STUDY REPORT SYNOPSIS

Evaluation of the Simplified Diagnosis Tool for Chinese IBS-C (irritable bowel syndrome with constipation) patients

A multi-centre, prospective observational study to conduct the sensitivity and specificity analysis of the Simplified Diagnosis Tool based on ROME IV criteria in Chinese patients

Milestones:	Clinical Study Protocol（2.0）: 3 Mar 2022 First Subject enrolled: 1 Nov 2021 Last Subject last visit: 28 Oct 2022 Clinical Study Report:
Phase of development:	NA
Sponsor:	AstraZeneca
Sponsor's Responsible Medical Officer:	Lihua Gu

Background/rationale:

Functional gastrointestinal disorders (FGIDs) accounted for at least 40% [1] of all referrals to gastroenterologists. Of the 33 recognized adult FGIDs, irritable bowel syndrome (IBS) was the most prevalent, with a worldwide prevalence estimated at 12% [2]. IBS was an important health care concern as it greatly affects patients' quality of life and imposes a significant economic burden to the health care system [3]. Cardinal symptoms of IBS included abdominal pain and altered bowel habits. The absence of abdominal pain maked the diagnosis of IBS untenable. The diagnosis of IBS could be made by performing a careful review of the patient's symptoms, taking a thoughtful history [4] (e.g., diet, medication, medical, surgical, and psychological history), evaluating the patient for the presence of warning signs (e.g., "red flags" of anaemia, haematochezia, unintentional weight loss, or a family history of colorectal cancer or inflammatory bowel disease), performing a guided physical examination.

Partly because of this uncertainty, symptom based diagnostic criteria were developed to help physicians make a positive diagnosis when consulting with patients with suspected IBS. The

Manning criteria[1] were proposed in the 1970s and, leading on from these, factor analysis studies demonstrated that the lower gastrointestinal symptoms thought to make up IBS clustered together[5]. This led to the development of the ROME criteria. In the 1990s, which had undergone three subsequent revisions, the most recent being the ROME IV criteria in 2016[6]. Previous validation studies of symptom-based diagnostic criteria demonstrate that they performed only modestly in diagnosing IBS. Nevertheless, their use was important to minimise over investigation, which could be anxiety-provoking for patients with IBS. In addition, if they performed accurately, this may help reassure patients that the physician's diagnosis of IBS was correct as well as reducing costs to the health service of managing the condition [7].

In China, in a previous study[8] showed that ROME IV-positive IBS patients represented approximately half of ROME III positive IBS patients at a tertiary hospital in China. More specifically, ROME IV-positive IBS was mainly a subgroup of ROME III-positive IBS with more serious symptoms. As difference of culture and language, it indicated that the practice of ROME IV may not be suitable to Chinese IBS patients. Dr. Lishou Xiong had developed a more suitable Simplified Diagnosis Tool for Chinese IBS patients, which was derived from IBS part in ROME IV and Asian FGID scales. Although there was not a formal publication released, he claimed that the Simplified Diagnosis Tool showed great satisfaction and response rate in clinical practice. Our study was a multi-center, prospective observational study to assess the sensitivity and specificity of the Simplified Diagnosis Tool based on Rome IV criteria in Chinese patients.

Objectives:

- Primary objective: To evaluate the sensitivity and specificity of the Simplified Diagnosis Tool in Chinese IBS-C patients based on Rome IV criteria.
- Secondary objective: To calculate the accuracy, Kappa coefficient, positive predictive value, and negative predictive value of the Simplified Diagnosis Tool.

Study design:
The study was a multi-centre, prospective observational study which enrolls 150 IBS-C patients and 150 non-IBS-C patients in China.

The potential study subject would be identified by the investigators by face-to-face visit, and there would be only 1 visit in this study. Every patient would complete both ROME IV and the Simplified Diagnosis Tool during the visit, and in the same day.

Patients would be assessed by ROME IV criteria at first for diagnosis, to ensure that the number of IBS-C patients was 150 and non-IBS-C was 150. Then 2 groups of patients would be assessed by the Simplified Diagnosis Tool. An experienced GI clinicians would do the diagnosis. ROME IV and the Simplified Diagnosis Tool were patients self-reported questionnaires, clinicians could explain the meaning of the item or content of two questionnaires, yet supporting patients to complete or emphasizing the difference and importance of the questionnaires were not allowed. The clinicians were not allowed to inform the patients the result of each questionnaire before they completing the two questionnaires. Accuracy and other analysis would be conducted after 2 assessments.

The study would collect results of ROME IV and the Simplified Diagnosis Tool. Sensitivity and specificity of the Simplified Diagnosis Tool compared with ROME IV would be analysed after all the data has been collected.

Data source:
This study would collect the data using Electronic Patients Report Outcome (ePRO) and Electronic Case Report Form (eCRF). During the subject enrolment, the investigator would firstly explain the purpose of the study to consecutive patients and written informed consents would be obtained. Then qualified patients would be given ROME IV on ePRO and finish it. After receiving questionnaires, IBS-C or non IBS-C diagnosis would be made by investigators based on ROME IV IBS diagnostic criteria.Then they would finish Simplified Diagnosis Tool on ePRO. Investigators would collect IC, IE, disposition, demographic and other information on eCRF.

Study population:
A total of 300 patients with constipation and abdominal symptoms were recruited. In order to evaluate the effectiveness of Simplified Diagnosis Tool for irritable bowel syndrome in China, data collection and analysis were needed in the corresponding population. There were 150 IBS-C patients and 150 non IBS-C patients.

Inclusion criteria:

- Group 1 (IBS-C)
  - ≥18 years old
  - Decrease of frequency of bowel movement (<3 time per week), change of stool consistency (stool that was hard and difficult to pass, Bristol Types 1 to 3), or other 'constipation symptoms' judged by investigators.
  - With abdominal symptoms such as abdominal pain, bloating, and abdominal discomfort, or other 'constipation symptoms' judged by investigators.
  - Result of ROME IV marked as 'IBS-C'.
- Group 2 (non-IBS-C)
  - ≥18 years old
  - Decrease of frequency of bowel movement (<3 time per week), change of stool consistency (stool that was hard and difficult to pass, Bristol Types 1 to 3), or other 'constipation symptoms' judged by investigators.
  - With abdominal symptoms such as abdominal pain, bloating, and abdominal discomfort, or other 'constipation symptoms' judged by investigators.
  - Result of ROME IV marked as 'Non IBS-C'.

Exclusion criteria:

- Individuals with a cognitive condition and unable to finish the questionnaire.
- Individuals had an acute or chronic non-GI condition that could be associated with constipation; e.g., central nervous system cause (Parkinson's disease, spinal cord injury, and

multiple sclerosis), pseudo-obstruction, colonic inertia, megacolon, megarectum, bowel obstruction, descending perineum syndrome, solitary rectal ulcer syndrome, systemic sclerosis

- Individuals who had been diagnosed with the following organic health problems likely to affect GI symptoms:
  - Inflammatory bowel disease (Crohn's disease or ulcerative colitis)
  - cancer anywhere in the GI tract or current infection of the GI tract.
  - Pelvic floor dysfunction. (i.e., disease that is not adequately treated or stable with therapy.)
  - Any history of colon surgeries.
- Individuals who participated in any interventional study currently.
- Not suitable for the study judged by investigators.

Statistical methods:

Analyses would be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) would be prepared and finalized before database lock.

In general, descriptive statistics would be provided for the data collected. For continuous variables, mean, standard deviation, median, quartiles, minimum and maximum would be provided, and for categorical variables, frequency counts and percentages for each category would be provided.

The sensitivity and specificity in the detection of IBS-C would be calculated with ROME IV used as the reference standard. Sensitivity was the probability that results of the Simplified Diagnosis Tool were IBS-C in those patients who were judged as IBS-C using ROME IV. And specificity was the probability that results of the Simplified Diagnosis Tool were non-IBS-C in those patients who were judged as non-IBS-C using ROME IV.

The accuracy, Kappa coefficient, positive predictive value, and negative predictive value of the Simplified Diagnosis Tool would also be calculated with ROME IV used as the reference standard.

Results:

A total of 301 subjects screened with 300 subjects enrolled. All of enrolled subjects were completed the study and were included in FAS.

300 Asian subjects aged 18-85 years were included with the median of 44 years old and 233 were female.

Primary Analyses

Based on FAS, there were 133 (44.3%) subjects judged as IBS-C using ROME IV and 205 (68.3%) subjects were judged as IBS-C using Simplified Diagnosis Tool. While, 115 subjects were judged as IBS-C and 77 subjects were judged as non-IBS-C based on both the

Simplified Diagnosis Tool and ROME IV. The sensitivity and specificity with their 95% CI were 86.5% (79.5%-91.8%) and 46.1% (38.4%-54.0%) respectively.

Based on sensitivity analysis, there were 133 (46.7%) subjects judged as IBS-C using ROME IV and 204 (71.6%) subjects were judged as IBS-C using Simplified Diagnosis Tool. While, 115 subjects were judged as IBS-C and 63 subjects were judged as non-IBS-C based on both the Simplified Diagnosis Tool and ROME IV. The sensitivity and specificity with their 95% CI were 86.5% (79.5%-91.8%) and 41.4% (33.5%-49.7%) respectively.

Secondary Analyses

Based on FAS, the accuracy, positive predictive value and negative predictive value were respectively 64.0% (95% CI: 58.3%-69.4%), 56.1% (95% CI: 49.0%-63.0%) and 81.1% (95% CI: 71.7%-88.4%). The Kappa coefficient was 0.31 (95% CI: 0.22-0.40).

Based on sensitivity analysis, the accuracy, positive predictive value and negative predictive value were respectively 62.5% (95% CI: 56.6%-68.1%), 56.4% (95% CI: 49.3%-63.3%) and 77.8% (95% CI: 67.2%-86.3%). The Kappa coefficient was 0.27 (95% CI: 0.17-0.37).

Conclusion:

The simplified diagnostic tool has been proven good sensitivity in Chinese IBS-C patients to be easy to operate and understand in clinical use, which is more suitable for Asian population.

Publications:

None at the time of writing this report.