MC1267 / 12-009448

A Randomized, Blinded Phase II Placebo-Controlled Trial With Oral Serum Bovine Immunoglobulin (SBI) to Assess Quality of Life and the Faster Post-Operative Recovery of Gynecological Cancer Patients

NCT01867606

Document Date: 05/07/2015

Mayo Clinic Cancer Center

MC1267, A Randomized, Blinded Pilot Placebo-Controlled Trial with Oral Serum Bovine Immunoglobulin (SBI) to Assess Quality of Life and the Faster Post-Operative Recovery of Gynecological Cancer Patients

Study Chairs: Aminah Jatoi MD and Carrie Langstraat MD
Mayo Clinic
200 First Street SW
Rochester, MN 55905
507/284-2511
507/284-5280 (FAX)

Study Cochairs: Jamie Bakkum-Gamez MD
Sean Dowdy MD
Megan Grudem RN CNP
Andrea Mariani MD
Casey Swanson PA

Statistician: Nathan R. Foster MS

Agent Availability Commercial Agents: None
Agent Company Supplied: Oral Serum Bovine Immunoglobulin (SBI)

Document History	(Effective Date)
Activation	10/4/2013
Mayo Addendum 2	10/4/2013
Mayo Addendum 3	10/4/2013
MCCC Addendum 4	11/26/2013
MCCC Addendum 5	8/25/2014
MCCC Addendum 6	Pending approvals

Protocol Resources

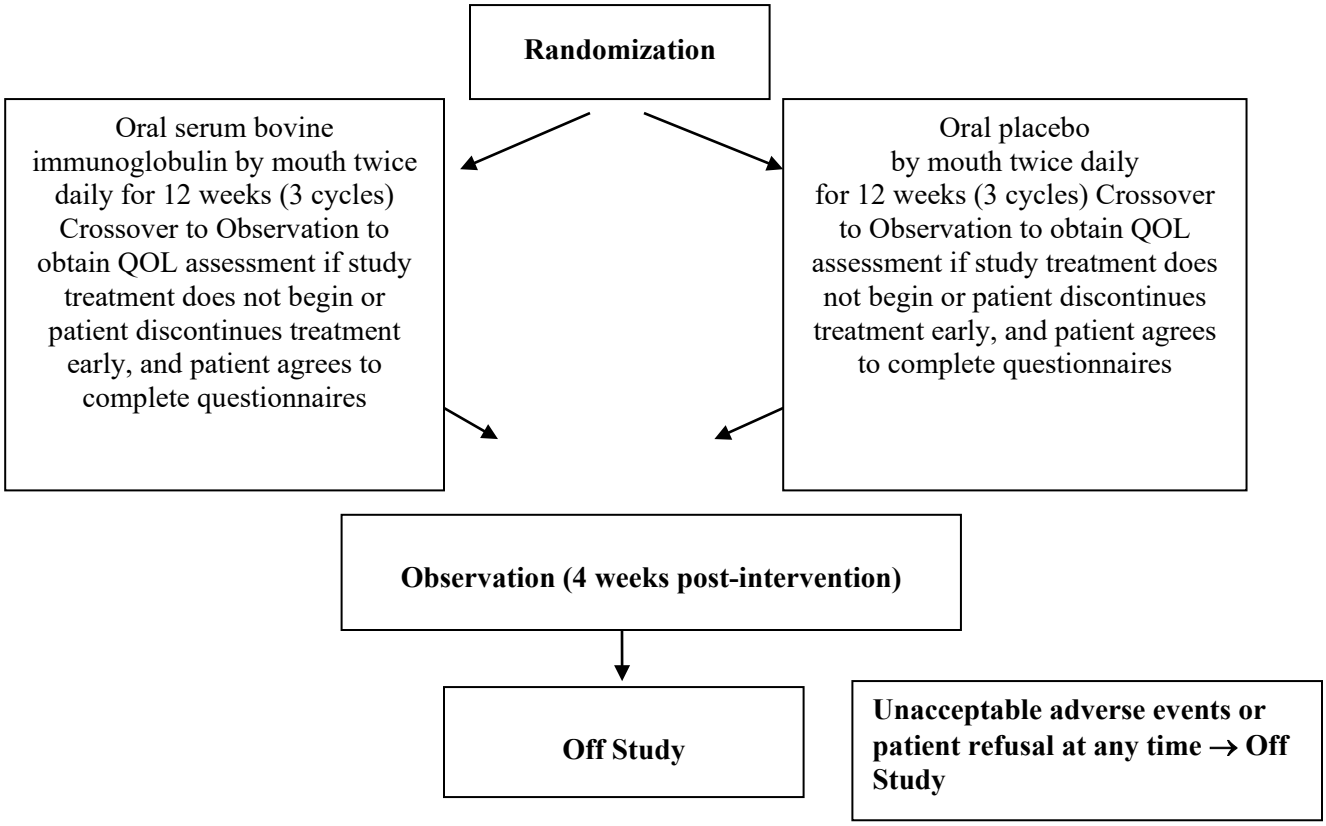
Questions:	Contact Name:
Patient eligibility*, test schedule, intervention delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	Cristina Zabel, Quality Assurance Specialist Phone: (507) 284-4565 E-mail: zabel.cristina@mayo.edu
Forms completion and submission	Jean Jensen, Clinical Research Coordinator Phone: (507) 538-1115 Email: jensen.jean@mayo.edu
Protocol document, consent form, regulatory issues	Lynn M Flickinger, Research Protocol Specialist Phone: 507/538-7034 Email: flickinger.lynn@mayo.edu
Adverse Events (AdEERS, Non-AER, AML/MDS)	Patricia G. McNamara, SAE C Phone: (507) 266-3028 E-mail: mcnamara.patricia@mayo.edu

*No waivers of eligibility per NCI

Table of Contents

.

Schema



Cycle Length = 28 days (4 weeks)

Generic name: Serum-Derived Bovine Immunoglobulin Protein Isolate Brand name(s): SBI, EnteraGam™ Mayo Abbreviation: SBI Availability: Entera Health Inc	Generic name: Placebo Brand name(s): Placebo Mayo Abbreviation: PLACEB Availability: Entera Health Inc

1.0 Background

1.1 Ovarian cancer is an aggressive malignancy that results in over 15,000 deaths per year in the United States [1]. Most patients diagnosed with this cancer die from it. Nonetheless, the fact that approximately 25% of patients with even stage IIIC -- that is, large (> 2cm) peritoneal metastases that extend beyond the pelvis and the most commonly diagnosed stage of ovarian cancer -- can be cured underscores the need to maximize the efficacy of the therapeutic approaches that are recognized as contributing to this small chance of cure [1].

1.2 Capitalizing on Therapeutic Modalities with Demonstrated Efficacy: Aggressive Surgery. Although novel therapeutic interventions continue to emerge, the medical literature clearly demonstrates the importance of thoroughly capitalizing on therapeutic modalities that have already demonstrated an essential therapeutic role. For example, a large body of literature shows that the definition of "optimal debulking" of tumor dramatically improves overall survival, and the definition of this term has evolved over time to the benefit of patients with ovarian cancer [2]. Previously, residual nodules of 1 cm or less in size defined an optimal debulking surgery, but now this definition has been further refined as yielding "no gross residual tumor." Indeed, Chi and others have illustrated the importance of operating to achieve "no gross residual tumor." Examining 465 patients, these investigators assessed various prognostic factors, most relevantly, the extent of postoperative residual disease [2]. In multivariate analyses, hazard survival ratios (95% confidence intervals) increased significantly based on postoperative assessment of extent of residual disease: no gross residual disease (reference); </= 1 cm of gross residual disease yielded a hazard ratio of 2.07 (1.23, 3.46); and > 1 cm gross residual disease yielded a hazard ratio 3.70 (2.27, 6.04). These investigators concluded that the goal of any surgery for ovarian cancer should be "no gross residual disease" and, in the absence of this outcome, surgical cytoreduction to the greatest extent possible should be undertaken. Such conclusions are relevant because they underscore the observation that highly aggressive surgeries that include enterotomies, resections of large portions of bowel, and manipulation of the bowel are not only commonplace but also highly justified in the state-of-the-art treatment of ovarian cancer.

Indeed, the aggressiveness of these surgeries has yielded grade 3 or worse complication rates, which include death, in the range of 15-22%, as reported from high-volume medical centers [3,4]. Such notable complication rates underscore the need to evaluate strategies not only to lessen postoperative complications but also to improve long-term survival by means of exploring interventions to enhance postoperative recovery and thereby enable the prompt administration of chemotherapy.

1.3 Capitalizing on Therapeutic Modalities with Demonstrated Efficacy: The Timely Administration of Post-Operative Chemotherapy. Mahner and others recently demonstrated that timely administration of postoperative chemotherapy to patients with ovarian cancer improves outcomes [5]. These investigators examined individual patient data from 3326 ovarian cancer patients who had participated in 3 prospective phase III trials. Within this large cohort, the median time to chemotherapy was 19 days (range 1, 56 days), but starting chemotherapy sooner appeared to confer a survival advantage. Among patients who had had an optimal debulking surgery, a longer time to chemotherapy initiation was associated with a poorer survival (per week delay hazard ratio=1.87; 95% confidence interval 1.005, 1.176; p=0.038). Indeed, a one week delay in

chemotherapy yielded an 8.7% increase in mortality in patients who had received an optimal debulking surgery. These data point to the importance of the timely administration of chemotherapy in patients who have undergone an optimal debulking surgery for ovarian cancer.

The above data become even more compelling when one considers preclinical data on surgery, the timing of chemotherapy, and tumor growth. Fisher and others used a murine mammary tumor model to assess mitotic activity within tumors [6]. Assessing mitotic activity at various time points with respect to surgery, these investigators observed that an increase in mitotic activity and tumor growth occurred during the first 3-4 days after surgery and that the administration of cyclophosphamide the day of surgery was more advantageous in suppressing tumor growth. In addition, Gunduz and others showed that tumor growth within residual malignant disease gained momentum to an extent that did not seem to occur in the absence of surgery, thus also suggesting that prompt administration of chemotherapy post-operatively is advantageous [7]. Taken together, such data provide preclinical justification to bolster further the conclusions from Mahner and others that the early administration of chemotherapy after optimal surgical debulking for ovarian cancer leads to more favorable clinical outcomes.

Admittedly, not all data provide a consistent message on the importance of the timing of the administration of chemotherapy in postoperative ovarian cancer patients. In an earlier review from Larsen and Blaakaer, this issue was discussed in detail in the context of a systematic analysis of seven previously-published studies [8]. Although two of the studies included in this review also suggested that prompt administration of chemotherapy led to improved outcomes, the other five reported no significant differences in outcomes -- neither in a positive nor negative direction -- with the prompt administration of chemotherapy. Many factors might account for the negative neutral findings in these 5 studies, including 1) retrospective bias, or the plausible possibility that patients with worse prognostic factors may have started chemotherapy sooner, thus balancing out these negative prognostic factors but not improving clinical outcomes; 2) small sample sizes but with the larger studies in this analysis suggesting in either univariate or sub-analyses that timely chemotherapy administration may in fact be clinically advantageous with improved survival; and 3) relatively small variability in chemotherapy timing in general which again suggests that a much larger sample size might be necessary to detect subtle clinical benefits with early administration of chemotherapy. Despite the above, the recent, robust data from Mahner and others, the other two supporting studies referenced by Larsen and Blaakaer, the fact that plausible explanations can be invoked to account for the neutral negative findings observed in the five previous studies, an absolute lack of negative studies that show clear clinical detriment with the early administration of postoperative chemotherapy in retrospective studies, and preclinical studies which also advocate for the early administration of chemotherapy -- all indicate a need to investigate ways to treat ovarian cancer patients promptly in a postoperative setting and justify proceeding with the current proposal.

1.4 Oral Serum Bovine Immunoglobulin (SBI): A Review of Preclinical and Clinical Findings. Serum-derived bovine immunoglobulin protein isolate is an orally administered prescription medical food containing a proprietary formulation of immunoglobulins (> 50% IgG) and other serum proteins. The term medical food, as defined in Section 5(b) of the Orphan Drug Act (21USC.360ee(b) (3) is “a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a…. condition for which

distinctive nutritional requirements based on recognized scientific principles, are established by medical evaluation." Serum-derived bovine immunoglobulin protein isolate is intended for the nutritional management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, the dietary management of which cannot be achieved by the modification of the normal diet alone. Serum-derived bovine immunoglobulin has self-affirmed generally recognized as safe (GRAS) status with no objections from the US Food and Drug Administration (FDA).

A large portion of SBI consists of immunoglobulins, primarily IgG and to a lesser extent IgM as well as other proteins and amino acids. SBI is derived from manufacturing processes for bovine serum albumin (BSA), making it a valuable but easily accessible byproduct. Previous studies show that SBI resists part of the digestive process and that some of active IgG remains present in the gastrointestinal tract. This combination of immunoglobulins and other proteins are thought to lead to the immunomodulatory effects of SBI and are thought to lead to maintenance of the intestine as a barrier and attenuation of malabsorption after an inflammatory assault to the gastrointestinal tract. Indeed, when taken together, previous studies show that oral ingestion of SBI improves the absorption of nutrients, reduces intestinal permeability, and decreases overall infection rates. The most striking clinical evidence in support of the above entails the administration of SBI to weanling farm animals with the observation of increased dietary intake and greater weight gain compared to control animals [9-11]. The published literature is replete with observations that show animals maintain their weight during the weaning process and continue to thrive as a result of SBI supplementation.

Although studied on a far smaller scale in humans, SBI has nonetheless been studied clinically, and these early clinical studies outline a need to further study SBI within other medical conditions. At least 5 previous clinical studies demonstrate the complete safety of SBI in both children and adults with even some early evidence of clinical improvement in various medical conditions. First, Lembecke and others focused on 10 male children, ages 9 to 25 months, with severe malnutrition. These children were supplemented with SBI over a 7-day period during their nutritional recovery [12]. With SBI supplementation, they manifested a drop in fecal wet and dry weight, an observation that might suggest greater absorption of fat and energy perhaps as a result of this supplementation. Although no major differences over time were seen in these children's growth patterns, importantly, this intervention did not result in any adverse events. Second, Begin and others conducted a randomized trial in children less than 1 year of age from an impoverished region of Guatemala. Children were randomly assigned to 4 different nutritional supplements, two of which included SBI [13]. One hundred seven of these children received SBI. Although this 8-month intervention did not improve growth patterns or morbidity as had been hoped, absolutely no adverse events related to SBI were observed. In a third study, Earnest and others evaluated 52 adults, both men and women, with hypercholesterolemia to test the hypothesis that milk proteins such as SBI might have a salutary effect on cholesterol [14]. In this randomized, double-blind, placebo-controlled trial, SBI did result in a statistically significant reduction in LDL cholesterol over 6 weeks with no similar changes in the placebo group. Once again, no adverse events occurred with the use of SBI. Fourth, in a small 8-patient study of AIDS patients who were suffering from HIV enteropathy, supplementation with SBI over 8 weeks at a dose of 2.5 grams orally BID yielded a drop in the frequency of bowel movements from 5.7 per day to 2 per day (unpublished date, personal communication from Gerald Klein, M.D., from Entera Health). Patients also reported an improvement in

gastrointestinal-related quality of life that occurred concomitantly with supplementation. As anticipated, this intervention was again well-tolerated.

Finally, a 51-patient unpublished study focused on irritable bowel disease, randomly assigning patients to SBI 10 grams per day versus SBI 5 grams per day versus placebo (unpublished date, personal communication from Gerald Klein, M.D., from Entera Health). Patients assigned to the 10 g/day SBI supplement reported a drop in the number of days of symptoms, including abdominal pain (P=.008), flatulence (P=.003); bloating (P=.044); loose stools (P=.011), and urgency of defecation (P=.050), although statistically significant differences between groups were not detected. At the same time, this dose of SBI was considered safe with no adverse events. These findings suggest a role for further SBI for its potential salutary bowel effects and for testing the 10 gram dose in the proposed postoperative study with a schedule of 5 grams twice a day.

Taken together these 5 studies provide the following two conclusions: 1) SBI is well-tolerated, with no previously-reported adverse events, even among children, malnourished patients, AIDS patients, and patients with irritable bowel disease, all of whom would be considered highly vulnerable to severe adverse events with the administration of an unsafe intervention and 2) these very preliminary studies indicate that in some circumstances, such as severely malnourished children, in AIDS patients with HIV enteropathy, and in patients with inflammatory bowel disease, SBI might confer a favorable effect on bowel integrity that appears in turn to translate into less diarrhea and fewer other gastrointestinal symptoms. In view of the fact that these very preliminary clinical data are consistent with multiple similar observations in animals, a strong argument can be made for further studying SBI in postoperative gynecological cancer patients who undergo major, extensive surgeries and could conceivably benefit from a swifter recovery to enable them to receive potentially curative chemotherapy in a more timely manner. Hence, in the current proposal/protocol, we test the hypothesis that SBI improves postoperative recovery to a greater extent than placebo.

1.5 Translational Component: In effect, we hypothesize here that SBI, as a medical food, will enhance postoperative recovery. However, to date, no biomarker or set of biomarkers have been demonstrated to serve as accurate predictors or correlates of convalescence. As a result, this laboratory-based exploratory portion of this proposal/protocol will examine well-accepted inflammatory biomarkers and proteins that have previously been characterized within the gut microbiome in an effort to assess candidate biomarkers that might be suggestive of successful convalescence in a postoperative setting. This approach is pragmatic and logical, in view of the fact that the surgeries conducted in ovarian cancer patients often entail a great deal of manipulation and sometimes resection of the bowel. Hence, we propose to measure neopterin, soluble CD14, fatty acid binding protein, zonulin, a variety of inflammatory cytokines, and other such markers outlined in section 14.21 with the goal of identifying candidate biomarkers that might be utilized in a larger study that focuses further on testing SBI to enhance convalescence in a postoperative setting in ovarian cancer patients [14a,14b,14c,14d, 14e]. This study will include a serial assessment at baseline, at a mid-time point, and at the end of the intervention. A complete listing of candidate markers appear in section 14.21 of this protocol.

1.6 Consideration of Alternative Study Designs. In view of the fact that this proposal tests a convalescent strategy that is novel and as yet has not received widespread attention, the investigators have considered a variety of alternative study designs, as outlined below:

1) A variety of other "nutritional boosters" have been touted, so why focus on SBI? Importantly, in addition to the scientific justification and prior clinical data described above, SBI's manufacturing processes have been carefully monitored via quality assurance protocols for consistency, reliability, and safety. Based in Iowa, Entera Health, Inc is providing SBI for this trial; this product is manufactured by Proliant Biologicals, Boone, Iowa, USA in accordance with Good Manufacturing Practice (GMP) and FDA guidelines for medical good ingredients (21 CFR Part 110). Entera Health is the largest manufacturer of bovine serum albumin (BSA), as used in research laboratories worldwide, and contributes protein products to major pharmaceutical companies throughout the United States to enable these other companies to proceed with the manufacturing and distributing of a variety of FDA-approved agents. This degree of experience, demonstration of safety, and product awareness has enabled Entera Health, Inc to acquire for SBI "generally recognized as safe" (GRAS) FDA status that allows for the prompt testing of this agent in a variety of clinical settings without the need for an IND application.

   This latter point merits further explanation. Numerous discussions with staff from Proliant Biologicals, including the Chief Medical Office, Dr. Gerry Klein, and members of the Mayo Clinic regulatory community, have provided direction to the study team, indicating that a submission to the FDA for an IND is not necessary (See Appendix VII). These discussions have highlighted the following three points. First, evidence of GRAS status (http://www.accessdata.fda.gov/scripts/fcn/gras_notices/GRN000169.pdf) has been provided. Again, this product is food-based and "generally recognized as safe," thus providing some reassurance of safe administration. Second, Proliant Biologicals personnel have pointed out that, as per 21 CFR Part 105.3, this company is not attempting to palliate a disease state. Rather the focus of the current study is postoperative convalescence. This complete lack of focus on a disease state again makes an IND unnecessary. Third, this protocol attempts to enhance convalescence after surgery with the use of this food product, as per Title 21, Part 105, section (a), (1), (i), with no associated drug claim. . SBI is not a drug but rather a nutritional agent. In the absence of a drug claim, that the testing of SBI does not require an IND.

2) Quality-of-life assessment appears to be a very "soft" outcome. Why not focus on another endpoint, such as time-to-chemotherapy administration itself? We point out that the Symptom Distress Scale and the Postoperative Quality of Life questionnaires have been validated and used for many years to measure quality of life [15]. Such questionnaires have also been used in many settings, including cancer settings and after other major illness, such as post-myocardial infarction. These instruments ask relevant questions related to bowel function, pain, fatigue, and other symptoms that are all highly germane to oncologists as they decide whether to begin chemotherapy in postoperative cancer patients. As most oncologists will acknowledge, specific criteria for starting chemotherapy are not well-defined, but it is of paramount importance to assess the symptoms above in conjunction with general postoperative healing in making a decision on when to start postoperative chemotherapy. Moreover, it should be noted that the instruments above are brief and enable a patient-reported, paper-based formatting that provides for a highly practical approach to symptom assessment. We point out that we had carefully considered evaluating time-to-chemotherapy administration as the primary endpoint for this study, but the

fact that this endpoint can be artifactually modified as a result of return appointment availability and other scheduling issues suggest that patient-reported quality of life is a more clinically accurate and meaningful primary endpoint for the current proposal/protocol.

3) This study does not focus specifically on ovarian cancer patients, yet the underlying premise is that reduction of time-to-chemotherapy administration is important specifically in the management of ovarian cancer patients. Why the discrepancy? The primary driving force for including all patients with gynecological surgeries is to complete this study quickly and consider future development strategies promptly. Given the fact that other gynecological surgeries also involve major operations and given that a quality of life outcome would be relevant to these patients as well, we decided to embark on a more encompassing study design that includes a wide-range of patients with difference gynecological cancer types. Were a larger study to be planned, then a more narrow focus on ovarian cancer patients would be called for.

4) What if SBI supplementation does not improve quality of life? A great deal of effort will have gone towards a negative neutral study. If our hypothesis proves incorrect and we observe no improvement in postoperative recovery, as suggested by improved quality of life scores, in the SBI versus placebo arm, we will nonetheless have acquired prospective quality of life data (based on pooling data in both arms in ovarian cancer patients) that will position us well to proceed with other future interventions to test ways to decrease the time-to-chemotherapy administration in postoperative ovarian cancer patients.

2.0 Goals

2.1 Primary Efficacy

2.11 To compare the time-to-quality of life (QOL) improvement from baseline in postoperative gynecological cancer patients who are receiving oral SBI vs. placebo.

2.2 Secondary Efficacy

2.21 To compare the surgical complication rates between oral SBI vs. placebo up to 1 month post-surgery (safety endpoint).

2.22 To compare the QOL, as derived from the previously-validated Symptom Distress Scale, the PQL (Postoperative Quality of Life questionnaire), and the uniscale (overall QOL item) between patients receiving oral SBI vs. placebo.

2.23 To compare the grade 2 or worse adverse event rates for patients receiving oral SBI vs. placebo.

2.24 To characterize the adverse event profile of oral SBI in postoperative gynecological cancer patients (safety endpoint).

2.25 To compare supplement adherence between patients receiving oral SBI vs. placebo.

2.3 Correlative Research

2.31 To explore whether candidate biomarkers are modified with SBI versus placebo.

2.32 As part of ongoing research, to bank leftover blood samples for future studies.

2.33 To explore quality of life during postoperative recovery after gynecologic surgery, regardless of whether or not patients take the study intervention/placebo or discontinue intervention/placebo early.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥ 18 years.

3.12 Diagnosis of gynecological cancer of any type or strong suspicion for cancer.

3.13 Patients must have begun postoperative oral intake of food prior to registration.

3.14 Open laparotomy or laparoscopic surgery undertaken with cancer therapeutic intent (not a subsequent surgery to manage a postoperative complication) that had occurred ≤7 days prior to registration and that entailed more than a simple hysterectomy.

3.15 The following laboratory values obtained ≤21days prior to registration.

- Creatinine ≤ 1.5 x the upper limit of normal (ULN)
- Absolute neutrophil count ≥ 1500/mm3
- Platelet count ≥ 100,000/mm^3

3.16 Ability to complete questionnaire(s) by themselves or with assistance.

3.17 Provide informed written consent.

3.18 Negative (serum) pregnancy test done ≤7 days prior to randomization, for women of childbearing potential only.

3.19 Willing to provide mandatory baseline blood samples for correlative research purposes (see Section 6.12 and 14.0).

3.2 Exclusion Criteria

3.21 Symptomatic and/or untreated brain metastases.

3.22 Ongoing parenteral nutrition (receiving intravenous nutrition support at the time of enrollment). Note: patients may be receiving maintenance IV fluids.

3.23 Current enrollment in any other trial that entails the concurrent administration of any other agent designed to enhance postoperative recovery.

3.24 Allergy to beef.

4.0 Test Schedule

Tests and procedures	Active Monitoring Phase				
	≤21 days prior to randomization	Day 1 of Cycle 2 and 3 (+/- 3 days)	Weekly from registration for 12 weeks total	At the end of intervention (+/- 3 days)	Observation/crossover (ends after 16 weeks of total study participation)
Patient assessment (includes weight**)	X				
Adverse event assessment	X	X**		X**	X**
Pregnancy test[1](Serum)	X				
Hematology group HgB WBC PLT ANC	X				
Chemistry group Creatinine	X				
Patient Questionnaire Booklets[2], (Appendix 2-5)	X		X	X	X
Blood specimens (see Section 14.0)[3,R]	X	X*			

1. For women of childbearing potential only. Must be done ≤7 days prior to registration.
2. Patient questionnaire booklets **must** be used; copies are not acceptable for this submission. Patients are required to fill out the questionnaires at baseline, and weekly for the duration of study participation, (16 weeks total, includes patients who never started therapy).
3. Blood specimens will be collected and submitted at baseline. Kits are required. Baseline blood specimen is to be collected after consent and prior to patient receiving study agent.

R Research funded (see Section 19.0)

*These blood draws are optional but strongly recommended.

** If patient cannot return, this assessment can be done by phone by the study coordinator (includes patient reported weight). However, study questionnaires must be mailed back.

5.0 Stratification Factors

5.1 Patient age: ≥ 65 years vs. < 65 years

5.2 Splenectomy and/or rectosigmoid resection: yes vs. no

5.3 Optimally debulked cancer (complete nodal and omental removal, as appropriate, with <1 cm of residual tumor, if appropriate): yes vs. no

5.4 Cancer type: ovarian vs. endometrial vs. other

5.5 Open laparotomy vs. laparoscopic surgery

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at (507) 284-2753 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page (http://hsrwww.mayo.edu/ccs/training) and detail the process for completing and confirming patient registration. Prior to initiation of the protocol intervention, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office (507) 284-2753. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 A mandatory baseline correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19 and 14.1*)*.

An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Section 14.0)

- Patient has/has not given permission to give his/her blood sample(s) for research testing for Cycles 2 and 3

6.13 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.14 Prior to accepting the registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.15 Intervention on this protocol must commence at Mayo Clinic Rochester, under the supervision of a medical oncologist.

6.16 Intervention cannot begin prior to registration and must begin ≤ 7 days after registration.

6.17 Pre-intervention tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.18 All required baseline symptoms (see Section 10.6) must be documented and graded.

6.19a Study agent is available on site

6.19b Blood draw kit is available on site.

6.19c Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

6.19d At the time of randomization, the following will be verified:

- Patient has/has not given permission for his/her blood sample(s) to be stored and used in future research of ovarian cancer at Mayo Clinic.
- Patient has/has not given permission for his/her blood sample(s) to be stored and used in future research at Mayo Clinic to learn about, prevent, or treat any other health problems
- Patient has/has not given Mayo Clinic permission to give his/her blood sample(s) to outside institutions

6.2 Randomization Procedures

6.21 The factors defined in Section 5.0 will be used as stratification factors.

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following intervention groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the intervention groups [16].

- Oral Serum Bovine Immunoglobulin (SBI)
- Placebo

6.3 Procedures for Double-Blinding the Intervention Assignment

6.31 After the intervention assignment has been ascertained by the registration/randomization application, the patient's study medication code number will be displayed on the confirmation of registration screen.

6.32 The data manager/nurse/pharmacist at the patient's institution must contact the MCCC Registration Office for a code number when additional study product is needed for the patient.

6.33 The number of the intervention bottle/packet assigned to the patient will be recorded on the dosing form.

6.34 MCCC Registration Office personnel will monitor the supply of coded bottles/packets at each participating institution and will arrange for the oncology pharmacist to send further supplies to the participating institutions as needed.

7.0 Protocol Intervention

7.1 Dosing Intervention Schedule**

Agent	Dose	Route	Day	Retreat
Serum bovine immunoglobulin or placebo packets	5 grams (1-packet) per each dose*	PO	Twice a day for 12 weeks (3 cycles)	Every 4 weeks

*total dose is 10 grams per day

** Patients must begin taking agent/placebo within 7 days of registration (exceptions can be made if delays occur related to shipping agent/placebo and should be documented in the patient study record).

7.2 Patients can be instructed in administration techniques and granted intervention independence with nursing staff approval.

7.3 Patients will be instructed to add the contents of one packet (5 grams) to a cup and dissolve the powder with approximately one-half cup (4 fl. ounces, or 120 mL) of water. The patient will stir to mix and drink the contents. The patient will take one dose twice a day, in the morning and evening, with or without food.

7.4 Breaking Codes in Double–Blinded Studies-The intervention code may *not* be broken except for emergencies.

In the event of an emergency, call the MCCC Registration Office at (507) 284–2753 to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call to the MCCC Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that MCCC Registration Office personnel can return the call the next business day.

8.0 Dosage Modification Based on Adverse Events

There are no dose modifications in this trial. If the patient experiences a grade 1 or worse adverse event that is thought to be related to the study intervention, the patient should discontinue the intervention and proceed to the 4 week post intervention observation.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline J Clin Oncol 24(19): 3187-3205, 2006.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study intervention administration until 30 days after the final dose will be recorded in the medical records.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2)

and if the adverse event is related to the medical intervention or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.52 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 **Expected vs. Unexpected**

- The determination of whether an AE is expected is based on the agent-specific information provided in Section 15.0 of this protocol.

- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 **Assessment of Attribution**

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical intervention suggest there is evidence to indicate a causal relationship between the agent and the adverse event.

10.4 Expedited Reporting Requirements for Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required		7 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.41 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via MedWatch within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Effective Date: May 5, 2011

Additional Instructions:

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from an agent overdose.

2. Mayo Clinic Cancer Center (MCCC) Institutions: Use FDA Medwatch (Form 3500A) available in forms packet for Investigational agents or commercial/investigational agents on the same arm. Submit to Entera Health, Inc. within 24 hours of notification to: CANCERCROSAFETYIN@mayo.edu and dave.mathews@enterahealth.com.*

   *Note: FDA Submission will not occur due to GRAS status of SBI - See Appendix VII

Event Type	REPORTING PROCEDURE
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form electronically via the MCCC Remote Data Entry System or paper form within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If an expedited written report has been submitted, this form does not need to be submitted.

10.41 Special Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2 and 3 Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supersede the standard Expedited Adverse Event Reporting Requirements:

System Organ Class (SOC)	Adverse event/Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
Blood and lymphatic system disorders	Hemoglobin decreased	≤Grade 2
	Lymphocyte count decreased	≤Grade 2
Investigations	Neutrophil count decreased	≤Grade 2
	Platelet count decreased	≤Grade 2
	White blood cell decreased	≤Grade 2

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

10.5 Other Required Reporting

10.51 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately to the study team.

10.52 Death

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention requires expedited reporting within 24-hours to the study team.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention requires expedited reporting within 24-hours to the study team.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur during the study require reporting to the study team. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
    - Myelodysplastic syndrome (MDS)
    - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.6 Required Routine Reporting

Adverse events to be graded at each evaluation and preintervention symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Gastrointestinal disorders	Abdominal pain	X	X
	Bloating	X	X
	Diarrhea		X
	Baseline number of stools per day	X	
	Flatulence	X	X
	Nausea	X	X
	Vomiting	X	X
General disorders and administration site conditions	Fatigue	X	X
Infections and infestations	Wound infection	X	X
Injury, poisoning and procedural complication	Wound complication	X	X
	Wound dehiscence	X	X

10.61 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6

10.611 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study intervention or procedure.

10.612 Grade 3 and 4 AEs regardless of attribution to the study intervention or procedure.

10.613 Grade 5 AEs (Deaths)

10.6131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study intervention or procedure.

10.6132 Any death more than 30 days after the patient's last study intervention or procedure that is felt to be at least possibly intervention related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

11.0 Intervention Evaluation: None

12.0 Descriptive Factors: None

13.0 Follow–up Decision at Evaluation of Participants

13.1 Participants will receive 3 cycles of therapy (12 weeks) with oral SBI or placebo, followed by a 4 week observation visit. No additional follow-up is required for these patients beyond the 4 week observation time point.

13.2 Participants who go off the intervention early for unacceptable adverse events or patient refusal of further treatment will go to the observation phase. Patients can continue in the observation phase for total of 16 weeks of study participation.

13.3 Participants where post-operative problems occur, study treatment cannot begin, and participant agrees to complete questionnaires will crossover to QOL assessment only. These participants will be followed per the test schedule (Section 4.0).

13.4 A participant is deemed *ineligible* if after registration, it is determined that at the time of registration, the participant did not satisfy each and every eligibility criteria for study entry. The patient will go directly off study.

- If the participant received therapy, all data up until the point of confirmation of ineligibility must be submitted.
- If the participant never received therapy, on-study material must be submitted.

13.5 A participant is deemed a *major violation*, if protocol requirements regarding intervention in cycle 1 of the initial intervention are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient may continue therapy off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.

13.6 A participant is deemed a *cancel/withdrawal* if he/she is removed from the study for any reason before any study intervention is given or participant does not agree to crossover to QOL assessment only. On-study material and the End of Active Intervention/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline	Day 1 of Cycle 2 and 3	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Correlative Studies	Mandatory	Blood	2 purple top tubes	Volume of 7cc	X		Yes	Frozen at -80 centigrade, Shipped frozen
Correlative Studies*	Optional	Blood	2 purple top tubes	Volume of 7cc		X	Yes	Frozen at -80 centigrade, Shipped frozen

*If the patient does not participate in the optional blood draws, it does not cause the patient to be ineligible; however, the collection of the blood is **strongly recommended**.

14.2 Collection and Processing

14.21 Correlative Research

This protocol will check the following laboratory-based translational studies from the blood at baseline and at the time of completion of the intervention:

1. Biomarkers to explore convalescence will be examined. Biomarkers associated with bacterial translocation, enterocyte damage and intestinal epithelial barrier function will be measured with and without lipopolysaccharide (LPS) stimulation in vitro. LPS binding protein (LBP), bactericidal/permeability increasing protein (BPI), soluble CD14 (sCD14),16s rDNA, intestinal fatty acid binding protein (I-FABP) and zonulin in plasma will be measured in this manner.

2. We will also measure plasma CRP and d dimer. Commercially available enzyme-linked immunosorbent assays will be used according to the manufacturer's instructions for measuring for inflammation-coagulation parameters.

3. Plasma cytokines involved in the pro-inflammatory cascade will be assessed. These cytokines include TNF-α, IFN-γ, IL 1, IL 6, IL 10, as well as neopterin. Standard enzyme-linked immunosorbent assay kits will be used according to manufacturer's recommendations.

For the translational component of this study, patients will have blood drawn at the time points specified in section 4.0.

Blood will be drawn in 2 purple top tubes capable of holding a blood volume of 7cc. Each tube will be spun down, and the plasma will be stored at -80 degrees centrigrade.

Frozen plasma will be batched and sent to EnterHealth at the end of the study (see below for shipping details.) ELISA kits will be used to assay all the proteins.

14.3 Shipping and Handling

14.31 Kits will be used for this study.

14.311 Kits will be supplied by the Biospecimen Accessioning and Processing Shared Resource (BAP).

14.312 The kit contains supplies and instructions for collecting, processing and shipping specimens.

14.313 Participating institutions may obtain kits by faxing the Supply Order Form to the number listed on the form. Because we are charged for all

outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Supply Order Forms must be filled in completely and legibly for quick processing.

14.314 Kits will be sent via Fed Ex® Ground at no additional cost to the participating institutions. Allow at least two weeks to receive the kits.

14.315 Kits will not be sent via rush delivery service unless the participating institution provides their own Fed Ex® account number or alternate billing number for express mail. Cost for rush delivery of kits will not be covered by the study.

14.316 All specimens **must be collected and shipped Monday – Thursday ONLY.**

14.32 Shipping Specimens

14.321 Samples will be shipped on dry ice via FEDEX at the end of the study to the following address:

ATTENTION: Eric Weaver PhD
Chief Scientific Officer
Entera Health
2425 SE Oak Tree CT
Ankeny, Iowa 50021-7102
Phone: 515-289-7662

15.0 Product Information

15.1 Serum-Derived Bovine Immunoglobulin Protein Isolate (SBI, EnteraGam^{TM}) or matching placebo

15.11 **Background**: Serum-derived bovine immunoglobulin protein isolate is an orally administered prescription medical food containing a proprietary formulation of bovine immunoglobulin (> 50% IgG) and other serum proteins. The product is manufactured in accordance with Good Manufacturing Practices and FDA guidelines for medical food ingredients.

It is indicated for the nutritional management of a patient with enteropathy who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients.

Serum-derived bovine immunoglobulin protein isolate must be non-digestible and able to reach the gastrointestinal tract to benefit an immunocompromised or otherwise dysfunctional GI mucosa. In humans, SBI is used as a passive, immunity-enhancing nutrient to augment traditional medications. Clinical studies have provided evidence that SBI lowers total and LDL cholesterol in patients with mild hypercholesterolemia, reduces symptoms of gastroenteropathy in IBS-D and HIV+ patients, increases GI absorption, and decreases GI permeability.

15.12 **Formulation**: Serum-derived bovine immunoglobulin protein isolate is a light-colored powder composed of finely ground flakes of immunoglobulin and other serum proteins (ie, transferrin, albumin, alpha and beta proteins). Serum-derived bovine immunoglobulin protein isolate is supplied in individual packets containing 5 grams of SBI and the following ingredients: dextrose, orange (natural and artificial flavors) and coloring (Yellow #6).
Matching placebo packets will be supplied and will appear identical to SBI with respect to volume, appearance, and taste. The ingredients of the placebo will include dextrose, orange (natural and artificial flavors) and coloring (Yellow #6).

15.13 **Preparation and storage**: Blinded investigational product (SBI or matching placebo) will be packaged in kits containing 5 grams of SBI per each packet or as matching placebo packets. An investigational product kit with a unique ID number will contain 14 packets (7 days of required product) and 4 extra packets (18 packets total) to accommodate the flexibility with return visits.
Packets are to be stored at 20-25°C (68-77°F), with excursions permitted between 15-30°C (59-86°F).

15.14 **Administration:** SBI is administered orally or enterally. Each patient will be instructed to add the contents of one packet (5 grams) to a cup and dissolve the powder with approximately on-half cup (4 fl. ounces or 120 mL) of water. The patient will stir to mix and drink the contents. The patient will take one dose twice a day, in the morning and the evening, with or without food. Foods such as applesauce or pudding may be used instead of liquid to blend the product if the patient desires.

15.15 **Potential Agent Interactions**: No significant interactions of SBI with commonly prescribed medications have been observed.

15.16 **Known potential toxicities**: Study subjects with known beef allergies or allergies to other components of SBI should not take SBI.

As with any ingested food or product, subjects who develop a hypersensitivity or food intolerance to SBI should discontinue its use.

Subjects who are pregnant or breastfeeding should not take SBI, as there are no data regarding the effects.

Serum-derived bovine immunoglobulin has self-affirmed generally recognized as safe (GRAS) status, with no objections from the FDA, and is demonstrated to be safe and well tolerated in pediatric and adult patients. SBI is marketed in Mexico, the Czech Republic, Japan, Egypt, and the United States. More than 100,000 kg of SBI in various dosages have been ingested by the general population since 2001. No serious adverse events have been reported to the manufacturer or the FDA.

Literature reports indicate AEs include worsening or reoccurrence of diarrhea, constipation, and worsening neuropathy. Increased urination, stomach cramps, fatigue, headache, sore throat, softened stools, and nausea have also been reported.

15.18 **Agent procurement:**
Serum-derived bovine immunoglobulin protein isolate and matching placebo will be manufactured by Proliant Biologicals, Boone, Iowa in accordance with Good Manufacturing Practice (GMP) and FDA guidelines for medical good ingredients (21 CFR Part 110) and will be provided by Entera Health Inc.

15.19 **Nursing Guidelines:**

15.191 Due to the early investigational nature of this medical food, not all side effects can be known at this time. Assess for side effects and monitor patients closely.

15.192 Patients with beef allergy or intolerance should not take SBI.

15.193 GI adverse events may occur. Treat symptomatically and monitor for effectiveness.

15.194 Warn of possibility of neuropathy. Instruct patients to report any development or increase in neuropathy to the study team.

15.195 Headache may occur. Treat symptomatically and monitor for effectiveness.

16.0 Statistical Considerations and Methodology

16.1 Overview

This randomized study is pilot in nature insofar as its main goal is to provide preliminary data to put in place the groundwork for a much larger, definitive study. The primary aim of the current study is to compare the time-to-quality of life (QOL) improvement from baseline in postoperative gynecological cancer patients who are receiving oral SBI vs. placebo. If this trial can provide preliminary evidence that oral SBI significantly improves the time-to-QOL improvement as compared to placebo, further study would be warranted to determine whether the administration of oral SBI shortens the time-to-chemotherapy administration post-operatively in ovarian cancer patients. In addition to time-to-QOL improvement, this trial will also compare adverse event rates, complication rates, QOL from validated QOL tools, and intervention compliance between patients receiving oral SBI vs. placebo.

16.11 Primary Endpoint and Statistical Design: To compare the time-to-QOL improvement from baseline in postoperative gynecological cancer patients who are receiving oral SBI vs. placebo.

Final Analysis:
The primary goal of this trial is to compare the oral SBI arm (experimental) to the placebo arm (standard), where the alternative hypothesis is that the experimental arm has a shorter time to QOL improvement from baseline as compared to the standard arm. For this primary endpoint, the total score of the 14-item Postoperative Quality of Life (PQL) tool [15] will be used, where the total score could range from 0 to 140 (0 being the worst and 140 being the best). These scores will be converted to the percentage scale, where a score of 140 will

be converted to 100 and a score of 0 will remain as 0. This QOL will be measured weekly for the entire 12 week length of the study and at the end of the intervention. QOL improvement will be defined as at least a 10 point increase in the QOL score from baseline, on the percentage scale. This 10 point change represents a clinically meaningful improvement in QOL based on work done by Jeff Sloan [17]. The date at which the QOL score is first known to increase by at least 10 from baseline (on the 100 point scale), will be considered the event date for the purpose of analysis. Patients without at least a 10 point increase in QOL from baseline, will be censored on their last QOL evaluation date up to a maximum of 12 weeks. We will enter a total of 70 evaluable patients (35 per arm) using a 1:1 randomization scheme. The primary analysis will be a comparison of oral SBI vs. placebo using a two-sided log-rank test between the 2 Kaplan-Meier curves [18]. This analysis will take place after an approximate 16 month accrual period, and after 66 total events across both arms combined (which should happen after about 12 weeks of follow-up in all evaluable patients). Additionally, we assume a constant accrual rate over the course of the study, and that no patients will drop-out of the study, since historically the lost to follow-up rate is <1%. To determine the appropriate sample size of 35 evaluable patients per arm, we assumed exponential survival and that the median time-to-QOL improvement is around 3 weeks in the oral SBI arm and 6 weeks in the placebo arm (HR=2). This hazard ratio is based on our institution's data which shows that patients often begin postoperative chemotherapy 6 weeks after surgery. These assumptions yield 80% power to detect a significant difference between the arms using a 2-sided log-rank test at alpha=0.05. All patients who meet the eligibility criteria, sign the consent form, and are randomized, will be considered evaluable for this endpoint. All eligible patients will be followed a maximum of 12 weeks. If the 2-sided log-rank test p-value is < 0.05 showing significantly shortened time-to-QOL improvement in the oral SBI arm as compared to placebo, further study will be warranted. Of course, any final decisions will be based on all primary and secondary endpoints.

16.2 Sample Size: The study design to be utilized is fully described in Section 16.11 (see above). There will be 35 evaluable patients randomized to each arm of this study. We anticipate accruing an additional 15 patients to each arm to account for ineligibility, cancellation, major intervention violation, or other reasons. Therefore, maximum accrual is 100 patients (50 per arm).

16.3 Accrual Time and Study Duration: The anticipated accrual rate is approximately 4-5 patients per month. Therefore, the accrual period for this randomized Pilot study is expected to be around 24 months. The final analysis can begin approximately 28 months after the trial begins, i.e., as soon as the last patient registered has been observed for 4 months.

16.4 Other Considerations: Adverse events as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.5 Data & Safety Monitoring:

16.51 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The trial is monitored continually by the study team who are notified of every grade 4 and 5 event in real time. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the intervention(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. CTCAE v4.0 will be used to determine grading for these stopping rules.

We expect about 10% of patients to experience grade 3 or worse adverse events (at least possibly related to the study intervention). In addition, we expect less than 1% of patients to experience a Grade 5 adverse event, at least possibly related to the study intervention. Accrual will be temporarily suspended to this study if at any time we observe adverse events that satisfy any of the following within each arm separately (i.e. if any of the following occur in arm A or arm B, we will suspend accrual to the trial):

- If at any time 4 or more in the first 20 treated patients (or 20% or more after the first 20) experience a Grade 3 or worse adverse event (possibly, probably, or definitely related to the intervention).
- If at any time, 1 patient experiences a grade 5 adverse event (possibly, probably, or definitely related to the intervention).

We note that we will review all Grade 5 adverse events on a case-by-case basis as well (regardless of attribution), and may suspend accrual after just one Grade 5 event, if we feel it is necessary for patient safety.

16.6 Definitions and Analyses of Secondary Endpoints: All these endpoints will be assessed individually and will also be compared between the 2 arms. Monthly phone calls may be used to collect the secondary endpoint information for each patient, including adverse events, surgical complications, and other data (e.g. patient reported weight, intervention compliance, etc.). We will be assessing, reporting on, and potentially analyzing all the data collected from these monthly telephone calls.

16.61 Adverse Events: All eligible patients who have intitiated therapy will be considered evaluable for adverse event analyses. The maximum grade for each type of adverse event will be recorded for each patient up to 16 weeks post-randomization (12 weeks of intervention + 1 month post-intervention observation timepoint), and frequency tables will be reviewed to determine adverse event

patterns. The overall adverse event rates for grade 2 or higher adverse events, will be compared using Chi-Square or Fisher's Exact tests. In addition, the surgical complication rates (up to 1 month post-surgery) will also be compared between the 2 arms using Chi-Square or Fisher's Exact tests.

16.62 Intervention Compliance: Intervention compliance will be assessed using the Compliance Questionnaire in Appendix V. The frequency and percentage for each Compliance Questionnaire category will be summarized descriptively by cycle and by intervention arm. In addition, cycle by cycle compliance data will be compared between the 2 arms using a Chi-square test.

16.63 Quality of Life: QOL will be measured with 3 QOL tools. For the primary endpoint, the total score from the 14-item Postoperative Quality of Life (PQL) tool [15] (Appendix II) will be used (16.11). As a secondary analysis, all 14 of the individual items from the PQL tool (Appendix II), along with the 4 additional items after the PQL questions (Appendix II) will be analyzed and compared between the 2 intervention arms. In addition, the time-to-QOL improvement will be compared between the 2 arms for any increase (> 0) from baseline for the total score from the PQL tool. This will be done descriptively, and using a Kaplan-Meier analysis [18], where any increase in the QOL from baseline will represent an event. QOL will also be measured using the Uniscale (Appendix III), and the previously-validated Symptom Distress Scale (SDS; Appendix IV). These QOL tools will measure QOL at baseline, every week up to 12 weeks post-randomization, and at the end of intervention. Differences between post-randomization and baseline QOL scores will be analyzed and compared between the 2 arms using a Wilcoxon Rank-sum test. Also, other graphical and statistical methods will be used to compare the QOL and time-to-QOL improvement between the 2 arms. As an exploratory analysis, we will also collect QOL data on patients who do not start intervention/placebo or discontinue intervention/placebo early and are willing to be followed per the test schedule (Section 4). This analysis will be descriptive in nature to see if these patients have a poorer QOL than patients who stay on study.

16.64 Translational Component: The hypothesis is that oral SBI will improve postoperative recovery. However, we know of no biomarkers indicative of postoperative recovery. Hence in an exploratory manner, we will measure a host of candidate biomarkers. This study will include serial assessment at baseline, at a mid-way timepoint, and at the end of the intervention intervention. The differences between biomarker values over time will be compared between the 2 intervention arms using a Wilcoxon Rank-sum test. In addition, other graphical and statistical methods will be used to compare the data over time between oral SBI and placebo. All these analyses will be considered hypothesis-generating.

16.7 Inclusion of Women and Minorities

16.71 This study will be available to all eligible patients, regardless of race, or ethnic origin.

16.72 There is no information currently available regarding differential effects of this regimen in subsets defined by race, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as

always, look for differences in intervention effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.73 The geographical region served by the Mayo Clinic has a population which includes approximately 5% minorities. We expect about 5% of patients will be classified as minorities by race and all will be women. Expected sizes of racial subsets are shown in the following table:

Accrual Estimates by Ethnicity/Race

Ethnic Category	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	0	0	0	0
Not Hispanic or Latino	100	0	0	100
Ethnic Category: Total of all subjects	100	0	0	100
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	2	0	0	2
Black or African American	3	0	0	3
Native Hawaiian or other Pacific Islander	0	0	0	0
White	95	0	0	95
Racial Category: Total of all subjects	100	0	0	100

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

- **Not Hispanic or Latino**

Racial Categories: **American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens: None

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

18.11 Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study Form	≤2 weeks after registration
Baseline Adverse Event Form	
Research Blood Submission Form - Baseline (see Section 14.0)	
End of Active Intervention/Cancel Notification Form	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire - Baseline Booklet	≤2 weeks after registration - Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
Patient Questionnaire Booklet Compliance Form	≤2 weeks after registration - This form **must** be completed only if the Patient Questionnaire – Baseline booklet contains absolutely **NO** patient provided assessment information.

18.12 Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)		
	At each evaluation during the intervention period	At end of intervention	Observation/Crossover
Nurse/CRA Evaluation/Intervention Form	X	X	
Nurse/CRA Observation Form (4 weeks after completion of intervention			X
Adverse Event Form	X	X	X*
Research Blood Submission Form	X (see Section 14.0)		
Patient Questionnaire	X[1]	X[1]	X
Patient Questionnaire Booklet Compliance Form	X[2]	X[2]	
End of Active Intervention/Cancel Notification Form		X	
Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form	At each occurrence (see Section 10.0)		
ADR/AER	At each occurrence (see Section 10.0)		

* If the patient does not start therapy, adverse events will not be collected.

1. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.

2.This form must be completed **only** if the Patient Questionnaire contains absolutely **NO** patient provided assessment information.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: Research samples.

19.3 Other budget concerns: None

20.0 References

1. Aletti GD, Gallenberg MM, Cliby WA, Jatoi A, Hartmann LC. Current management of strategies for ovarian cancer. Mayo Clin Proc 2007; 82:751-70, 2007.

2. Chi DS, Eisenhauer EL, Zivanovic O, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. Gynecological Cancer 2009; 114:26-31.

3. Chi DS, Zivanovic O, Levinson KL, et al. The incidence of major complications after the performance of extensive upper abdominal surgical procedures during primary cytoreduction of advanced ovarian, tubal, and peritoneal carcinomas. Gynecological Cancer 2010; 119:38-41.

4. Magtibay PM, Adams PB, Silverman MB, et al. Splenectomy as part of cytoreductive surgery in ovarian cancer. Gynecologic Oncology 2006; 102: 369-374.

5. Mahner S, Eulenburg C, Staehle A, et al. Prognostic impact of the time interval between surgery and chemotherapy in advanced ovarian cancer: analysis of prospective randomized phase III trials. Eur J Cancer 2012, August 23rd.

6. Fisher B, Gunduz N, Saffer EA. Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases. Cancer Research 1983; 43:1488-1492.

7. Gunduz N, Fisher B, Saffer EA. Effect of surgical removal on the growth and kinetics of residual tumor. Cancer Res 1979; 39:3861-3865.

8. Larsen E, Blaakaer J. Epithelial ovarian cancer: does the time interval between primary surgery and postoperative chemotherapy have any prognostic importance? Acta Obstetricia et Gynecologica 2009; 88:373-377.

9. Jiang R, Chang X, Stoll B, et al. Dietary plasma protein reduces small intestinal growth and lamina propria cell density in early weaned pigs. J Nutr 2000; 130:21-26.

10. Peace RM, Campbell J, Polo J, et al. Spray-dried porcine plasma influences intestinal barrier function, inflammation, and diarrhea in weaned pigs. J Nutr 2011; May 25th.

11. Perez-bosque A, Miro L, Maijo M, et al. Dietary supplementation with bovine immunoglobulins ameliorates colitis in mdr1a-/mice (submitted)

12. Lembcke JL, Peerson JM, Brown KH. Acceptability, safety, and digestibility of spray-dried bovine serum added to diets of recovering malnourished children. J Pediatri Gastroenterol Nutr 1997; 25:381-4.

13. Begin F, Santizo MC, Peerson JM, Torun B, Brown KH. Effects of bovine serum concentrate, with or without supplemental micronutrients, on the growth, morbidity, and micronutrient status of young children in a low-income, peri-urban Guatemalan community. Eur J Clin Nutr 2008; 62:39-50.

14. Earnest C, Jordan A, Safir M, et al. Cholesterol-lowering effects of bovine serum immunoglobulin in participants with mild hypercholesterolemia. Am J Clin Nutr 2005; 81:792-8.

14a. Fasano A. Intestinal permeability and its regulation by zonulin: diagnostic and therapeutic implications. Clin Gastoenterol Hepatol 2012; 1096-100.
14b. Kralisch S. Fasshauer M. Adipocyte fatty acid binding protein: a novel adipokine involved in the

pathogenesis of metabolic and vascular disease? Diabetologia 2013; 56: 10-21.

14c. Gosalbes MJ, Abellan JJ, Durban A, et al. Metagenomics of human microbiome: beyond 16s rDNA. Clin Microbiol Infect 2012; 18 Suppl 4:47-9.

14d. Reiner AP, Lange EM, Jenny NS, et al. Soluble CD14: genomewide association analysis and relationship to cardiovascular risk and mortality in older adults. Aterioscler Thromb Vasc Biol 2013; 33:158-64.

14e. Husain N, Tokoro K, Popov JM, et al. Neopterin concentration as an index of disease activity in Crohn's disease and ulcerative colitis. J Clin Gastroenterol 2013; 47:246-51.

15. Delaney CP, Lindsetmo RO, O'Brien-Ermlich B, et al. Validation of a novel postoperative quality of life scoring system. Am J Surg 2009; 197:382-5.

16. Pocock SJ, Simon R. Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial. Biometrics 31(1):103-115, 1975 Mar.

17. Sloan JA. Assessing the minimally clinically significant difference: scientific considerations, challenges and solutions. COPD 2005;2: 57–62.

18. Kaplan E, Meier P: Nonparametric estimation for incomplete observations. J Am Stat Assoc 53:457-481, 1958.

Appendix Ia BASELINE PATIENT INFORMATION SHEET

Patient Completed Baseline Quality of Life Booklet

You have been given a booklet to complete for this study. The booklet contains questions about your symptoms.

These forms sometimes ask repeatedly for very similar information. This is done intentionally in order to get a clear understanding of your condition. Please answer all of the questions, even if they sound similar to a question you have already answered.

1. This booklet contains the following questionnaires:
   a. Postoperative Quality of Life (PQL) Questionnaire
   b. UNISCALE
   c. Symptom Distress Scale (SDS)

2. These questionnaires are to be filled out at baseline.

3. Please complete the booklet and return it to your nurse or doctor before you start the study intervention.

4. It is very important that you return the booklet to us.

Thank you for taking the time to help us.

Appendix Ib DURING Intervention PATIENT INFORMATION SHEET

Patient Completed Quality of Life Booklet (during therapy/observation/crossover)

You have been given a booklet to complete for this study. The booklet contains questions about your symptoms.

These forms sometimes ask repeatedly for very similar information. This is done intentionally in order to get a clear understanding of your condition. Please answer all of the questions, even if they sound similar to a question you have already answered.

1. This booklet contains the following questionnaires:
   a. Postoperative Quality of Life (PQL) Questionnaire
   b. UNISCALE
   c. Symptom Distress Scale (SDS)
   d. Compliance Questionnaire

2. These questionnaires are to be filled out weekly for a total of 16 weeks; within the 12 weeks of Intervention/Observation/Crossover.

3. Please complete the booklet at the appropriate times and return it to your nurse or doctor on a monthly basis and then at the end of your study intervention.

4. It is very important that you return the booklet to us, whether you finish the study or not.

Thank you for taking the time to help us.

Appendix II Postoperative Quality of Life Questionnaire

Name and
Patient number _____ Date_____

The following questions are designed to gauge your current quality of life. Circle the answer that best indicates how you feel.

1. Quality of Life (0 = worst; 10 = best)

0	1	2	3	4	5	6	7	8	9	10

2. Quality of Health (0 = worst; 10 = best)

0	1	2	3	4	5	6	7	8	9	10

3. Level of Energy (0 = worst; 10 = best)

0	1	2	3	4	5	6	7	8	9	10

4. Pain at Rest

No Pain										Worst pain
0	1	2	3	4	5	6	7	8	9	10

5. Pain at Current Maximum Level of Activity

No Pain										Worst pain
0	1	2	3	4	5	6	7	8	9	10

6. Severity of Nausea or Vomiting

No nausea or vomiting										Worst nausea or vomiting
0	1	2	3	4	5	6	7	8	9	10

7. Fatigue

No Fatigue										Worst fatigue
0	1	2	3	4	5	6	7	8	9	10

8. How close is your bowel function to normal? (0 = most abnormal; 10 = normal)

0	1	2	3	4	5	6	7	8	9	10

9. How close are you to overall normal functioning for you? (0 = most abnormal; 10 = normal)

0	1	2	3	4	5	6	7	8	9	10

10. How close are you to your normal ability to get around the house? (0 = most abnormal; 10 = normal)

0	1	2	3	4	5	6	7	8	9	10

11. How close are you to your usual level of leisure activity? (0 = most abnormal; 10 = normal)

0	1	2	3	4	5	6	7	8	9	10

12. At what level is your sexual activity compared with normal? (0 = most abnormal; 10 = normal)

0 1 2 3 4 5 6 7 8 9 10

13. What is your current level of happiness: (0=sad; 10=happy)

0 1 2 3 4 5 6 7 8 9 10

14. What is your satisfaction with your overall level of medical care, including and since any surgery? (0=dissatisfied; 10=100%satisfied)

0 1 2 3 4 5 6 7 8 9 10

<u>Additional Questions related to Quality of Life Post-surgery</u>

1. Level of sleepiness

Totally alert **Very sleepy**

0 1 2 3 4 5 6 7 8 9 10

2. How many times per day on average did you experience nausea or vomiting?

Never **1-2 times** **3-5 times** **> 5 times**

3. How many times per day on average did you have a bowel movement

None **1 time** **2-3 times** **3-5 times** **> 5 times**

Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

4. What picture represents the typical bowel movement you had over the past 7 days. Please place an "X" over the appropriate picture.

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

Appendix III UNISCALE – Patient Form

Patient Name: _____ Date: _____

Patient Number: _____

Directions: Please circle the number (0-10) best reflecting your response to the following question that describes your feelings during the past week, including today.

How would you describe your overall Quality of Life?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

Appendix IV SYMPTOM DISTRESS SCALE (SDS)

Each of the following sections lists 5 different statements. Think about what each statement says, and then place a circle around the one statement that most closely indicates how you have been feeling during the past 7 days. Please circle one statement for each section.

Appetite	1.	I have my normal appetite
	2.	My appetite is usually, but not always, pretty good
	3.	I don't really enjoy my food like I used to
	4.	I have to force myself to eat my food
	5.	I cannot stand the thought of food
Insomnia	1.	I sleep as well as I always have
	2.	I have occasional spells of sleeplessness
	3.	I frequently have trouble getting to sleep and staying asleep
	4.	I have difficulty sleeping almost every night.
	5.	It is almost impossible for me to get a decent night's sleep
Pain (a):	1.	I almost never have pain
	2.	I have pain once in a while
	3.	I frequently have pain-several times a week
	4.	I am usually in some degree of pain
	5.	I am in some degree of pain almost constantly
Pain (b)	1.	When I do have pain, it is very mild
	2.	When I do have pain, it is mildly distressing
	3.	The pain I do have is usually fairly intense
	4.	The pain I have is usually very intense
	5.	The pain I have is almost unbearable
Fatigue	1.	I am usually not tired at all
	2.	I am occasionally rather tired
	3.	There are frequently periods when I am quite tired
	4.	I am usually very tired
	5.	Most of the time, I feel exhausted
Bowel	1.	I have my normal bowel pattern
	2.	My bowel pattern occasionally causes me some discomfort
	3.	I frequently have discomfort from my present bowel pattern
	4.	I am usually in discomfort because of my present bowel pattern
	5.	My present bowel pattern has changed drastically from what was normal for me.
Concentration	1.	I have my normal ability to concentrate
	2.	I occasionally have trouble concentrating
	3.	I often have trouble concentrating
	4.	I usually have at least some difficulty concentrating
	5.	I just can't seem to concentrate at all

Appearance:	1.	My appearance has basically not changed
	2.	My appearance has gotten a little worse
	3.	My appearance is definitely worse than it used to be, but I am not greatly concerned about it
	4.	My appearance is definitely worse than it used to be, and I am concerned about it
	5.	My appearance has changed drastically from what it was
Breathing:	1.	I usually breathe normally
	2.	I occasionally have trouble breathing
	3.	I often have trouble breathing
	4.	I can hardly ever breathe as easily as I want
	5.	I almost always have severe trouble with my breathing
Outlook:	1.	I am not fearful or worried
	2.	I am a little worried about things
	3.	I am quite worried, but unafraid
	4.	I am worried and a little frightened about things
	5.	I am worried and scared about things
Cough:	1.	I seldom cough
	2.	I have an occasional cough
	3.	I often cough
	4.	I often cough, and occasionally have severe coughing spells
	5.	I often have persistent and severe coughing spells
Nausea (a)	1.	I seldom feel any nausea at all
	2.	I am nauseous once in awhile
	3.	I am often nauseous
	4.	I am usually nauseous
	5.	I suffer from nausea almost continually
Nausea (b)	1.	When I do have nausea, it is very mild
	2.	When I do have nausea, it is mildly distressing
	3.	When I do have nausea, I feel pretty sick
	4.	When I do have nausea, I feel very sick
	5.	When I do have nausea, I am as sick as I could possibly be
Depression	1.	I seldom feel sad and depressed
	2.	I am sad and depressed once in a while
	3.	I am often sad and depressed
	4.	I am usually sad and depressed
	5.	I am sad and depressed almost all the time

Appendix V Compliance Questionnaire

Please answer the question below about how often you took your study treatment during the past cycle.
Check only <u>one</u> box that reflects your response.

Over the past week, I took my study supplement:

☐ Always or almost always

☐ Usually

☐ Occasionally

☐ Rarely

☐ Never or almost never

Patient reported weight: ___ ___ ___.____ Unit of measure: *(check one)* ___ lbs. ___ kg

Appendix VI Nurse/CRA Phone Worksheet

Phone Contact Guide
NOTE: This should serve only as a guide to collect information while on the phone with the patient and does not replace any data forms which are required to be filled out. Do not fill out and submit this form, rather submit the data forms using the RDE system.

1. Call patient on day 2 of cycle 1 to reinforce daily questionnaire completion and answer any questions they may have. If day 2 falls on a weekend or holiday, you may call the patient on the next business day. .

2. Call patient on day 2 of cycle 2 and day 2 of cycle 3 to assess compliance and answer questions below. Note: phone calls are only required for patients not returning to the accruing institution for monthly therapy/assessment. Patients returning to the accruing institution for monthly therapy should be seen and assessed in person. Patients not returning to the accruing institution for therapy should be assessed via phone.

1. Items to document include:

□ Date of phone call.

□ Study cycle.

□ Compliance: Has the participant completed the questionnaire booklet each week (always, usually, rarely, never)? If not always, document reason(s) and reinforce weekly booklet completion. If never, document reason(s) in the Patient Questionnaire Booklet Compliance Form and reinforce weekly booklet completion.

□ Side effects

Abdominal pain
Bloating
Diarrhea
Baseline number of stools per day
Flatulence
Nausea
Vomiting
Fatigue
Wound infection
Wound complication
Wound dehiscence

□ Has the patient been taking the agent (Always or almost always; Usually; Occasionally; Rarely; Never or almost never)?

4. Reinforce compliance with booklet and remind participant to return booklet to study staff at their next appointment or in the envelope provided at the end of each 4 weeks.

5. Reinforce completion of questionnaires. NOTE: if patient decides to stop study early, ask them to fill out the questionnaires at the end of the booklet and return in the envelope provided.

7. Items to document include:
□ Date of phone call.
□ Study cycle.
□ Patient reported weight. (lbs/kg)
□ Has cancer therapy started (yes/no). If yes, chemo/RT/hormonal/other, specify-List start date of each.
□ Compliance questionnaire

Appendix VII Entera Health Clarification Letter

To whom it may concern:

Please find enclosed for review Protocol …..

Serum-derived bovine immunoglobulin protein isolate (SBI) is an orally administered prescription medical food containing a proprietary formulation of bovine immunoglobulins and proteins. The term medical food, as defined in Section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee (b) (3)) is "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."

Serum-derived bovine immunoglobulin protein isolate is intended for the nutritional management of a patient with enteropathy who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, the dietary management of which cannot be achieved by the modification of the normal diet alone. Serum-derived bovine immunoglobulin has self-affirmed generally recognized as safe (GRAS) status with no objections from the US Food and Drug Administration (FDA), and is demonstrated to be safe and well-tolerated in pediatric and adult patients.

Medical foods are regulated by the US Food and Drug Administration under the Food Drug and Cosmetic Act regulations 21 CFR 101.9(j) (8), however, medical foods do not undergo premarket review or approval by FDA since they do not meet the definition of the term *drug* in section 201(g)(1) of the FD&C Act includes, among other things, “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease . . .” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.” In addition, substances designated as GRAS for use in food are not approved as drug products since they are not intended to evaluate the product's ability to diagnose, cure, mitigate, treat, or prevent disease; therefore an IND under part 312 is not required.