Pragmatic, multicentre, cluster, cohort randomised controlled treat-to-target trial for treatment of small intestinal bacterial overgrowth in systemic sclerosis (SSc) – A Pilot Project

This is an outline of a 9 month **pilot project** to determine the feasibility of a full scale 3 year pragmatic, multicentre, cluster, cohort randomised controlled treat-to-target trial for treatment of small intestinal bacterial overgrowth (SIBO) in systemic sclerosis (SSc).

Background:

SSc, or scleroderma, is a serious multi-system disorder of connective tissue disease characterized clinically by thickening and fibrosis of the skin and involvement of internal organs, most commonly the lungs, gastrointestinal tract and heart. SSc affects predominantly women in the prime of their life and is associated with increased morbidity and mortality. **SSc is a rare disease** with prevalence estimates varying from 30-443/million population[1,2] which at the upper bound of 4.43/10,000 is less than 5/10,000 (500/million), the definition used by most funders for a rare disease.

The gastrointestinal tract (GIT) is the most commonly involved internal organ in SSc. GIT involvement is the presenting feature in 10%, occurs during disease course in up to 95%, and is responsible in 6-12% of all deaths in SSc patients[3-9]. Hypomotility of the bowel in SSc leads to **small intestinal bacterial overgrowth (SIBO) in 30–62% of patients**[10-13]. The most carefully performed study of the relationship of symptoms to the presence of SIBO found that symptoms occurring more commonly in patients with SIBO compared to other SSc patients are: abdominal pain/discomfort (86.4 vs 31%), bloating (77.3 vs 44.8%), diarrhea (50 vs 10.3%), constipation (59.1 vs 3.4%) and abdominal tenderness (54.5 vs. 6.9%)[10].

There is reason to believe that GI symptoms contribute significantly to quality life in SSc. We found that GI symptoms are an important independent predictor of global pain in SSc[4] as well as fatigue[5]. We also found that the number of GI symptoms was a significant contributor to global health related quality of life (HRQoL) as measured by the SF-36[6] and the World Health Organization Disability Assessment Schedule II[7], both patient-reported generic HRQoL instruments. Also, depression is common in SSc and the number of GI symptoms are significantly associated with that[9]. We also noted that malnutrition occurs in 18% of our patients and that GI symptoms, especially those often associated with small intestinal bacterial overgrowth (SIBO) such as abdominal bloating and diarrhea, are significantly associated with malnutrition[8].

As such, it seems possible that the appropriate treatment of SIBO in SSc could substantially improve not only GI symptoms but also HRQoL, global pain, fatigue and depression. There are 2 major problems that must be addressed. The first is the lack of adequate recognition of the symptoms of SIBO and the need to treat these patients. We will address that challenge with a novel approach to detecting and flagging such symptoms. The second major problem this application addresses is the **lack of evidence based treatment algorithms. We will address that challenge by developing an expert based consensus algorithm of therapy** which will take the clinician through a sequence of steps in assigning drugs, assessing the response and then making further decisions based on the initial response and its durability.

Current treatment(s) of the disease(s)

Treatment for SIBO has yet to be standardized. There is significant heterogeneity in clinical practice. In general, though, it consists of a course of antibiotics, followed by assessment of the response, then re-treatment of relapses or failures. A recent systematic review and meta-analysis

assessed clinical trials of antibiotic therapy among symptomatic patients with documented SIBO in several diseeases[14]. They included trials comparing two or more antibiotics, trials comparing two or more dosing strategies for the same antibiotic, or trials comparing one or more antibiotics with placebo. They required SIBO to be formally diagnosed with lactulose, glucose, sucrose, or xylose hydrogen or methane breath test, and/or quantitative small bowel culture. They required 'cure' or 'treatment response' to be defined as normalisation of repeat hydrogen breath testing. Only 10 studies met inclusion criteria. Rifaximin, a non-absorbable antibiotic, was the most commonly studied antibiotic (8 of 10 studies). For all trials of rifaximin monotherapy combined, the aggregate breath test normalisation rate was 49.5% (95% CI 44.0–55.1). Metronidazole was the only other antibiotic used in more than one study. The combined breath test normalisation rate of two studies of metronidazole was 51.2% (95% CI 40.1–62.1). Ciprofloxacin had the highest rate of breath test normalisation (100%, 95% CI 76.8–100.0), but this was based on a single study with only 14 subjects in each treatment arm. For all antibiotic regimens combined, breath test normalisation occurred in 51.1% (95% CI 46.7–5.5). Conversely, only 9.8% (95% CI 4.6–17.8) of placebo-treated subjects among four studies had breath test normalisation. The authors concluded: "Given the prevalence of SIBO and its potential for significant consequences when left untreated, we found a surprising lack of depth in the literature describing antibiotic therapy for SIBO."

Delayed gastric emptying and gastroparesis, which produce symptoms of early satiety, nausea, bloating and abdominal pain, are thought to contribute to SIBO. Thus, prokinetic drugs are often used as adjuncts in the treatment of SIBO[15].The only prokinetic medications that have been shown to affect gastric emptying in SSc are erythromycin and ghrelin[16].Thus, the empiric use of most prokinetic drugs in SSc is limited by absence of proven efficacy or the presence of adverse effect, in particular prolonged QTc intervals on ECG. Lastly, octreotide, a somatostatin analog, which is occasionally used, and which has been shown to be useful for the treatment for chronic intestinal pseudo-obstruction in SSc[17,18], can decrease gastric emptying which is already a problem in this patient population.

Adverse effects of prokinetics can include diarrhea, which is one of the symptoms of SIBO[19]. Cholestyramine or other bile acid sequestrants are suggested as treatment options for diarrhea[19], however it should be noted that these drugs can cause constipation, nausea, flatulence, bloating and abdominal pain.

It is thus obvious that there are many limitations in terms of the literature regarding treatment of SIBO. Rifaximin, the antibiotic best studied, is in fact a fairly expensive drug, not readily available or covered by public insurers in many countries. Although many antibiotics may be used in clinical practice[20], almost none have been carefully validated. There are, to our knowledge, no studies demonstrating how to treat relapses or first drug failures, how long to treat, how often to cycle antibiotics for relapses, or when to add other non-antibiotic agents. There are no specific trials in SSc that we could find and none were in fact included in the systematic review.

The study: What will the full project look like if the pilot is successful?

What is/are the principal research question(s) to be addressed? We will determine if a structured, treat-to-target algorithm based on treatment response and relapse performs better than standard care for the treatment of symptoms SSc-SIBO.

Overview: This will be a 3 year, pragmatic, multi-centre, cluster, cohort randomised controlled treat-to-target (T2T) trial of SIBO. The pragmatic aspect relates to the intent to test the effectiveness of the T2T SIBO intervention in routine clinical practice in order to maximize applicability and generalizability. Our research question is *whether our proposed T2T SIBO intervention actually works in real life*. The intervention will be evaluated against standard care, in routine practice settings. As in most pragmatic trials, our outcomes will be mostly patient-centered[21,22]. There will be a setup period of 6 months, recruitment over 1 year with a follow-up of one year and an additional 3 months for data analyses.

The cluster component reflects the fact that treatment will be randomized to sites rather than patients. The cohort component reflects the fact that patients will be recruited from ongoing longitudinal cohorts via web-based interactions to determine eligibility. This aspect is a variant of the cohort multiple randomized controlled trial but in which only one trial will be performed (as opposed to multiple trials)[23].

In brief, SSc patients in the International Systemic Sclerosis Inception Cohort (INSYNC) sites, of which all participants in this trial will belong, are seen for study purposes on a yearly basis, to complete detailed, standardized protocols. Data are entered into databases and subsequently harmonized across all INSYNC sites. Although the initial purpose of INSYNC was to pursue research on inception cases, (defined as < 2 years disease duration), all INSYNC sites collect data on prevalent cases as well. Thus, for the purposes of this study, all patients seen, regardless of disease duration, will be assessed at a yearly visit to see if they are able to, and will consent to, accessing a web based Gastrointestinal Symptom Score (GSS) questionnaire that they will fill out at home at regular 3 month intervals. These questionnaires will both determine their eligibility for the SIBIO study and will be the major outcome measure. Before the study begins, individual sites, which will total about 30 around the world, will be randomly assigned to be treatment protocol or standard of care arms. Every 2 weeks the study coordinator will have access to the patient questionnaire results. As soon as an eligible case is detected, ie a score of ≥ 5 on the GSS, the site will be notified of this patient.

Protocol treatment sites will be expected to see the patient within a pre-specified window of time. The doctors at that site will apply the treatment algorithm and will make decisions about response to treatment based on the algorithm and on specific patient answers to questionnaires. The treatment protocol will only be made available to IRBs, not to any site personnel before randomization. This was derived from a survey of rheumatologists in many countries and gastroenterologists, mostly in North America, who were asked multiple questions about how they would treat and follow up patients with suspected SIBO. (Appendix 1- Survey of Experts)

The algorithm created for this data represents the best consensus of those opinions.

For the target for "success" we will use the GSS questionnaire which will be administered on paper when the patient visits the doctor's office for follow-up. In the study validating the GSS in SSc-associated SIBO, patients in whom the breath tests became negative after treatment had a significantly lower total GSS score than those with SIBO who did not become breath test

negative (mean (range) 1.5 (0–9) vs. 8 (5–23), p=0.001)[10,24]. None of the patients with eradication of SIBO had diarrhea. Hence, "no diarrhea plus a total GSS of < 5" will be the treatment target.

Meanwhile, those physicians randomly assigned to standard of care will also be informed of their patients who met eligibility criteria. They will not be aware of the detailed treatment protocol but will be informed of which medications are in the protocol eg antibiotics, prokinetics etc. They will be free to contact the patients at their convenience and to treat them in any way they deem suitable, preferably using these medications but at doses and frequencies according to their own wishes. As symptoms of SIBO tend to recur after short courses of treatment, and as the treatment protocol will be designed to adapt to this, we will follow each patient for one year from the time their physician was notified that they were eligible for the study. The primary outcome of the trial will be based on the patient reported outcomes regarding symptoms over the entire year.

***What are the proposed primary and secondary outcome measures of the main trial*?**

Primary: The primary outcome is the total GSS score.

Secondary: Secondary outcomes include all GSS subscales. HRQoL will be assessed by the social scale of the UCLA GIT 2.0 and the NIH Promis29. Hospitalization for SIBO will be recorded during the 2 year study.

What are the known safety concerns of the treatment(s), and are the concerns different for the proposed repurposed indication? This study will investigate the use of antibiotics and possibly other medications (eg. promotility, bile sequestrants, anti-diarrheals) for SSc SIBO treatment. For all antibiotics, hypersensitivity reactions such as exfoliative dermatitis, rash, urticaria, flushing, angioneurotic edema, pruritus, and anaphylaxis are a concern. Prolonged use may result in fungal or bacterial super-infection, including C. difficile-associated diarrhea and pseudomembranous colitis. Cholestyramine resin, which may be one of the drugs selected for use, should be used with caution in patients with triglyceride levels 250-299 mg/dL. Chronic use may be associated with bleeding problems (especially in high doses. Cholestyramine (especially high doses or long-term therapy) may decrease the absorption of folic acid, calcium, fat-soluble vitamins (vitamins A, D, E, and K), and iron. However, antibiotics and drugs such as cholestyramine are already in use for SIBO, although not in a standardized fashion, so the risks are not increased in this proposal. The use of certain promotility drugs is associated with a prolonged QT interval.

THE PILOT PROJECT

***Objectives*: To determine the feasibility of the full project.** This will be a trial with 3 months of recruitment and 6 months of follow up for each case.

***Specific Aims*:**

1. Determine if ethics committees perceive any major issues regarding the ultimate trial

2. Determine if the sites are approaching all eligible patients with study and offering consent forms.

3. Determine the signing rate of consent.

4. Determine patient adherence to web access for questionnaires.

5. Assess our method for detecting eligible cases from web questionnaires.

6. Assess whether physician notifications are being sent out quickly after detecting eligible cases.

7. Assess the timeliness and completeness of physician receipt of notification of patient eligibility.

8. Assess physician adherence to treatment protocol:

   a. how soon protocol patients are brought in to see doctor after receipt of notice.

   b. does doctor record what he does accurately.

   c. does he/she schedule return visits according to protocol.

   d. does he/she use in office questionnaires for treat to target.

   e. does he/she base decisions on these questionnaires.

   f. does he/she follow algorithm sequentially.

9. For control sites,

   a. Record how soon protocol patients are brought in to see doctor after receipt of notice.

   b. Assess whether the doctor accurately records what he/she does.

Methods: The pilot project will reproduce the full trial but at only 10 sites, 5 standard care and 5 treatment protocol.

Sites: We will choose 2 sites in Australia, 2 in the Netherlands, 2 in Canada, 2 in Spain and 2 in Germany. In each country one site will be randomly selected to be a protocol site and one standard care site. If a PI on the grant comes from a site, then another rheumatologist unaware of the treatment protocol will act as the treating physician. Sites in INSYNC are located in Australia, Canada, the U.S., the Netherlands, Spain, Germany and Sweden. This selection will give us representation from English and non-English speaking centers and from an array of countries with different medical cultures. It will also test our ability to monitor sites far from the study center in Montreal.

For the full study, these sites will retain their treatment status as assigned for this pilot.

The inclusion criteria for a site is that they agree in writing to adhere to the overall study protocol, and specifically that they agree, before seeing the treatment algorithm and before being assigned to protocol or standard care, to accept to treat according to the algorithm if they are assigned to that.

Patient Inclusion /Exclusion: Every patient who visits the participating doctor at a site over the recruitment period will be approached for consent to participate in the trial.

Inclusion: The patient must have an email address and must be computer literate enough to fill out the online questionnaires. From our experience where patients are asked if they have emails to see if they can participate, about 70% do. The online questionnaires will be available in the language of all countries participating.

Exclusions:

- patients with allergies to any of the drugs in the protocol which cannot be substituted for another protocol drug, and this will apply to standard care patients as well.
- patients with concomitant severe disease that would make it unlikely that they will survive for one year;
- patients with other illness or use of substances known to cause diarrhea;
- history of antibiotics in the 12 weeks prior to inclusion;
- history of intestinal pseudo-obstruction;
- inability to complete the symptom questionnaires;
- no functional level of written & spoken languages;
- previous *C. Dificile* infection;
- previous gastrointestinal surgery;
- prolonged QT interval;
- pregnancy or breastfeeding.

Screening for exclusions will be done at the site before the patient is consented. (Appendix 2- Exclusion Criteria Questionnaire)

As is typical of a pragmatic trial, we will keep inclusions broad and exclusions narrow.

Patients already on prokinetics will not be excluded but that prokinetic will be considered a failed drug and the treatment algorithm will proceed as such.

Consent and Patient Recruitment: Patients will be recruited at their regular yearly visit to their INSYNC physician or to any other participating physician. The study will be explained and they will asked to sign a consent, (Appendix 3 – Consent Form), which will ask for their consent to be contacted by email. The email will contain a link to a website where they will be asked to fill in 2 forms, the UCLA GIT 2.0 and the GSS, on a monthly basis. They will be explained that their site will be using a specific treatment protocol or standard care and that the treatment protocol will employ much the same drugs that most physicians use for the problem of SIBO but in a very defined way. They will get a call or notice to see their doctor if they have evidence of SIBO based on their GSS test scores no matter what type of site they are assigned to.

Once a patient signs a consent, the global study coordinator will be informed that the patient is in the study via email. The email will include the patient's local study ID and their email address.

Website Questionnaires: Subjects will access and fill in the GSS questionnaire which will be used both for screening for SIBO and for assessment of improvement with treatment. If the score of the GSS is ≥ 5 then the UCLA GIT and PROMIS GI questionnaires will also be triggered. (Appendix 4 – Questionnaires) They will be sent the link to the questionnaires via email from the central study coordinator. In this pilot, we will only screen subjects for 3 months total so the questionnaires will be filled in once a month for those 3 months. This will allow us to better assess the use of the website over a short period of time. Subjects will be notified immediately after consent is signed and thereafter once a month by email that they should fill in the questionnaire. A link will be provided. If the questionnaire is not filled out within 5 days an automatic repeat email will be sent out. We will repeat this every 5 days for a total of 3

additional reminders. If there is no response after that the site coordinator will be informed and asked to phone the subject to determine and record the reason for the non-response and if the subject no longer wishes to be in the study they will be withdrawn.

Notification of Doctor of Eligible Case: If a score on the GSS is ≥ 5, the computer will send an automatic notice to the office of the doctor and to the doctor him/herself telling them of this. The email notification will be repeated in 5 days to be sure that it has not been missed, and the provider will be asked to verify that is was received.

First Appointments: Upon receipt of the notice, the protocol doctors will be expected to make an appointment within the timeframe outline in the protocol. Standard care doctors, who will not know the details of this protocol, will decide on their own if and when to see the patient. Upon receipt of this notice the secretaries or clerks at the site will be asked to insert a treatment sheet (Appendix 5 – Treatment Sheet) in the doctor's chart. This sheet will be used to assess the timeliness of the first visit after notification, about the adherence of protocol doctors to protocol treatment and the types of medications and general pattern of treatment of the standard of care doctors.

Subsequent Appointments: The timing of subsequent appointments will be left to the discretion of the doctors but the protocol doctors will be expected to adhere to the protocol for follow up frequency and intervals. The treatment sheets will assess adherence. At each protocol visit the patient will fill out the GSS in the office as the doctor will use the score to determine success of treatment rather than relying simply on history. This is outlined in detail in the treatment protocol.

Recruitment and follow-up period: Patients will be recruited over a period of 3 months and followed up for 6 months. The total duration of the study will thus be 9 months. However, the protocol doctors will be asked to try to continue to adhere to the protocol. If there are no major changes in the protocol based on this pilot, all the patients enrolled in these 3 months may be rolled into the larger full study. This will be decided after the pilot data has been fully assessed.

Safety Monitoring: The treatment sheets will have fields to record any suspected side effects of treatment and the physicians will record this. A Data Monitoring and Safety Board (DSMB) will be established before the start of the pilot. We will request that a copy of all treatment sheets be faxed or emailed to the coordinating site after each visit. These will be forwarded to the DSMB members. If any member detects a serious side effect that they feel should lead to a change in protocol an immediate teleconference of the DSMB will be arranged.

Chart Audit: To determine if there is a disagreement between the treatment questionnaires and what the doctors actually did, we will perform a chart audit of a sample of charts. Permission to do this will be included in the consent forms. We will audit 30 % of charts randomly selected from each doctor. The audits will be of all relevant visits over the study period. We will ask to have the relevant pages from these charts faxed to us. We will find non-English speaking volunteers from the translation service at the central coordinating hospital to help fill out data extraction forms (Appendix 6 – Data Extraction Sheet) for the chart review of non-English speaking centers. The study coordinator will perform the audit.

Data Analyses: Each of the aims will be assessed. Statistics will be essentially descriptive. The success of the pilot will not depend on one global assessment. As individual elements of the

study can each be addressed separately, by making changes to specific parts of the protocol, the success of each element will be as follows:

1. Determine if ethics committees perceive any major issues regarding the ultimate trial.

Success: There will be 10 sites and thus 10 ethics committee responses. Success will be **NO** substantive suggested changes to the protocol.

If Not Successful: **Any** suggestion for a change will be addressed for full trial.

2. Determine if the sites are approaching all yearly INSYNC patients with study and offering consent forms at the time of the visit.

Success:≥ 80% of yearly INSYNC patients are offered the consent.

If Not Successful: Interview the local research assistants or nurses and see if there seems to be a systemic issue that could be addressed to improve the frequency with which patients are approached.

3. Determine the signing rate of consent within 1 week of the time of the visit.

Success:≥ 80% acceptance rate by patients.

If Not Successful: Interview the local research assistants or nurses and see if there seems to be a systemic issue that could be addressed to improve the acceptance rate.

4. Determine patient adherence to web access for questionnaires.

Success:≥ 70% of patients go to website and answer first set of questionnaires. ≥ 90% of those who answer do so within 10 days. For those who do answer first questionnaire, consider them as successes and study participants. For these subjects, do similar assessments for each subsequent questionnaire. Successful retention will be ≥ 80% of those who answered each month will do so at following month.

If Not Successful: We will consider changes to the wording and frequency of reminders.

5. Assess our method for detecting eligible cases from web questionnaires.

Success: We expect that about 25% of cases will show SIBO positive responses (score ≥ 5 on GSS) to the questionnaires at some point over 3 months. In the study of 51 unselected patients with SSc, 22 (43.1%) patients were identified who fulfilled the breath test criteria of SIBO[10]. The sensitivity and specificity of GSS of digestive symptoms >5 to predict SIBO 0.909 and 0.862, respectively. In the 51 cases, 19 patients (37%) has scores > 5.

If Not Successful: We will modify the sample size calculations and power of the full study

6. Assess whether physician notifications are being sent out quickly after detecting eligible cases.

Success: All notifications should go out immediately after scoring GSS by computer.

If Not Successful: Address computer program.

7. Assess the timeliness and completeness of physician receipt of notification of patient eligibility.

Success: Receipt of notification by email should be within one day in all cases.

If Not Successful: Address computer program. Make sure correct email addresses.

8. Assess physician adherence to treatment protocol:

a. How soon protocol patients are brought in to see doctor after receipt of notice.

Success: The window is in the treatment protocol. 90% of visits should be within the window.

If Not Successful: Speak to physicians and see what the issues are that delay appointments. Determine if something can be done to protocol to address this.

b. Does doctor record what he does accurately.

Success: This will be assessed by chart audit. We expect the chart to reflect the answers on the treatment forms on 90% of all filled in fields on each form.

If Not Successful: We will discuss with the physicians why there was a difference between charts and forms and determine if the protocol can be changed to enhance the adequacy of completion of the forms.

c. Does he/she schedule return visits according to protocol.

Success: This will be assessed by chart audit. 90% of visits should be within the window.

If Not Successful: Speak to physicians and see what the issues are that delay appointments. Determine if something can be done to protocol to address this.

d. Does he/she use in office questionnaires for treat to target.

Success: Use chart audit. At >90% of protocol visits the questionnaires should be filled out and found in chart. We also expect to find notes suggesting that physician treatment decisions take into account the score on the GSS.

If Not Successful: Speak to physicians and see why questionnaires not being used appropriately and determine if protocol changes can be made.

e. Does he/she base decisions on these questionnaires?

Success: as above

If Not Successful: as above

f. Does he/she follow algorithm sequentially.

Success: Use chart audit. We expect ≥ 80% adherence to protocol over the 3 months by ≥ 80 of physicians.

If Not Successful: Speak to physicians and see why algorithm not always being followed and determine if protocol changes can be made.

9. For control sites,

a. Record how soon protocol patients are brought in to see doctor after receipt of notice.

Success: No criteria for success. Just observational

If Not Successful: N/A

b. Assess whether the doctor accurately records what he/she does.

Success: This will be assessed by chart audit. We expect the chart to reflect the answers on the treatment forms on 90% of all filled in fields on each form.

If Not Successful: We will discuss with the physicians why there was a difference between charts and forms and determine if the protocol can be changed to enhance the adequacy of completion of the forms.

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