APPLICATION FOR

WSF SPECIAL WORKING GROUPS

WSF GASTROINTESTINAL DISEASE WORKING GROUP

Joint Principal Investigators:

Dr Michael Hughes & Dr Zsuzsanna McMahan

Description of the project:

OVERVIEW

Gastrointestinal (GI) involvement is almost universal (>90%) in patients with systemic sclerosis (SSc) and may involve the upper and/or lower portions of the GI tract throughout the course of the disease. GI disease is an important cause of morbidity and mortality in SSc, and it often arises from GI dysmotility in the esophagus, stomach, small or large bowel, and/or the anorectum. Because the esophagus and anorectum are two regions of the gut which are most commonly impacted by SSc, and because non-invasive objective assessment tools are limited for GI manifestations of SSc, here we focus on the following key strategies: [a] expanding therapies for refractory GERD (Focus 1); [b] standardizing care for patients with significant anorectal dysfunction; [c] expanding clinically relevant, non-invasive, objective assessments of GI manifestations of SSc.

Focus 1: Surgery for refractory GERD

Upper GI tract dysfunction is one of the most common symptoms among patients with SSc, typically presenting as gastroesophageal reflux disease (GERD). Symptoms can be challenging to manage in patients who do not adequately respond to anti-acid therapies. While the integration of proton pump inhibitors (PPIs) into clinical care has significantly improved patient

quality of life, PPIs are seldom fully effective in SSc patients, even when PPI dosages are maximized or used in combination with H2 blocker therapy.

For patients with refractory GERD, some data suggest that surgery may be beneficial, however serious consequences (e.g., worsening of dysphagia) are reported and there is significant variation in surgical approaches and associated risks. As a result, key priorities for this multidisciplinary group (e.g., rheumatologists, gastroenterologists, gastrointestinal surgeons, and other stakeholders), are to study and define the clinical criteria to consider upper GI surgery/interventions in SSc using Delphi methodology. Indeed, the optimal timing for surgery and the best surgical procedure(s) for patients with refractory GERD in SSc are yet to be defined.

Focus 2: Anorectal dysfunction

Lower GI disease is also a major cause of disease-related morbidity and disability in patients with SSc. Embarrassment, social isolation, depression and the significant anxiety attributed to lack of bowel control all negatively impact patient quality of life. As a result, using a Delphi methodology, this muti-disciplinary groups aims to develop practical recommendations to diagnose and manage anorectal dysfunction in SSc (e.g., constipation and fecal incontinence) and thereby guide physicians in improving the quality of life for SSc patients.

Focus 3: Novel GI imaging

Diagnosing the specific types of GI dysfunction in patients with SSc using convenient, non-invasive visualization tools could be very helpful to guide medical management. In the absence of such tools, physicians are challenged by timely selection of the optimal regional prokinetics (i.e., medications that promote motility in certain areas of the gut), and the high costs and invasive nature of the existing assessment tools (e.g., high resolution manometry). GI research in SSc is also limited by the lack of standardized, cost-effective, non-invasive objective outcome measures. Here we seek to determine whether bedside ultrasound can be utilized in the assessment of GI disease to become a less expensive, more convenient alternative to existing assessment tools. This would be a practical and cost-effective imaging modality to enhance patient care and inform clinical decision-making.

While these projects are currently proposed, prior to moving forward with them, we will lead a ***well-balanced focus group****, per the reviewers' recommendations. This will be composed of patients with SSc who have a variety of GI complications, so that we can determine the highest priorities in this population. Furthermore, we will also* ***conduct a systematic literature review*** *to examine the GI outcome measures currently utilized in SSc studies and clinical trials to better understand the landscape and current limitations in the field.*

Overall Hypothesis:

Our multi-disciplinary community can optimize the diagnosis and management of specific GI complications in SSc through the development of novel diagnostic and treatment strategies and integration of patient input.

Current Aims of the Proposal (subject to change):

Aim, Focus 1: To study and define the clinical criteria for upper GI surgical interventions in SSc using Delphi methodology and a multi-disciplinary panel of experts.

Aim, Focus 2: To develop practical recommendations to diagnose and manage anorectal dysfunction in SSc using Delphi methodology and thereby guide physicians and other healthcare providers in improving the quality of life for SSc patients.

Aim, Focus 3: To determine whether bedside ultrasound can be utilized in the assessment of GI disease to become a less expensive, more convenient alternative to existing assessment tools.

Objective of Patient Focus Group:

To identify and prioritize the unmet needs related to GI disease among SSc patients, and directly integrate patient feedback into the study design and objective. This will highlight high-priority deficiencies that are not a focus of the current proposal as it stands.

OVERVIEW OF METHODS

Establishment of patient focus groups: An international group of patients will convene via Zoom to establish the priorities of patients as they pertain to the assessment and management of SSc GI complications. Patients will be recruited from international SSc centres (e.g., Manchester and Baltimore). Questions will be developed by the steering committee including with key input from patient research partners.

Conduction of Systematic Literature Reviews: To systematically assess the current landscape and existing outcome measures, we will work with an expert EULAR recognised methodologist and librarian to search the literature for clinical studies in SSc which have focused on various GI outcomes. We will determine the outcome measures utilized, in previous observational research trials and clinical trials.

Approach to currently proposed projects (Focuses 1-3): An overall Steering Board will coordinate the works of the subgroups to deliver the specific objectives. We will convene 3 WSF subgroups, with one WSF GI working subgroup assigned to execute each Focus (see details below).

Establishment of the Working Group, Patient Focus Group, and Study Design [pertaining to currently proposed work (Focuses 1-3)]; Subject to change based on results of the Patient Focus Groups and SLR.

Step 1: Formation of the WSF Steering Board and Working Group:

We shall create an international task force (WSF GI Working Group) consisting of worldwide experts in SSc-GI disease. Relevant stakeholders shall include rheumatologists, gastroenterologists, GI surgeons, dietitians, and patient representatives.

The Working Group shall recruit and promote junior fellows throughout the activities of the Working Group.

Proposed Steering Board:

1. Murray Baron (Ca)

2. Lorenzo Dagna (I)

3. Christopher Denton (UK)

4. Tracy Frech (US)

5. Susan Gearhart (US) (GI)

6. Dinesh Khanna (US)

7. Isabelle Marie (F)

8. Marco Matucci-Cerinic (I)

9. Charles Murray (UK) (GI)

10. Susanna Proudman (Au)

11. Elizabeth Volkmann (US)

12. GI surgeon

13. Dietitian

13. FESCA and/or SRUK leader/s, others

The participating enlarged task force members are named later and will contribute to the Working Group activities including Delphi procedures and involve EUSTAR, SCTC, Japanese, Chinese and Korean colleagues to

ensure broad geographical representation.

Invitations for other WSF GI Working Group Members (international leaders including rheumatologists, gastroenterologists, rheumatology providers (e.g., nurses), dietitians, expert statisticians, and patients).

Step 2: Creation and Implementation of Patient Focus Groups

We will undertake an international survey of patients using a web-based platform to identify and prioritize the unmet GI needs in SSc. To facilitate recruitment, we shall utilize SSc-networks (e.g., EUSTAR and SCTC) to recruit rheumatologists, expert faculty's (e.g., for organ-based specialists), and patient-led organizations (e.g., FESCA). We will develop a purposeful sampling framework to include SS patients with a wide spectrum of GI involvement. ***We will thereby solidify the Working Group's priorities and research agenda.***

Step 3: Formal Assessment of the Landscape and Delphi Exercises

Formal Assessment of the Current Landscape through Systematic Literature Reviews: Our team (MH, ZM, AA, fellows, and patient research partners) will undertake dedicated systematic literature reviews (SLR) to assess support the development of the treatment recommendations *(currently Focus 1 and 2, but subject to change based on Step 2 results)*. The results from the SLRs shall be presented to the task force along with recommendations for guideline items for discussion including possible addition of new items. Online voting rounds will be used to decide on whether items should be accepted in the final guideline. An item will be immediately accepted if >75% of the task force members voted for it. For items where this is not achieved, the text will be amended and subjected to a second voting round, where a 67% majority will be required. For items not included after this, the text will be revised a third time and subject to a final voting round, for which a majority vote (>50%) will be required for inclusion. After this process is complete, each item, as agreed by the task force, will be assigned an appropriate level of evidence and strength of recommendation based upon the SLR. The level of agreement will be assessed using online voting on a 0-10 scale where 0 means no agreement and 10 in full agreement.

Multi-disciplinary Delphi Exercises (*Currently for Focuses 1 and 2*, subject to change based on Step 2 results): We will undertake an international survey using a web-based platform of GI surgeons and SSc experts to establish consensus on the proposed topics. To facilitate recruitment, we shall utilize contacts from the professional societies of our working group, and established SSc-networks (e.g., EUSTAR and SCTC).

As a Working Group, we will identify potential collaborative projects and suitable external funding sources

Statistical approach:

Relevant descriptive statistics and appropriate statistical analyses will be used to report and describe the data.

Step 4: Dissemination and next steps. We shall present our findings at international conferences and prepare manuscripts for publication in high-impact peer-reviewed journals. Throughout the duration of the WSF GI working group we shall consider next steps (including but not limited to) further funding applications based on our research, the need for the development of a novel GERD PRO, and re-application to launch the second iteration of the working group.

Proposed Milestones (24 months – 09/2022 to 09/2024) – *subject to change based on Step 2 results:*

- September 2022 - October 2022: *Assemble task force for the WSF GI Working Group.*
- October 2022 - late 2022: *Development and launching patient unmet needs survey.*
- *Late 2022 – early 2023: Analysis of patient unmet needs survey and review of Working Group objectives.*
- Late 2022 – early 2023: *Development and launching surgery survey.*
- Early 2023 – Mid 2023: *Development of surgery consensus recommendations.*
- Late 2022 – Mid 2023: *Developing novel methods to assess GI disease/collaborative research projects including funding applications.*
- Mid 2023 – Mid 2024*: Undertake novel imaging studies of GI disease in SSc, including (but not limited to) ultrasound.*
- Late 2022 – Mid 2023: *Develop and undertake incontinence SLR.*
- Late 2023 – Mid 2024: *Development of incontinence treatment recommendations.*

Importance to patients

Optimised approaches to the treatment and assessment of GI disease will improve quality of life and function for these very challenging manifestations in SSc. Here we will specifically integrate patient feedback to ensure that our work directly addresses critical unmet clinical needs.

WSF GI Working Group Task Force Members: Expanded

Rheumatologists

1. Professor Yannick Allanore (F)
2. Professor Oliver Distler (CH)
3. Dr Cosimo Bruni (I)
4. Professor Dilia Giuggioli (I)
5. Professor Marco Matucci-Cerinic (I)
6. Dr Alessia Alunno (*Methodologist*, I)
7. Professor Christopher Denton (UK)
8. Professor Ariane Herrick (UK)
9. Dr Anna-Maria Hoffman-Vold (N)
10. Dr Murray Baron (CA)
11. Dr Francesco Boin (USA)
12. Dr Lorinda Chung (USA)
13. Dr Tracy Frech (USA)
14. Dr Elizabeth Volkmann (USA)
15. Dr. Monique Hinchcliff (USA)
16. Professor Dan Furst (USA)
17. Dr Laura Hummers (USA)
18. Professor Dinesh Khanna (USA)
19. Professor Masataka Kuwana (Jp)
20. Dr Mandana Nikpour (AU)
21. Prof Susana Proudman (AU)
22. Dr Eung Bong Lee (Ko)
23. Dr Meng Tao Li (China)
24. Dr Yukai Wang (China)

Gastroenterologists:

Riccardo Rosati, Petri, Massimo Vecchiato, Charles Murray (UK), Simon Lal (UK), John McLaughlin (UK), P. Jay Pasricha (USA), John Clarke (USA), John Pandolfino (USA)

***GI surgeons*:**

Silvio Danese (I), Savarino (I), Giulia Bandini (*GI-US*, I), Pietro Matucci-Cerinic (I)

Dietitians

To be added/confirmed based on international though leader opinion and recommendation.

Patient representatives

- Ilaria Galetti (I)

- Allison (China)
- Sue Farrington (UK)

Detailed Budget:

- Online survey manager €2000
- Open access peer-reviewed publications to facilitate dissemination of knowledge (X2): €3000
- Administrative support: €500

Grand Total: €5500 (2750 x year)
