e.g., 10 g/day anti-ETEC bovine milk IgG [47]; 30 g/day anti-*C. parvum* bovine milk IgG [58]; 30 g/day anti-*S. flexneri* bovine milk IgG [33]. In comparison, each CampETEC unit (1 g of product in foil packet), will be reconstituted in 150 mL water containing 2 g sodium bicarbonate for ingestion by a single individual. CHIM studies utilizing this formulation have been successful, with participants exhibiting minimal complications other than flatulence [35].

This study is evaluating a human challenge with live *Campylobacter* bacteria, and therefore all the symptoms of *Campylobacter* infection are solicited AEs with severity grades ranging from 1-4. The most common effects of *Campylobacter* infection are moderate

to severe diarrhea (which may lead to dehydration, electrolyte abnormalities and the need for oral or intravenous rehydration), abdominal cramping, and fever. Nausea with or without vomiting, chills, gross blood in stools, loss of appetite, headache, muscle aches and bloating may also occur. Recrudescent events have been documented in up to 17% of previous participants receiving this dose [67].

8.4.1.2 Surveillance Period for Adverse Event Occurrence

Inpatient surveillance

Solicited symptoms of campylobacteriosis will be assessed daily during the inpatient periods. These symptoms/signs include:

1. Abdominal cramping
2. Abdominal pain
3. Anorexia (poor appetite)
4. Arthralgias
5. Bloating
6. Chills
7. Constipation
8. Excessive flatulence
9. Generalized myalgia
10. Headache
11. Lightheadedness
12. Malaise
13. Nausea
14. Urgency

Symptoms that will be assessed objectively include:

- Diarrhea (via stool logs)
- Vomiting
- Fever (oral temperature > 100.4° F)
- Hypovolemia
- Dysentery (confirmed by hemoccult testing)

These symptoms of Campylobacter illness are only considered solicited during the inpatient period. If a participant reports any of these symptoms during the outpatient period, they will be considered unsolicited, per the Data Management Handbook.

Open-ended questions will also be used to capture any unsolicited symptoms during the study period. All AEs should be recorded on the appropriate AE form of the participant's source documents per the Data Management Handbook.

Outpatient surveillance

Participants will be educated to contact the study staff if they experience any symptoms of diarrhea (3 loose stools/24 hours) or fever ≥ 38°C (100.4°F) with any severe associated symptoms (nausea, abdominal cramps, vomiting, myalgia, headache, arthralgia, or gross blood in their stool).

8.4.1.3 Serious Adverse Event or Serious Suspected Adverse Reaction

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect (abortion, stillbirth and any malformation/disease must be reported as an SAE).

Although not considered SAEs, cancers will be reported in the same way as SAEs. Pertinent definitions include:

- Life threatening - An AE is life threatening if the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Disabling/incapacitating - An AE is incapacitating or disabling if it results in a substantial disruption of the participant's ability to carry out normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza or accidental trauma (e.g. sprained ankle).
- Hospitalization: Hospitalization signifies that the participant spent 24 hours or longer in a hospital for treatment that would not be appropriate in a primary care office or on an outpatient basis. Hospitalization for either elective surgery related to a pre-existing condition (which did not increase in severity or frequency following initiation of the study), or for routine clinical procedures (including hospitalization for "social" reasons), need not be considered AEs and are therefore not SAEs.
- Routine Clinical Procedure: A procedure which takes place during the study and does not interfere with the test article administration or any of the ongoing protocol specific procedures.

Note: If anything untoward is reported during an elective procedure, that occurrence must be reported as an adverse event, either `serious' or non-serious according to the usual criteria. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE will be considered serious. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.5 Serious Adverse Events

8.5.1 Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An adverse event or suspected adverse reaction is considered "unexpected" if

- it is not listed in the investigator brochure
- it is not listed at the specificity or severity that has been observed; or,
- an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.5.2 Other Adverse Events

Other adverse events will be identified by the PI during the evaluation of safety data. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the participant from the study, will be classified as other adverse events. For each, a narrative may be written and included in the clinical study report.

8.6 Relationship to Investigational Product (Assessment of Causality)

The investigator or designee must assign a relationship of each AE to the receipt of the IP. The investigator or designee will use clinical judgment in conjunction with the assessment of a plausible biologic mechanism, a temporal relationship between the onset of the event in relation to receipt of the IP, and identification of possible alternate etiologies including underlying disease, concurrent illness or concomitant medications. Every effort will be made to explain AEs and assess causal relationships, if any, to administration of the CampETEC test article, challenge, study procedures or antibiotic treatment. AEs occurring on study days -1 to 1 will be assessed as to their relationship with the CampETEC test article or study procedures (i.e. being on unit). AEs occurring after receipt of the *C. jejuni* challenge (Study Day 1) will be assessed as to their relationship with the CampETEC test article, *C. jejuni* CG8421 challenge strain, study procedures or the antibiotic, if applicable. The degree of certainty with which an AE can be attributed to these products (or alternative causes, e.g., natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of one or more of the following:

- Reaction of similar nature having previously been observed with other similar bovine colostrum products, *C. jejuni* challenge strains, or antibiotic administration
- Published literature accounts supporting causality
- Temporal relationship with administration

The following guidelines should be used by investigators to assess the relationship of an AE to study product administration. Only a physician, physician's assistant or nurse practitioner can make this determination. The investigator will assess causality of all AEs as below. Non-serious and serious adverse events will be evaluated as two distinct types of events given their different medical nature. If an event meets the criteria to be determined 'serious' it will be examined by the investigator to the extent possible to determine ALL contributing factors applicable to the event. Other possible contributors include:

- Underlying disease
- Other medication
- Protocol required procedure
- Other cause (specify)

8.6.1 Causality

Causality of all AEs will be assessed by the investigator using the following criteria:

In the investigator's opinion, is there a reasonable possibility that the AE may have been caused by the product or procedure under consideration?

Definitely related: AE can only be explained by receipt of the product

Probable (likely related): AE occurs within a reasonable time after the administration of the product and cannot be reasonably explained by other factors (i.e., clinical condition, environmental / toxic factors or other treatments)

Unlikely related: AE does not have a reasonable temporal relationship or good evidence for a more likely alternative

Unrelated: AE is not suspected to be related to the product, there are other more likely causes, and administration of the product is not suspected to have contributed to the AE.

8.7 Recording of Adverse Events

8.7.1 Methods for Assessing, Recording, and Analyzing Safety Endpoints

All AEs either observed by the investigator or one of his/her clinical collaborators or reported by participants spontaneously or in response to a direct question, will be evaluated by a study investigator. The nature of each event, date of onset, outcome, severity, and relationship to test article, challenge, study procedures and/or antibiotic will be established. Details of any symptomatic/corrective treatment will be recorded in the source and on the appropriate page of the eCRF. Participants will be asked specifically if they have experienced solicited symptoms (listed above) Participants will be asked non-leading questions initially when assessing other AEs, followed by more direct questions as necessary. AEs already documented in the eCRF, i.e., at a previous assessment, and designated as 'ongoing' will be reviewed at subsequent follow-up assessments. If resolved, documentation in the eCRF will be completed. If an AE changes in frequency or intensity during a study period, a new record of the event will be started as per the Data Management Handbook (DMH).

AEs, solicited AEs, AESIs and SAEs will be reviewed at all scheduled points of contact, documented in the source records, and recorded on the eCRFs using accepted medical terms and/or the diagnoses that accurately characterize the event. Solicited AEs will be recorded as individual events. Unsolicited AE may be recorded as a diagnosis. When a diagnosis is known, the AE term recorded on the eCRF will be the diagnosis rather than a constellation of symptoms. The investigator will assess all AEs for seriousness, relationship to IP, challenge, study procedures, and/or antibiotic, severity, and other possible etiologies. When an event has not resolved by the proscribed reporting period, it will be left open/without an end date on the AE eCRF and will be updated with end date or "ongoing at visit."

8.7.2 Recording Period for Adverse Events

- . AEs will be assessed through D85 and AESI and SAEs will be collected through the day 181.

8.7.3 Duration of Follow-Up of Participants after Adverse Events

Investigators are required to follow SAEs to resolution, even if this extends beyond the prescribed reporting period. Resolution is the return to baseline status or stabilization of the condition with the probability that it will become chronic. The SAE outcomes will be reported to the sponsor.

Investigators are not obligated to actively seek SAEs in former participants; however, if a SAE, considered to be related to either the HBC or challenge strain is brought to the attention of the investigator at any time until closure of the study, the event will be reported.

Investigators should follow-up adverse events at least until the final study visit. This may include repeat safety laboratory analysis. Outcome should be assessed as:

- Resolved
- Resolved with sequelae
- Severity change - the highest severity captured in a day will be recorded in the eCRF. E.g. if the severity on day 1 is moderate, then mild and then moderate again, it will be entered as moderate for that date in the eCRF. If on day 2, the severity is mild, the moderate AE will end and a new AE will be entered with a mild severity)
- Ongoing at day 85 /181
- Died
- Lost to follow-up

All SAEs must be documented and followed until the event either resolves, subsides, stabilizes, disappears, or is otherwise explained or the participant is lost to follow-up, but not longer than 6 months after the last receipt of the CampETEC HBC. All follow-up activities have to be reported, if necessary, on one or more consecutive SAE report forms, in a timely manner. All fields with additional or changed information must be completed and the report form will be forwarded to the study contact for reporting SAEs as soon as possible, but not more than 7 calendar days after receipt of the new information. Clinically significant laboratory abnormalities will be followed up until they have returned to normal or until stable. Reports relative to the subsequent course of an AE noted for any participant must be submitted to the Sponsor. The outcome of SAEs will be assessed in the same manner as all AEs.

8.7.4 Safety Assessment

All AEs will be assessed for severity by an investigator. Inherent in this assessment, is the medical and clinical consideration of all information surrounding the event, including any medical intervention required. Each event will be assigned one of the following categories: mild, moderate, severe or potentially life-threatening. The criteria below may be used for any symptom not included in the grading scales. Any life-threatening AE must be reported as an SAE.

The eCRF for unsolicited AEs will reflect only the highest severity reported for continuous days an event occurred, per the Data Management Handbook.

Mild	Grade 1	Does not interfere with routine activities; minimal level of discomfort
Moderate	Grade 2	Interferes with routine activities; moderate level of discomfort

Severe	Grade 3	Unable to perform routine activities; significant level of discomfort
Potentially Life Threatening	Grade 4	ER visit or potentially life-threatening event

FDA guidelines for toxicity will be followed; however, if a participant is evaluated in an emergency room for non-life threatening illness or symptoms (i.e., visits emergency department on weekend for mild problems because the physician's office is closed), the information from that visit will be reviewed and severity of the adverse event will be assessed according to the participant's clinical signs and symptoms.

As defined by the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP), the term "severe" is often used to describe intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

During the challenge phase of the study, Campylobacter disease-specific adverse events will be graded in accordance with the table below.

Table 9: Challenge Phase Campylobacter Infection Anticipated Adverse Event / Endpoint Assessments

Adverse Event	Severity[a]	Parameter
Diarrhea, based on highest output of loose/liquid stools in any 24-hour window. (A diarrhea episode ends when there is a 24-hour window with no grade 3-5 stools.)	1	Mild: 2-3 grade 3-5 stools totaling ≤400 grams
	2	Moderate: 4 to 5 grade 3-5 stools or 401-800 grams of loose/liquid stool
	3	Severe: 6 or more grade 3-5 stools totaling >800 grams
	4	ER visit or potentially life-threatening event
Body temperature (t)	1	≥100.4°F and ≤101.1°F (38.0-38.4°C)
	2	>101.1°F and ≤102.0°F (38.5-38.9°C)
	3	>102.0°F (39.0°C) and ≤ 104°F (40.0°C)
	4	>104°F (40.0°C)
Vomiting	1	One episode within a 24-hour period
	2	Two episodes within a 24-hour period
	3	More than two episodes with a 24-hour period
	4	ER visit or potentially life-threatening event
Other solicited and non-solicited adverse events	1	Discomfort noted, but no disruption of normal daily activities; slightly bothersome; relieved with or without symptom treatment.
	2	Discomfort sufficient to reduce or affect normal daily activity to some degree; bothersome; interferes with activities, only partially relieved with symptom treatment.
	3	Discomfort sufficient to reduce or affect normal daily activity considerably; prevents regular activities; not relieved with symptom treatment.
	4	ER visit or potentially life-threatening event

[a] 1=mild; 2=moderate; 3=severe; 4= ER visit or potentially life-threatening.

8.8 Reporting Adverse Events

The PI will report all AEs to the sponsor and the local IRB in the appropriate safety, annual, and/or final reports. The NMRC staff in conjunction with the clinical site will draft annual and final clinical study reports and provide files to the sponsor for review and submission to the FDA.

8.8.1 Reporting Serious and Unexpected Adverse Events

All SAEs must be reported immediately by the investigator without filtration, whether or not regarded as possibly attributable to the test articles, placebo, study procedures or antibiotic. SAE reports will be provided to the Sponsor, medical monitor, JHSPH IRB, and NMRC IRB. The investigator must report SAEs within one calendar day of becoming aware of the event via the EDC per the Data Management Handbook. This initial notification will include minimal, but sufficient information to permit identification of the reporter, the participant, the test articles, AEs, and date of onset. The investigator will not wait for additional information to fully document the event before notifying. The first notification will be confirmed by an acknowledgement letter. The report is then to be followed by submission of a completed SAE Report Form as soon as possible, but not more than 3 calendar days past the initial report, detailing relevant aspects of the SAE in question. All investigator actions and event outcomes must also be reported in a timely manner. SAE Report Forms are to be used for documentation of these various aspects regarding the event. Hospital records and autopsy reports will be obtained if applicable.

The research monitor is required to review all unanticipated problems involving risk to participants or others, SAEs, and all participant deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor will comment on the event outcomes, and in the case of a SAE or death, comment on the relationship to participation in the study. The medical monitor will indicate concurrence or nonconcurrence with the details of the report provided by the investigator. Reports for events determined by either the investigator or medical monitor to be probably or definitely related to participation and reports of events resulting in death will be promptly forwarded to the JHSPH IRB and NMRC IRB.

8.8.1.1 Reporting to the Sponsor

All SAEs and unexpected or unexpected suspected AEs must be reported promptly (within 72 hours) to the sponsor as per 21 CFR 312.64, whether or not the event is considered related to study product. Further, the investigator should comply with relevant study site SOPs on reporting SAEs.

The minimum information that the investigator will provide to the sponsor is specified in Table 10.

Table 10 : Study Contacts for Reporting Serious Adverse Events

Sponsor	David Sack, M.D. Department of International Health Johns Hopkins Bloomberg School of Public Health dsack1@jhu.edu 615 N. Wolfe Street E5537 Baltimore, Maryland 21205 Telephone: 443-287-8795
Institutional Review Board	JHSPH IRB Office 615 N. Wolfe Street Suite E1100 Baltimore, Maryland 21205 Phone: 410-955-3193 Toll-Free: 1-888-262-3242 Fax: 410-502-0584 Email: JHSPH.irboffice@jhu.edu
Collaborating Institutional Review Board	Naval Medical Research Command (NMRC) IRB Research Services Directorate Office of Research Administration Code 025, Building 500, Rm 004 Silver Spring, MD Telephone: 301-319-7276 Fax: 301-319-7277
Research Monitor	Nekhonti Adams, MD

Table 11: SAE Information to Be Reported to the Sponsor

Notification Method	**Information to be provided**
Email or Telephone (within 72 hours)	IND number, sponsor study number, name of the IP, and investigator name and contact number
	Participant identification number
	SAE, onset date, date of IP administration, severity, relationship, and participant's current status
AND	
Email or Fax	Cover sheet or letter
	Adverse event case report form
	Serious adverse event report form
	Concomitant medication case report form or a list of concomitant medications
	Medical record progress notes including pertinent laboratory/diagnostic test results
NOTE: When submitting SAE reports via email, the participant line of each email notification will read as follows: **SAFETY REPORT – IND # _____, Study #_____, Participant# _____, Event term: _____**	

In order to comply with regulations mandating sponsor notification of specified SAEs to the FDA within 7 calendar days, investigators must submit additional information as soon as it is available. The sponsor will report unexpected SAEs associated with the use of the challenge strain to the FDA as specified at 21 CFR 312.32 (c).

Investigators must follow all relevant regulatory requirements as well as specific policy at each institution regarding the timely reporting of SAEs to the local IRB and research monitor.

Reporting to the sponsor does not fulfill the investigator's duty to report all unanticipated problems involving risk to human participants or others to the IRB. The PI will notify the local IRB and the research monitor.

8.8.1.2 Reporting to the IRB

Unanticipated problems involving risk to participants or others, serious adverse events related to participation in the study and all participant deaths should be promptly reported by phone, email, or fax to the JHSPH IRB. A written report will follow the initial notification.

Investigators are required to forward safety information provided by the sponsor's representative to the IRB. All SAEs will be reported to the JHSPH IRB according to IRB guidelines.

JHSPH IRB Guidelines: IRB Phone 410-955-3193; Fax 410-502-0584. Investigators are required to promptly report adverse events that fit the following criteria using the Problem/Event Report Form:

Event (including adverse event reports, injuries, side effects, breaches of confidentiality, or other problems) that occurs any time during or after the research study, which in the opinion of the principal investigator:

1. Involved harm to one or more participants or others, or placed one or more participants or others at increased risk of harm;
2. Is unexpected (an event is "unexpected" when it is not described with specificity in the protocol and informed consent document; or if described with specificity, it occurs beyond the expected frequency and/or severity identified); and
3. Is related to the research procedures (an event is "related to the research procedures" if in the opinion of the principal investigator, it was more likely than not to be caused by the research procedures.)

8.8.2 Immediately Reportable Events

8.8.2.1 Pregnancy

For subjects who receive challenge strain, each pregnancy must be reported **within 72 hours of identification** by email, eCRF, or fax to the sponsor and the IRB. The investigator must report all pregnancies to the Research Monitor within 14 calendar days of learning of this occurrence.

Participants who become pregnant after Day 1 through visit 85 after receiving the investigational product will be followed to final outcome, and the following information will be gathered for outcome: date of delivery and health status of the participant and child, including the child's gender, height, and weight. Complications and/or abnormalities should be reported including any premature terminations. A pregnancy is reported as an SAE only when there is suspicion that the IP may have interfered with the effectiveness of contraception or there was a serious complication in the pregnancy including a spontaneous abortion or an elective termination for medical rationale.

A pregnancy outcome other than abortion or stillbirth, and any malformation/congenital disease, as well as follow-up of the neonate must be reported by the Investigator within 14 days of learning of its occurrence using local site procedures.

8.8.2.2 AE-Related Withdrawal of Consent

Any AE-related withdrawal of consent during the study must be reported **within 24 hours of identification** by email or fax to the sponsor and the IRB.

8.8.2.3 Pending Inspections/Issuance of Reports

The knowledge of any pending compliance inspection/visit by the following bodies, including the FDA, Office for Human Research Protections (Department of Health and Human Services), or other government agency, concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to IRB and the sponsor.

8.8.3 IND Reporting

8.8.3.1 Annual Reports

The NMRC lead investigator will be responsible for the preparation of a detailed annual synopsis of clinical activity, including adverse events, for submission to the sponsor. Each annual report will summarize IND activity for 1 year beginning approximately 3 months before the IND FDA anniversary date. The sponsor will notify the NMRC lead investigator of the due date with sufficient time for the NMRC lead investigator to assemble the required information.

8.8.3.2 Final Clinical Study Report

A final study report will be prepared in accordance with "Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications" and ICH E3 Guideline "Structure and Content of Clinical Study Reports" and provided to the sponsor for review and approval. The sponsor representative will use this report to prepare the final clinical study report for submission to the FDA. The investigative team will report all AEs to the sponsor and the local IRB in the appropriate safety, annual, and/or final reports.

8.9 Safety Criteria for Stopping Doses

The PI, along with the research monitor, may determine if certain events warrant discontinuation of challenges and/or HBC administration for all participants in a cohort. If any of the additional following events occur, administration of the HBC will be discontinued for all participants in that cohort, and the PI and the research monitor will undertake a thorough review of the events:

- The occurrence of one or more Grade 3 adverse event or serious adverse events (SAEs) determined to be related to the HBC.
- The occurrence of one serious or unexpected AE, which in the opinion of the PI, research monitor and sponsor is determined to be an unacceptable risk to the health and safety of the participants.
- The occurrence in two or more participants of a systemic allergic reaction, including, but not limited to, generalized urticaria, generalized petechiae, or erythema multiforme.

- The occurrence in any participant of bronchospasm or anaphylaxis.

Based on prior experience with *C. jejuni* challenge studies, it is expected that some participants will have severe AEs (such as severe diarrhea) after the challenge. This will not be stopping criteria.

Once pausing/stopping criteria are met, the study will be paused (no IP or challenge will be given) to allow for review and causality assessment by the research monitor prior to resumption of the study. The sponsor, IRB and FDA will be informed.

AEs which will prompt stopping the CampETEC HBC administrations for an individual participant include:

- Grade 4 AE or SAEs unrelated to the test articles (event will be discussed with the medical monitor to determine if the event precludes further participation and administration of the HBC or challenge)
- The investigator deems that stopping test article administration is in the best interest of the participant

Additional reasons for participant withdrawal include:

- The participant does not wish to continue with the study
- The participant is lost to follow-up

Further challenge, in accordance with the protocol, may be resumed with the concurrence of the research monitor, sponsor, PI, and the FDA.

8.10 Treatment of Adverse Events

Treatment of an AE is the responsibility of the investigator according to the best treatment currently available. The applied measures will be recorded in the eCRF of the participant.

8.11 Study Termination Criteria

The PI, research monitor, NMRC IRB, JHSPH IRB, Sponsor, or FDA may stop or suspend the use of the CampETEC HBC at any time.

8.12 Six Month Follow-Up Safety Surveillance

Data will begin to be entered into the study database beginning on or after the inpatient period. It will subsequently be verified and locked. Approximately 6 months after challenge, participants will be contacted by phone to track the occurrence of any medically significant new chronic illnesses or serious health events and verbally complete a functional bowel disorder survey. If a participant cannot be contacted after three attempts, a registered letter will be mailed asking them to contact study staff. These attempts will be documented in a contact log and summarized in an annex to the final clinical study report.

9.0 CLINICAL TRIAL MONITORING

Monitoring will be conducted according to an approved monitoring plan. Local monitoring may commence prior to beginning, at initiation, during the study, and at closeout.

The study monitor shall be available for consultation with the investigator. The study monitor or other authorized representatives of the Sponsor may inspect all documents and records maintained by the investigator, including, but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participant in this study. The clinical study site will permit access to such records. The investigator will obtain, as part of informed consent, permission for authorized representatives of the Sponsor, or regulatory authorities, to review, in confidence, any records identifying individuals in this clinical study.

The investigator will notify the Sponsor within 24 hours following contact by a regulatory agency. The investigator and study coordinator will be available to respond to reasonable requests and audit queries made by authorized representatives of regulatory agencies. The investigator will provide the Sponsor with copies of all correspondence that may affect the review of the current study or his/her qualification as an investigator in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance in responding to regulatory audits or correspondence. The investigator will permit independent auditors (employees of the Sponsor or an external company designated by the Sponsor) to verify source data validation of the regularly monitored clinical trial. The auditors will compare the entries in the eCRFs with the source data and evaluate the study site for its adherence to the clinical study protocol and GCP guidelines and applicable regulatory requirements.

The study team and data management group will arrange visits prior to beginning, at initiation, during the study, and at closeout by the study monitor or designee.

10.0 STATISTICAL CONSIDERATIONS

10.1 Introduction

Safety, efficacy, clinical outcomes, and immunogenicity data will be entered into the eCRFs using standard software for data management. Data will be edited with standard strategies for range and consistency checks. All participants who receive CampETEC HBC or placebo, irrespective of the number of doses of CampETEC HBC or receipt of the challenge and all AEs, will be included in the safety analyses. The null hypothesis for this study is that the diarrhea rates will be the same in groups receiving the placebo and CampETEC HBC product.

10.2 Sample Size Considerations

Using a Fisher's Exact Test with a two-sided *alpha*=0.05 and a conservative campylobacteriosis rate of 70% in placebo recipients, a sample size of 15 participants per study arm (CampETEC HBC or placebo) yields an approximate 80% power to detect a significant difference in the moderate-severe diarrhea rate in placebo and CampETEC HBC participants when the efficacy of the HBC product is >70%. Of note, a one-sided *alpha* is utilized based on the extensive existing data supporting a 1-way effect of bovine colostrum products on disease rates in CHIM studies.

10.3 Analysis

10.3.1 Safety

Assessment of the CampETEC product safety is limited to the two days prior to receipt of the *C. jejuni* challenge dose (day –2 and –1). Unless AEs are temporally related to receipt of the IP, most will likely be attributed to the Campylobacter inoculum. During each day of the inpatient period, participants will be monitored for loose stools (not meeting the diarrhea definition), diarrhea, nausea, vomiting, abdominal cramps, fever, headache, abdominal tenderness, abdominal distention, and an abnormal abdominal exam. Additionally, participants will have vital signs taken at least 3 times per day. As clinically indicated, postural blood pressure and heart rate may be taken to facilitate clinical decision-making per the judgement of the study providers.

The sample size is designed to indicate trends but not to show statistically significant differences between groups. Adverse events will be summarized and compared between study groups for the periods prior to and after challenge. Safety data, including adverse events, vital signs, and laboratory tests will be listed by study participant. Side effects to the challenge will be coded as defined in the protocol, and will be listed (group, time of onset, duration, and severity). Summaries of the number and proportion of participants who report a given coded term will be reported. Safety data, including AEs, vital signs, and laboratory tests will be listed by study participant.

10.3.2 Protective Efficacy Determination

The primary endpoint for determination of efficacy is Campylobacter-induced moderate-severe diarrhea occurring during the post-challenge period; however, participants will be monitored for additional GI and non-GI complaints daily. Data will be analyzed to determine the incidence of illness among participants in the placebo vs. the CampETEC HBC group.

Equation 1. Protective Efficacy

$$PE\ (\%) = \frac{incidence\ (placebo) - incidence\ (Bovine\ IgG)}{incidence\ (placebo)} \text{ x } 100\%$$

Additional comparisons between the placebo and the CampETEC groups include:

- Maximum 24-hour loose stool (Grades 3-5) output
- Total loose stool (Grades 3-5) output
- Percent of participants with severe diarrhea
- Percent of participants with diarrhea of any severity
- Percent of participants with fever, nausea, vomiting, anorexia, or abdominal pain/cramps rated as moderate to severe
- Time to diarrhea onset and diarrhea resolution
- Number of colony-forming units of the challenge strain per gram of stool at 48 hours post challenge
- Percent of participants requiring early antibiotic treatment
- Percent of participants requiring IV fluids
- Comparison of groups using a Campylobacteriosis severity score in development

Initial efficacy analyses will be based on an intent-to-treat and will include all participants who receive the test article/placebo and the challenge. A secondary, per protocol analysis, may limit the number of participants evaluated. Participants who miss more than one dose of test article (or placebo) in the 24 hours prior to receipt of the challenge inoculum will be excluded from this secondary analysis. Participants who miss more than one dose of test article in the 72 hours following receipt of the challenge inoculum and who do not meet the primary outcome before missing their second dose will also be excluded. A similar analysis will be performed for the secondary outcomes outlined above. Analysis of participants who miss doses and are not included in this time period will only be descriptive in nature.

10.3.3 Immunogenicity

Immunological outcomes, including serology and fecal IgA will be summarized in a tabular format and graphed to demonstrate kinetics of response. Qualitative (responder rates) and quantitative assessments (log transformed values) will be analyzed. Between-groups comparisons will be examined with nonparametric tests (Kruskal-Wallis for continuous data and Fisher's Exact test for categorical data) unless assumptions are fulfilled for Student's t or chi-squared test. Paired t-tests will be used to compare individual post-vaccination to baseline response within each treatment group. Only participants receiving the experimental infection will be included in these analyses. All statistical tests will be performed using GraphPad Prism version 9.4.1 or SAS version 9.2 and will be interpreted utilizing a two-sided alpha=0.05 and 95% confidence intervals for proportions will be estimated utilizing exact binomial distributions.

11.0 DATA MANAGEMENT

The investigator will maintain complete and accurate documentation for the study in accordance with applicable regulatory obligations and Good Clinical Data Management Practices (GCDMP) guidance. All study records will be kept confidential to the extent provided by national and local laws. (State laws require that positive HIV, hepatitis B and hepatitis C tests be reported to state health agencies).

When collecting clinical data, participants will be identified by a unique participant identification number and on source documents by initials and the participant study number. No personal identifier will be used in any publication or communication used to support this research study. The participant study number will be used if it becomes necessary to identify data specific to a single participant. All laboratory specimens, reports, study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. Samples are identified by coded participant number only.

Complete source documentation (study visits, laboratory reports, etc.) is kept for each participant in his/her individual study chart. Study charts and documents will be retained at the study site in locked cabinets in locked rooms with limited access. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file cabinet in an area with limited access.

An electronic data capture (EDC) database will be used to collect study data in an electronic format by the staff at the clinical study site. The EDC database system will be designed based on the protocol requirements, the approved eCRF layouts and specifications, and in accordance with 21 Code of Federal Regulations Part 11. The eCRF layouts and specifications define and identify the applicable source data that will be collected and captured into the EDC database system. The applicable source data will be electronically transcribed by the site designee onto the eCRF (data entry screens) in the EDC database system. Information in the electronic database is password-protected and access is available only to authorized research team members. Additionally, each authorized research team member is assigned a level of security clearance (also password-protected) with mandatory password changes every 90 days) for the purpose of limiting access to certain areas or functions of the database. Any information printed from this database is stored in locked files until its use is complete and then shredded. Access to the database system is defined by the role and responsibility of the project staff.

11.1 Ethics and Legal Compliance

Ethical Data Issues- Prior to the involvement of any human subjects, an appropriate Human Subjects Research Determination will be made. Research that is determined to be considered Human Subjects Research will obtain the appropriate Institutional Review Board (IRB) and Department of Navy Human Research Protection Program (DoN-HRPP) review and approvals. Any data collected from participants will be protected in accordance with Federal and Navy regulations. PII will not be released as part of data sets. Any data shared will be stripped of all identifiers to protect participant identity. All sensitive data will be securely stored; electronic data will be encrypted and password protected with only IRB approved researchers permitted access. All paper data will be considered as PII/PHI and stored in locked cabinets within locked rooms.

Copyright regulations will follow Title 17 U.S.C. 101

Intellectual Property Rights will be determined by review of all data created by the NMRC Office of Partnerships and Business Development and The Office of Legal Counsel. Patents applications will be filed as applicable. Patented work may be licensed to third parties under the guidance of the Office of Partnerships and Business Development.

Data generated by NMRC are considered to be property of the United States Government and its contracted support, as outlined in specific support contract agreements.

Prior to public release, all data are reviewed for IP concerns. Should potential IP be identified, release of data will be delayed until such time that IP rights can be secured.

11.2 Storage of Data and Samples

All records pertaining to this protocol will be stored in a locked filing cabinet at JHU or at an offsite, locked storage facility per regulations for a minimum of 5 years. Access to these records will be limited to researchers in the Enteric Disease Department at NMRC and the JHU CIR as well as those responsible for regulatory monitoring of data to include representatives of the DoD and JHU. A copy of study records will be made available to the Sponsor. The investigator will obtain permission from the sponsor in writing before destroying any study records and the sponsor will notify the investigator in writing when records can be destroyed. Relevant IRBs will be notified in writing prior to destruction of any research records. Specimens will be stored indefinitely in the JHU or the Campylobacter laboratory at NMRC.

12.0 OBLIGATIONS AND ROLES OF THE SPONSOR, INVESTIGATOR, AND STUDY PERSONNEL

This study will be conducted using GCP and in accordance with all federal regulations regarding the protection of human subjects in research including The Nuremberg Code, The Belmont Report, US 21 CFR Part 50 – Protection of Human Subjects, 32 CFR 219 (The Common Rule) and all regulations pertinent to the Department of Defense.

The investigators agree to conduct the research in strict accordance with this protocol, the ICH Guideline for GCP (CPMP/ICH/135/95), as well as in conformity with any federal, provincial or local regulations regarding the conduct of clinical studies. The sponsor and investigator must comply with all applicable regulations. In addition, the investigator must follow local and institutional requirements including, but not limited to, IP, clinical research, informed consent, and IRB regulations. The Sponsor will provide notification to the investigator of protocol and amendment approvals by regulatory authorities when applicable. Except where the investigator's signature is specifically required, it is understood that the term "investigator" as used in this protocol and on source documents refers to the investigator or appropriate study personnel that the investigator designates to perform a certain duty. The investigator is ultimately responsible for the conduct of all aspects of the study. Sub-investigators or other appropriate study personnel are eligible to sign for the investigator on designated source documents.

13.0 QUALITY CONTROL AND ASSURANCE

13.1 QA/QC Monitoring

Data monitoring and management will be performed in the EDC database system by the study monitor and the designated Data Management group. A detailed data management, monitoring and quality assurance plan will be written and approved by the study team and the principal investigator.

During the study, the principal investigator (PI) is responsible for procuring data, and for the quality of data recorded in the eCRFs. The study monitor will ensure accuracy of the eCRFs. At the end of the clinical trial, the data will be transferred to NMRC as part of a data transfer package. The data and the documentation to be transferred will be checked for quality control. Review will include:

Comparison of the data transfer with the terms of the transfer with respect to contents, identification, documentation, and timeline.

- Specific safeguards that all applicable guidelines for protecting patient confidentiality have been made, including complete absence of any personal identifiers.
- Proofreading the documentation relative to the data set(s), for completeness and accuracy.

13.2 Protocol Deviation Management

All amendments to the protocol, consent form and/or questionnaires, including a change of PI, will be submitted to the JHSPH IRB and NMRC IRB for review and approval prior to implementation. Other-than-minimal-risk changes and all unanticipated major problems involving human subjects or others will be reported promptly to the IRBs, and no such changes will be made to the research without IRB approval unless necessary to eliminate apparent immediate hazards to human subjects. Minor minimal risk deviations necessitated during the course of the trial will be made on site as needed and documented for subsequent review within a reasonable time period. Deviations from the protocol that potentially impact participant safety will be promptly reported to the Research Monitor, IRBs, and the Sponsor. Other deviations will be reported at the time of continuing review.

14.0 HUMAN PARTICIPANTS PROTECTIONS CONSIDERATIONS

14.1 Risks/Benefits

14.1.1 Risks

14.1.1.1 Risks Related to the Investigational Product

The HBC products are expected to be safe with possible mild to moderate discomfort, likely related to consumption of the sodium bicarbonate buffer, such as bad taste, bloating, nausea, gas, etc. As with any investigational drug or biologic, there is a possibility of severe allergic reaction.

14.1.1.2 Risks Related to the Challenge Inoculum

Naturally acquired illness caused by *Campylobacter* organisms ranges from mild-to-severe watery diarrhea that may contain mucus and/or blood. Nausea, vomiting, abdominal cramping, headache, abdominal gurgling or gas, anorexia, fever, muscle and/or joint aches, and malaise, may occur. For most adults the illness is not life-threatening but often leads to mild to moderate dehydration and significant inconvenience associated with loss of sleep and activity. There is also a risk of recrudescence of *Campylobacter* infection. Study facilities will have personnel and resources capable to manage diarrheal illness and potential complications. Side effects from the antibiotic (azithromycin and ciprofloxacin) used to treat the *Campylobacter* infection are possible.

A less common, but potentially life-threatening, complication of *C. jejuni* infection is Guillain-Barré syndrome (GBS), a post-infectious polyneuropathy that is a leading cause of paralysis and the related syndrome, Miller Fisher Syndrome (MFS) [69-75]. Although many infectious agents are associated with GBS, *C. jejuni* is the most frequent pathogen associated with the syndrome and it has been estimated that between 1:1000 to 1:3000 cases of *C. jejuni* enteritis progress to some form of GBS [76-79]. A more recent direct estimate of GBS incidence in a cohort of patients presenting with *Campylobacter* enteritis in England was found to be 1.17/1000 person-years [79]. The association between GBS and *Campylobacter* infection is supported by both serologic, culture, and experimental data. Published data from a large case-control study of *Campylobacter*-associated GBS by Rees and colleagues showed evidence of *C. jejuni* infection in 26% of the 103 GBS and Miller Fisher syndrome patients, compared to 2% of household controls, and 1% of hospital controls. The pathogenesis of *Campylobacter*-associated GBS is hypothesized to involve "molecular mimicry," where peripheral nerves share epitopes with some *C. jejuni* antigens. Thus, an immune response, which is initially mounted against the infection, may be misdirected to peripheral nerve in some convalescing patients.

Research supports the hypothesis that the association between *C. jejuni* and GBS is due to molecular mimicry between the outer lipooligosaccharide cores (LOS) and human gangliosides [80-82]. Thus, the outer LOS cores of some strains of *C. jejuni* have a similar structure to multiple human gangliosides, including GM1. It is hypothesized that the *Campylobacter* epitopes stimulate the human immune system to attack gangliosides that are components of neural coverings throughout the human nervous system, thereby leading to the development of GBS. This mimicry results from the ability of most strains of *C. jejuni* to synthesize N-acetyl neuraminic acid (Neu5Ac) endogenously for incorporation into the outer LOS core. Cross-reactive antibodies between *C. jejuni* LOS and gangliosides have been identified in GBS and Miller Fisher patients [83,84]. Thus, during infection antibodies directed against these Neu5Ac-containing ganglioside mimics results in an autoimmune disease affecting the ganglioside-rich peripheral nerves. This association with GBS has impacted vaccine strategies and the design of potential human vaccine challenge studies. Based on this knowledge, an extensive search followed by detailed characterization of strain CG8421 documented the lack of ganglioside mimicry and therefore decreases the risk of GBS.

Like *Salmonella*, *Shigella*, and *Yersinia*, *Campylobacter* enteritis has been associated with development of a reactive arthritis/arthropathy (RA) [85-92]. Studies of outbreaks [87-92] have found an incidence of reactive arthritis ranging from about 0.7 to 1.8% in participants with evidence of *C. jejuni* infection. A more recent report documented a 2.6% rate in a waterborne outbreak in Finland among 350 exposed persons [93]. A population-based survey also in Finland found a higher rate of 8% with most cases being very mild [94]. Based on the survey results, the authors estimated an incidence of reactive arthritis following *Campylobacter* infection in Finland at 4.3 per 100,000. Also observed was a higher likelihood of reactive musculoskeletal complications among *Campylobacter* cases with a longer median duration of illness, 10 vs. 7 days of diarrhea. Most cases were mild with only 20% visiting a physician and one hospitalization. A genetic predisposition to acquiring a seronegative spondyloarthropathy after a bacterial enteric infection (approximate risk gradient: *Yersinia* spp. > *Shigella* spp. (*S. flexneri*) > non-typhoid *Salmonella* > *C. jejuni*) has been observed in individuals with the human leukocyte antigen (HLA)-B27 [95]. An overall estimated 18-fold increased risk of reactive arthritis exists for HLA-B27 positive as compared to negative individuals following one of these infections [95]. The presence of HLA-B27 antigen in *Campylobacter*-associated reactive arthritis has been variable, ranging from 14% to as high as 53% [94]. Restricting the assessment

to the more severe cases increases the proportion of individuals who are HLA-B27 positive in the range of 70%, suggesting a greater risk for these individuals to have more severe or prolonged disease. No bacterial factor has been identified in the pathogenesis of reactive arthritis; however, the increased risk observed in HLA-B27 positive individuals permits screening of prospective participants as a risk mitigation strategy. All participants will be screened for HLA-B27, and a positive result will be an exclusion criterion from the study.

14.1.1.3 Risks Related to Antibiotic Treatment

Therapeutic antibiotics for use in this study are licensed approved medications that have been used extensively and shown to be very safe with only rare side effects. The most reported side effects for ciprofloxacin are gastrointestinal symptoms (nausea, vomiting, and diarrhea) in as many as 5 persons in 100. Other reported symptoms, in less than 1 person in a 100, include rash, dizziness, and headache. Rarely, allergic reactions to these medications have been observed. Azithromycin has been associated with gastrointestinal symptoms (nausea, vomiting, diarrhea and abdominal pain), hepatotoxicity (abnormal liver function tests, cholestatic jaundice) and QT prolongation. There is no evidence related to adverse effects to support an increase in risk due to combination of azithromycin and ciprofloxacin, although hypothetically, both can increase the cardiac QT interval. Ciprofloxacin is not recommended for use in pregnancy due to concerns of joint damage to the unborn child (based on studies in young animals). Pregnancy is exclusionary for study participation and is documented through testing prior to study interventions and provided discussion on methods to prevent pregnancy during study. Fluoroquinolones, including ciprofloxacin, are associated with an increased risk of tendonitis and tendon rupture in all ages. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney heart or lung transplants, all of whom are excluded from this study. Second line antibiotics to be used in this study like Augmentin and oral 3rd generation cephalosporin are associated with anaphylaxis reaction and rarely, Steven Johnson syndrome . *Clostridium difficile* associated diarrhea (CDAD/pseudomembranous colitis) has been reported with use of nearly all antibacterial agents.

14.1.1.4 Risks Related to Study Procedures

There is a minor, transient pain associated with blood draw and intravenous (IV) fluid administration. Hematomas or bleeding can occur at the puncture site. Rarely, there is lightheadedness, syncope or infection. Intravenous catheters may additionally infiltrate and cause swelling and/or discomfort.

Volunteers may experience minor discomfort, annoyance, or embarrassment related to stool collection and rectal swabs. Rarely, rectal swabs may cause bleeding or irritation.

Isolation from friends, family, work, school and sharing space with strangers can cause discomfort.

There may be physical, psychological and social risks if participants test positive for hepatitis B, hepatitis C and/or HIV. Participants testing positive will be counseled and referred for treatment.

14.1.1.5 Risk to Privacy and Confidentiality

All data and medical information obtained about participants will be considered privileged and held in confidence. A breach of confidentiality in which private health information is made public is possible. Participants will not be identified by name in any published report/presentation of the results. The Sponsor, their delegates, and the FDA may inspect the records of this research as part of their responsibility to oversee research and ensure protection of participants. Study results and data may be published in scientific/medical journals; the identity of individual participants will not be disclosed.

Complete confidentiality cannot be promised to participants who are military personnel, because appropriate medical command authorities may require reporting information bearing on the health of their personnel. Representatives of the Sponsor, NMRC IRB, JHSPH IRB, or FDA may inspect the records of this research as part of their responsibility to oversee research and ensure protection of participants.

The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. The investigator will inform the participants that the above-named representatives will review their study related records.

Participants' study information will not be released without the written permission of the participant, except as required, these groups may include:

1. Audit and Compliance Officers and Legal Counsel
2. Office for Human Research Protections (OHRP)
3. The U.S. Food and Drug Administration (FDA) and other similar regulatory agencies
4. The study sponsor or designee
5. Study monitors, Medical Monitors
6. Department of Health and Human Services (DHHS) agencies
7. Governmental health agencies to which HIV and hepatitis testing must be reported
8. The Johns Hopkins University Bloomberg School of Public Health

14.1.1.6 Risk of SARS-CoV-2 Exposure and Risk Mitigation

SARS-CoV-2, the virus that causes COVID-19 infections and disease, is the cause of the global pandemic that started in 2020. COVID-19 can cause respiratory symptoms and pulmonary disease. Symptoms include fever, increased cough, shortness of breath, trouble breathing, fatigue, chills, body aches, headache, sore throat, congestion/runny nose, loss of taste or smell, nausea, and diarrhea. The virus can lead to more severe illness including pneumonia, respiratory failure, heart problems, liver problems, blood clots, septic shock, and death.

The CIR will follow recommendations from the CDC when implementing clinical trials. The CIR will also follow institutional guidelines and policies. Current recommendations include vaccination with one of the FDA-approved bivalent vaccines. To mitigate risk and provide a safe environment for participants while they are inpatient on the unit during the study, the CIR staff will educate and encourage all potential study volunteers to be fully vaccinated prior to enrolling in this study. Volunteers will not be required to be vaccinated against COVID-19; however, vaccinated volunteers will be prioritized for enrollment.

All volunteers will sign a disclaimer regarding vaccination status and possible exposure to the virus. All volunteers will be tested for COVID-19 upon admission to the inpatient unit and any person found to be positive will be discharged.

14.1.2 Risk Mitigation Strategies

14.1.2.1 During Acute Diarrhea Episode

Participants will be questioned and examined daily for evidence of Campylobacter illness. Vital signs will be recorded at least three times per day. Based on prior studies, infected participants tend to develop illness with incubation periods of approximately 1-3 days. The range varied from as short as 10-12 hours in a minority of participants up to 5.5 days. Therapeutic benefit seems to be optimal if treatment is given within the first three days of symptom onset. The risk of diarrhea complications will be minimized by a conservative approach to timing of antibiotic administration well within an interval that has been shown to be efficacious as well as daily clinical monitoring. Stool output will be closely monitored. The plan will be to treat all participants no later than day 6 post-dosing. The participants will be monitored for evidence of relapsed *Campylobacter* infection by clinical symptoms and repeat stool cultures on study days 15, 29, 42, 57, and 85.

Aggressive fluid management will be undertaken to ensure the most common complication, dehydration, does not occur. The procedures to institute early oral and/or intravenous rehydration therapy are detailed above. In addition to rehydration therapy, prospectively defined criteria and procedures to institute early antibiotic therapy are also fully described above. To ensure clinical resolution and limit the potential for secondary spread upon discharge, predefined discharge criteria have been established. Participants will be discharged from the inpatient phase of the study when clinical symptoms are resolved or resolving, at least two doses of antibiotics have been taken AND two consecutive stool cultures are negative for *C. jejuni*.

Systemic or severe gastrointestinal complications rarely occur with *Campylobacter* infection. The following clinical findings necessitate immediate consideration and management of complicated enteritis:

- Physical examination compatible with an acute abdomen
- Severe GI bleeding (any evidence of GI blood loss other than hemoccult positivity only, with evidence of hemodynamic instability, decrease in hemoglobin, hypovolemia)
- Sepsis (high fever: temp. >102ºF (39ºC), rigors, hemodynamic instability)

Any of these findings require prompt clinical management and discussion with the independent Research Monitor.

The *C. jejuni* strain has the potential for risk to both the environment and to the research personnel. *Campylobacter* spp. are common commensals of many birds and mammals with the usual route of transmission to humans through consumption of contaminated meat, poultry, milk and occasionally large waterborne outbreaks. Therefore, the of potential transmission outside of the JHU CIR facility is low. There is a minimal risk of acquiring *C. jejuni* infection associated with participant inoculum administration, patient care activities on the ward, or processing *C. jejuni*-infected stool. The risk to the environment will be reduced by ensuring that all human waste products from inpatients are disinfected with bleach prior to disposal per the MOP, ensuring all participants comply with discharge criteria (including two consecutive negative stool cultures for *C. jejuni*), emphasizing importance of hand washing for participants and staff, ensuring proper disposal/cleaning of linen, and cohorting participants in the JHU CIR while they are shedding *C. jejuni*. Additionally, participants will not be discharged until they are no longer shedding the challenge strain per the procedures outlined in the protocol.

If a recrudescent infection is detected, the follow-up clock will be reset according to expert panel's recommendation. The risk of recrudescent infection will be minimized by the participation of only immunocompetent individuals, the use of an extended duration of concurrent antibiotics (five days), monitoring of clinical symptoms, and evaluation of stool cultures. Follow up stool cultures at in-person outpatient visits will be performed to demonstrate continued eradication of infection.

If a participant is found to have recrudescence of infection, as defined in the definition section, the follow procedures will be completed per Section 6.6.

If there is an allergic reaction or adverse event, or if resistance emerges to both antibiotics, the planned course of treatment will be Augmentin (875 mg PO BID for 10 days) or the oral third generation cephalosporin, cefpodoxime (400 mg PO BID for 10 days). Decisions regarding antibiotic use and combination of these second-line agents will be made by Principal Investigators on a case-by-case basis in consultation with the Research Monitor.

Post-Infectious Sequelae

Post-infectious sequelae include neurologic, rheumatologic, and gastrointestinal syndromes. The risk mitigation strategies for post-infectious sequelae differ between GBS and reactive arthritis. GBS risk reduction is based on selection of a strain with no evidence of inducing potential ganglioside mimicry coupled with participant screening for personal or immediate family history of autoimmune or neurologic disease that may predispose the participant to greater risk. Similar participant eligibility screening for personal or immediate family member medical history of autoimmune or inflammatory arthritis will be used to reduce risk of reactive arthritis. Also, participants will be excluded if they are positive for HLA-B27 since that is associated with higher risk as well as poorer prognosis. Predefined criteria to assure early treatment as appropriate also may further reduce risk of post-infectious sequelae as has been observed with reactive arthritis [94]. Recent studies also suggest an increased risk of post-infectious irritable bowel syndrome (IBS) following bacterial enteritis [96]. Participant eligibility will be restricted to individuals without IBS history. As observed with reactive arthritis, the duration of illness is a strong predictor of post-infectious IBS risk [97]. Individuals with > 21 days of diarrhea

had an IBS relative risk of 11.4 compared to illness lasting < 7 days. All participants will receive treatment no later than 6 days from time of inoculation, which should reduce this potential risk.

The participants will be monitored for evidence of post-infectious sequelae (including reactive arthritis and GBS) on clinic visits at study days 15, 29, 42, 57, and 85 and a phone call at Day 181. IBS symptoms will be screened for by completing the Functional Bowel Disorder Survey on Study Day 181.

The following describes the clinical evaluation required in the event of suspect post-infectious sequelae (GBS or reactive arthritis).

Suspect reactive arthritis

Participants reporting new complaints consistent with the clinical definition of "arthralgia," "arthritis" or "reactive arthritis" will be evaluated as soon as possible by one of the on-site clinical investigators. The participant will be promptly evaluated by history, directed examination, ± indicated laboratory analysis, which may include, but is not limited to a complete blood cell count (CBC), erythrocyte sedimentation rate (ESR) and/or a C-reactive protein (CRP). The participant's symptoms/exam findings will be discussed with the independent Research Monitor and a rheumatologist. If the participant meets the clinical definition of "arthritis" or "reactive arthritis," then the participant will be evaluated as soon as possible. If the participant meets the definition of "arthralgia" only, then ESR and CRP will be obtained. If ESR/CRP is abnormal, then the participant will be referred for evaluation. If ESR/CRP is normal, then the participant will have a repeat examination at one week (sooner if new problems arise). The case will be discussed with a staff rheumatologist. The mechanism to provide a timely evaluation and prompt referral to a rheumatologist will be arranged prior to study initiation.

Suspect Guillain-Barré syndrome

Participants reporting new complaints concerning for GBS (i.e., new onset extremity weakness, numbness/paresthesia especially if symmetric and/or progressive) require immediate evaluation. The independent Research Monitor will be notified promptly, and the participant will likely receive an urgent Neurology referral. The presence or absence of an abnormal exam will be very important early on to determine the necessary management. Regardless of the findings, all suspected cases of GBS or equivocal symptoms that raise some concerns regarding GBS will require discussion with a staff neurologist. The mechanism to provide a timely evaluation and prompt referral to a neurologist will be arranged prior to study initiation.

Irritable Bowel Syndrome

Recent studies also suggest an increased risk of post-infectious irritable bowel syndrome (PI-IBS) following bacterial enteritis with limited studies associating *Campylobacter* infection specifically with this sequela [98, 99]. PI-IBS, a functional bowel disorder characterized by unexplained abdominal discomfort or pain associated with changes in normal bowel patterns, has been described in a recent systematic review to occur 6-7 times more frequently after an acute enteric infection compared to similar matched controls without such a history [99]. Participants with prior history of abnormal bowel patterns who might be at higher risk of this post-infectious sequelae are excluded and predefined criteria to assure early treatment as appropriate also may further reduce risk of post-infectious sequelae as has been observed with reactive arthritis and is likely to reduce the risk associated with PI-IBS given the positive association between diarrheal illness duration and PI-IBS risk [100,101].

Medical records associated with this protocol are subject to provisions of the Privacy Act of 1974, 5 U.S.C., Section 552A, and AR 340-21. All data and medical information obtained about participants will be considered privileged and held in confidence. See Privacy and Confidentiality

14.1.3 Benefits

There is no benefit to participants for participating in this research study. However, there is potential societal benefit of the development of a product to prevent Campylobacter.

14.2 Participant Compensation

Compensation for participation will occur as detailed below. Compensation will be provided only for completed study procedures designated for compensatory payment. If a participant is eligible to participate in the study after screening, is enrolled in the study, and completes all study visits, procedures and follows all the rules they will receive full compensation as described below:

- $150 total for screening (only if enrolled in the study or presents as an alternate)
- $4200 ($350 per night) for the inpatient period (as long as all study requirements are met)
- $750 ($150 per visit) for outpatient study visits: Days 15, 29, 42, 57, 85
- $60 for the follow-up telephone contact: Day 181
- $250 bonus upon completion of inpatient phase and outpatient visits

Maximum compensation for the planned schedule of the study is $5410,

If there is a day 113 visit, participant will be compensated an additional $150.

If a participant is not eligible for discharge on day 10, they will receive $300 per additional inpatient day. Participants will not be paid for missed outpatient visits and may forfeit some or all their bonus because of missed visits or noncompliance.

If a participant recrudesces some of the visits may still be included in the compensation as above. It is likely that there will be additional visits required, participants will be compensated $ 150 for each additional visit not covered above.

14.3 Research-Related Injury

All study-related medical care will be provided to participants without cost. Should a participant be injured as a direct result of participating in this research project, they will be provided medical care by the staff at the Walter Reed National Military Medical Center (or other military-affiliated medical center), at no cost to the participants, for that injury. The participants will not receive any

injury compensation, only medical care. The participants will not be compensated for care if they choose to seek care from their own medical care provider.

If a participant is injured because of participation in this research and is a DoD healthcare beneficiary (e.g., active duty in the military, military spouse or dependent), the participant is entitled to medical care for that injury within the DoD healthcare system, as long as the participant remains a DoD healthcare beneficiary. This care includes, but is not limited to, free medical care at Army hospitals or clinics.

If a participant is injured because of participation in this research and is not a DoD healthcare beneficiary, the participant is entitled to free medical care for that injury at a DoD hospital or clinic. It cannot be determined in advance which DoD hospital or clinic will provide care. If the participant receives care for research-related injuries outside of a DoD hospital or clinic, the participant or the participant's insurance will be responsible for medical expenses.

During the challenge phase, participants who require medical treatment beyond what can be provided safely at the CIR will be transferred to a tertiary medical facility, ideally Johns Hopkins Bayview Medical Center. If a participant is injured during the study, the investigators will help the participants find medical care. Medical care at Johns Hopkins is open to all participants, as it is to all sick or injured people. Neither Johns Hopkins Bloomberg School of Public Health nor the John Hopkins Hospitals have any plan to provide compensation to the participants if they experience injury or other bad effects which are not the fault of the study doctors. Participants will only be treated for injuries that are directly caused by the research study. Follow-up as necessary may be provided at the Walter Reed National Military Medical Center.

Transportation to and from military hospitals or clinics will not be provided. No reimbursement is available if the participant incurs medical expenses to treat research-related injuries from outside or private providers. No compensation is available for research-related injuries. The participant is not waiving any legal rights. The participant should contact the PI if the participant believes he or she has sustained a research related injury or has any questions.

Requests for other benefits, such as compensation for lost time from work, are processed independently of this protocol. The right of other parties to seek redress against the United States Government is limited to that set forth by existing agency regulations and the Federal Tort Claims Act. The participant should understand that this does not constitute a waiver or release of legal rights. This issue is addressed in the informed consent and will be discussed with the participant by the investigator or designee before the participant signs the informed consent to participate in the study.

14.4 Compensation for Investigators

There is no financial compensation for investigators in this study. All investigators will be required to complete a form for the disclosure of significant financial interest.

14.5 Fair and Equitable Selection of Participants

Participants will not be discriminated against based on race, sex, or religion. Due to the early stage of development of this IP, we have excluded individuals under 18 and people who are pregnant or nursing and we have excluded individuals who are over the age of 50 due to the frequency of exclusionary medical conditions. Any individual who is unable to consent due to any reason will not be included in this study.

14.6 Informed Consent

The informed consent process and document(s) will be reviewed and approved by the NMRC IRB and the JHSPH IRB prior to initiation of the study. The consent document(s) will contain a full explanation of the possible risks, advantages, and alternate treatment options, and availability of treatment in the case of injury, in accordance with 21 CFR 50. Study information will be presented in audio and visual formats in lay terms to facilitate understanding. The participant's signature on the informed consent document will indicate the participant's permission to access relevant medical records by the sponsor's representative and by representatives of the FDA. The sponsor's representative will submit a copy of the initial IRB- and sponsor's representative-approved consent form to the FDA and will maintain copies of revised consent documents that have been reviewed and approved by the IRB/ethics committee. See Study Specific Screening and Consenting.

The participant should understand that the study product is investigational and is not licensed by the FDA for commercial use but is permitted to be used in this clinical research. Informed consent includes the principle that it is critical the participant be informed about the principal potential risks and benefits. This information will allow the participant to make a personal risk versus benefit decision and understand the following:

- Participation is entirely voluntary.
- Participants may withdraw from participation at any time.
- There is no penalty for declining to participate in the study.
- The individual is free to ask any questions that will allow him/her greater understanding of the study.
- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US law.

All non-exempt research involving human participants shall, at a minimum, meet the requirement of 32 CFR 219.116(a)(6) in the Code of Federal Regulations.

14.7 Recruitment

All study-related advertisements will be reviewed and approved by the JHSPH IRB, NMRC IRB and HRPO-ORP, if applicable. Active-duty military members will not specifically be recruited for this study. See Sections 4.0 and 5.0.

15.0 PRIVACY AND CONFIDENTIALITY

15.1 Provisions Protecting Privacy and Confidentiality

Individual participant medical information obtained because of this study is considered confidential and disclosure to third parties, other than those cited below, is prohibited. Participant confidentiality will be further ensured by utilizing participant identification

code numbers and participant initials. Neither NMRC nor the JHSPH are HIPAA-covered entities. See also Data Management and Safety.

Confidentiality agreements may be developed with other clinical trials groups (e.g., at the University of Maryland Vaccine Research Center or WRAIR Clinical Trials Center), and the investigative team may check verbally with these sites to see if participants have participated in studies that would preclude their participation in this study. No written list will be exchanged with these sites.

All assessments will be conducted in private exam or procedure rooms.

15.2 Safeguards for Vulnerable Participants

This study will not include individuals less than 18, incarcerated or unable to meet the requirements to sign the informed consent form. Military personnel will not be specifically recruited for this study. All active duty military participants will need to have written permission from their superior to participate in this study.

16.0 PROTOCOL REVIEW PROCESS

The protocol will undergo scientific and ethical review at the two primary collaborating institutions: CIR and NMRC. In addition to these reviews, the JHU Biosafety Committee and Pharmacy and Therapeutics Committee will review the protocol. The protocol will also require FDA review as part of the IND application. The IND sponsor will be Dr. David Sack. Continuing review will be undertaken in accordance with existing regulations.

The investigator may deviate from the protocol without prior approval when the change is necessary to eliminate an apparent immediate hazard to the participant. In that event, the investigator will notify the sponsor promptly by phone, will notify the CIR (JHSPH IRB) and NMRC IRB, and will confirm notification to the sponsor in writing within 5 working days after the change is implemented. All protocol deviations, including minor deviations not impacting participant safety, will be noted in the continuing review reports, the annual report to the Sponsor, and in the final study report. Any modification to the protocol, consent form and/or questionnaires, including changing the PI, must be submitted to both IRBs for review and approval prior to implementation of the modification. Any deviation to the protocol that may have an effect on the safety or rights of the participant or the integrity of the study, must be reported to the NMRC ORA, JHSPH IRB and USAMRMC HRPO-ORP, if applicable, as soon as the deviation is identified.

17.0 PUBLICATION POLICY

All data collected during this study will be used to support this IND. All publications and presentations are governed by the standards and norms detailed in NAVMEDRSCHCENINST 5721.1. All authors will submit the proposed publication/presentation at least 30 days prior to the submission date. Prior to submission, the directorate will conduct a substantive scientific and professional review. The document is routed to the Office of Research Administration (ORA) for review and routing for Command review and approval, ultimately by the NMRC Public Affairs Officer. Once it is cleared at NMRC, it will be forwarded to BUMED through NMSC, if appropriate. Prior to publication, an author must have a completed Publication Clearance Request Submission Form with signatures from all approving and reviewing authorities.

18.0 REFERENCE

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