Medical Device Clinical Trial Protocol

Real-World Clinical Study on the Efficacy of Disposable Gastrointestinal Vibrating Capsule (Vibrabot Capsule) for Chronic Functional Constipation

Protocol Number: ANKONYX2023006

Name of Investigational Device: Disposable Gastrointestinal vibrating capsule (Vibrabot Capsule)

Model: ADVC-3

Management Category of the Investigational Device:

Is it a Class III medical device approved for marketing: Yes☑ No□

Is there any predicate device in China: Yes□ No☑

Protocol Version No./Date: V1.0/20230718

Clinical Trial Site: The First Affiliated Hospital of Naval Medical University

Principal Investigator: Liao Zhuan

Confidentiality

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Protocol Summary

Study Title	Real-World Clinical Study on the Efficacy of Disposable Gastrointestinal Vibrating Capsule (Vibrabot Capsule) for Chronic Functional Constipation
Study Purpose	Through this real-world study, to analyze the response of functional constipation patients with different severity, treatment status, capsule dosage, and combined medication to Vibrabot capsule, as well as the duration of efficacy maintenance during the follow-up period; to compare the efficacy with patients treated with drugs or other therapies during the same period, explore the possibility of curing functional constipation patients, further improve the treatment satisfaction of constipation patients, and promote the establishment and application of consensus or guidelines for the use of Vibrabot capsule in treating functional constipation.
Investigational Device	Device Name: Disposable Gastrointestinal Vibrating Capsule (Vibrabot Capsule) Model: ADVC-3 Manufacturer: ANKON Medical Technologies (Shanghai) Co., Ltd.
Study Population	Patients with chronic functional constipation
Number of Subjects to be Included	300
Study Design	This study is a multi-center prospective cohort study, which plans to include 300 patients with chronic functional constipation to treat with Vibrabot capsules, and at the same time, include ≥300 patients receiving constipation treatment during the same period. During the study, it is necessary to collect the patients' basic

	information, baseline constipation status and treatment information, capsule intake during treatment, and concomitant medication. During the treatment phase, patients follow the doctor's advice to receive Vibrabot capsule treatment and maintain stable dietary intake and exercise according to the constipation diagnosis and treatment guidelines. During the study, patients need to scan the QR code or search for the electronic questionnaire "Vibrabot Health" Official Account on WeChat, and fill in the relevant information during the treatment in the electronic questionnaire in a timely and truthful manner. The treatment effect of the patients is evaluated by assessing the number of occurrences of spontaneous bowel movements (SBM) and complete spontaneous bowel movements (CSBM).
Primary Endpoints	After treatment, whether the response rate of patients using the Vibrabot vibrating capsules alone reaches 50%. The definition of the responder is a patient with an average weekly increase of ≥1 complete spontaneous bowel movement (CSBM) compared to the baseline.
Secondary Endpoints	1) Proportion of constipated patients who use/do not use other constipation treatment methods during treatment and after the vibrating capsule treatment and at the end of follow-up; 2) Proportion of patients with an average increase of ≥1 CSBMs per week compared to the baseline period; 3) Proportion of respondents with an average of ≥3 SBMs per week during the treatment period; 4) Proportion of subjects with ≥3 SBMs per week and an increase of ≥1 CSBMs during at least 4 weeks of treatment compared to baseline; 5) Proportion of patients with an average increase of ≥1 CSBMs per

	week during the follow-up phase compared to the baseline period; 6) Proportion of patients with an average of ≥3 SBMs per week during the follow-up phase; 7) Proportion of patients with a reduction of ≥1 point in total PAC-QOL and PAC-SYM scores after treatment compared to the baseline period; 8) Proportion of patients with a reduction of ≥1 point in total PAC-QOL and PAC-SYM scores after follow-up compared to the baseline period; 9) Time of first use of laxative or enema after a course of vibrating capsule treatment (6 weeks); 10) Proportion of constipated patients (including different constipation types, occupations, age groups, BMI, gender, and baseline treatment status) responding to vibrating capsule treatment and at the end of follow-up.
Safety Endpoints	1. The incidence (%) and the number of device-related adverse events (AEs) and serious adverse events (SAEs); 2. The incidence (%) and the number of device defects.

1. About the Sponsor

Name:	ANKON Medical Technologies (Shanghai) Co., Ltd.
Address:	Building 2, No. 435 Chuanqiao Road, Pudong New Area, Shanghai
Contact No.:	18811789021

2. List of All Clinical Trial Sites and Investigators in the Multi-Center Clinical Trial

Site No.	Clinical Trial Site Name	Principal Investigator	Professional Title
01	The First Affiliated Hospital of Navy Medical University (Shanghai Changhai Hospital)	Liao Zhuan	Chief Physician, Professor

02	Ruijin Hospital, Shanghai Jiao Tong University School of Medicine	Zou Duowu	Chief Physician, Professor
03	Shanghai Tongji Hospital	Yang Changqing	Chief Physician
04	Shanghai Tenth People's Hospital	Liu Feng	Chief Physician, Professor
05	Shanghai First People's Hospital	Wanrong	Chief Physician
06	Shanghai Sixth People's Hospital	Zhu Jinshui	Chief Physician, Professor
07	Shanghai Ninth People's Hospital	Meng Xiangjun	Chief Physician
08	Shanghai Yangpu District Central Hospital	Li Li	Chief Physician
09	Shanghai Pudong New Area Gongli Hospital	Shi Yihai	Chief Physician

3. Purpose and Content of the Clinical Trial

3.1 Purpose of the Clinical Trial

Through this real-world study, to analyze the response of functional constipation patients with different severity, treatment status, capsule dosage, and combined medication to Vibrabot capsule, as well as the duration of efficacy maintenance during the follow-up period; to compare the efficacy with patients treated with drugs or other therapies during the same period, explore the possibility of curing functional constipation patients, further improve the treatment satisfaction of constipation patients, and promote the establishment and application of consensus or guidelines for the use of Vibrabot capsule in treating functional constipation.

3.2 Content of the Clinical Trial

This study is a multi-center clinical trial. Patients are considered eligible for this study if they meet the inclusion criteria and do not meet any of the exclusion criteria. This study plans to include 300 patients with chronic functional constipation to treat with Vibrabot capsules for at least 6 weeks, and ≥300 patients with constipation receiving

other treatments concurrently. The patients, based on their treatment needs and preferences, and after comprehensive consideration by clinical doctors, will undergo vibrating capsule treatment, other treatments, or combination therapy. After entering the study, patients should maintain stable dietary intake (including high-fiber diet, fiber supplements, probiotics, etc.) and exercise according to the recommendations of the constipation diagnosis and treatment guidelines.

During the entire clinical study period, patient-related information will be collected according to the specified time points in the protocol to evaluate the response of functional constipation patients with different severity levels to Vibrabot capsules.

Patients are considered eligible for this study if they meet the inclusion criteria and do not meet any of the exclusion criteria. This study plans to include 300 patients with chronic functional constipation to treat with Vibrabot capsules for at least 6 weeks or more.

The patients, based on their treatment needs and preferences, and after comprehensive consideration by clinical doctors, will undergo vibrating capsule treatment. After entering the study, patients should maintain stable dietary intake (including high-fiber diet, fiber supplements, probiotics, etc.) and exercise according to the recommendations of the constipation diagnosis and treatment guidelines.

4. Background of the Clinical Trial

Constipation is characterized by a decrease in bowel movements, dry and hard stools, and difficulty in defecation. With changes in diet, faster pace of life, and social psychological factors, the prevalence of chronic constipation is on the rise. The global incidence of chronic constipation is 14%, while the prevalence of chronic constipation in adults in China is 4.0% to 10.0%. The prevalence of functional constipation in China is 6%. The high-risk groups for constipation include the elderly, women,

diabetics, those taking opiates, antipsychotic drugs, or bedridden patients. Occupation, lifestyle, dietary habits, mental health, family history of constipation, and BMI are factors related to constipation.

Constipation affects patients' quality of life, and some patients abuse laxatives or repeatedly seek medical treatment, increasing medical costs. The main treatments for constipation are adjusting lifestyle, medication, psychotherapy, biofeedback, and surgery. However, these methods often have side effects, and patient satisfaction is still relatively low. A new approach needs to be explored to address this clinical problem.

The Disposable Gastrointestinal Vibrating Capsule System (Vibrabot capsule) (NMPA Device Approval No. 20223090282) is the world's first approved and marketed product for treating constipation through purely physical means. It can provide intermittent comfortable massages to the digestive tract, activate the intestinal neural network, awaken intestinal motility, and help alleviate constipation issues. Clinical study results show that the product is safe to use and can increase the frequency of bowel movements in patients with chronic functional constipation.

This study focuses on post-marketing clinical study for patients with functional constipation of varying severity, further evaluating the efficacy of the product in a large sample population.

5. Product Features, Composition, Working Principle, and Action Mechanism

5.1 Product Features

1. Safe and hygienic: disposable, preventing cross infection.
2. Easy to use: simply take one capsule each time
3. Painless and non-invasive: the use process is painless and non-invasive
4. No side effects: the capsule produces physical stimulation to provoke the intestine's natural peristaltic wave, free of any toxic side effects.

5.2 Product Composition, Working Principle, and Action Mechanism

5.2.1 Structural Characteristics

Main parameters of Vibrabot capsule: nominal diameter: 11.8±1mm; nominal length: 26.7±1mm; nominal weight: 4.5±1g.

5.2.2 Working Principle

After the patient swallows the Vibrabot capsule, the capsule runs through the stomach → duodenum → jejunum and ileum → colon. According to the clinical data and configuration settings, the capsule will reach the colon and vibrate 8 hours after activation for ≥ 180 minutes in a cycle at low, medium, and high frequencies sequentially. The capsule relieves and treats constipation by massaging the colon wall through motor vibration to relieve colon muscle spasms and promote colonic peristalsis.

6. Selection of Subjects

6.1 Inclusion Criteria

1. Patients who can be diagnosed with functional constipation according to the Rome IV criteria.
2. Patients who consent to participate in this trial and voluntarily sign the informed consent form (ICF).

6.2 Exclusion Criteria

1. People who are not eligible for surgery or refuse to undergo any abdominal surgery;
2. People with known or suspected gastrointestinal obstruction, stenosis, diverticulum, bleeding, malformation, and fistula.
3. People allergic to polymeric materials;

4. People implanted with cardiac pacemakers and using gastrointestinal pacemakers;

5. People with abdominal aortic aneurysms, gastrointestinal vascular lesions, ulcers, and lesions with bleeding tendencies.

6. People with dysphagia;

7. Pregnant women;

8. People with severe depression and anxiety and severe acute gastrointestinal lesions.

9. People with other conditions, so the investigator considers them not eligible for this study.

7 . Overall Design

This study is a multi-center, prospective cohort study based on real-world clinical trial design, planning to include 300 patients with chronic functional constipation to treat with Vibrabot capsules, and concurrently include ≥300 patients with functional constipation to treat by other methods.

During the study, it is necessary to collect the patient's basic information, baseline constipation status and treatment information, capsule intake during treatment, and concomitant medication. During the treatment phase, patients follow the doctor's advice to receive Vibrabot capsule treatment and maintain stable dietary intake and exercise according to the constipation diagnosis and treatment guidelines.

During the study, the patients need to scan the QR code or search for the electronic questionnaire "Vibrabot Health" Official Account on WeChat, and fill in the relevant information during the treatment in the electronic questionnaire in a timely and truthful manner. The treatment effect of the patients is evaluated by assessing the number of occurrences of spontaneous bowel movements (SBM) and complete spontaneous bowel movements (CSBM).

Note:

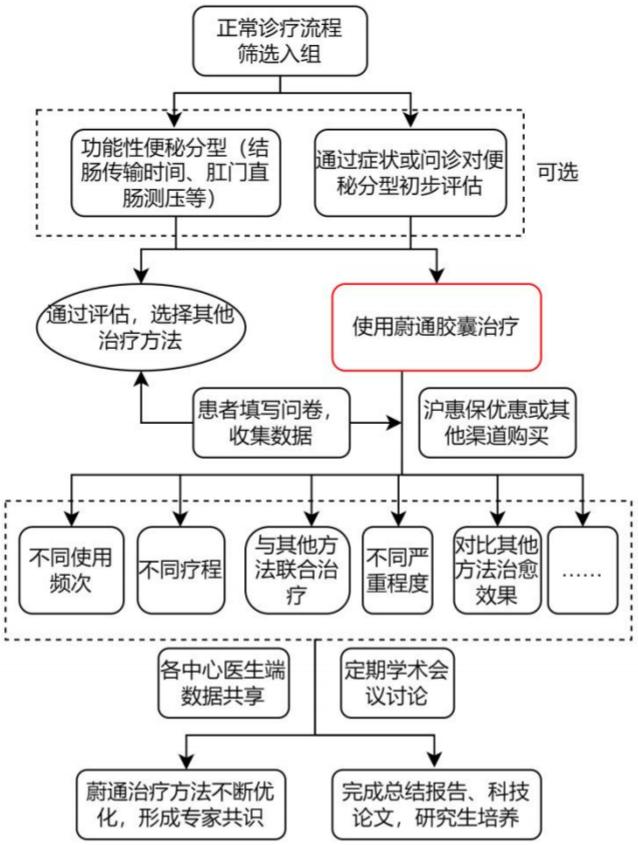
Spontaneous bowel movement: No medication used within 24 hours before bowel movement.

Spontaneous bowel movement: No medication was used within 24 hours before defecation, and there is a feeling of complete fecal evacuation.

7.1 Trial Procedure

7.1 .1 Trial Flow Chart

	Visit 1 (0~1 day)	**Visit 2 (Week 2 ±3 days)**	**Visit 3 (Week 4 ±3 days)**	**Visit 4** (Week 6±3 days)	**Visit 5 (Week 10 ±3 days)**
Informed Consent	X				
Baseline Information	X				
Inclusion/Exclusion Criteria	X				
Prescription Vibrabot capsule treatment/Medication treatment	X	X	X		
Guide patients to use the "Vibrabot Health" Official Account	X				
Fill out the *Baseline Period Questionnaire* (including scale) in the Official Account	X				
Fill out the *Daily Bowel Movement Questionnaire*' and *Constipation Symptom Self-Assessment Scale* and *Assessment Scale for Quality of Life with Constipation*		X	X	X	X
Concomitant treatment	X	X	X	X	X
Adverse event	X	X	X	X	X



正常诊疗流程筛选入组

Screening for Inclusion Based on Normal Diagnosis and Treatment Procedure

<table>
<tr><td colspan="2">功能性便秘分型(结肠传输时间、肛门直肠测压等)

Functional Constipation Subtyping (Colon Transit Time, Anorectal Manometry, etc.)</td><td colspan="2">通过症状或问诊对便秘分型初步评估

Preliminary Assessment of Constipation Subtype Based on Symptoms or Interview</td><td colspan="3">可选 Optional</td></tr>
<tr><td colspan="3">通过评估，选择其他治疗方法

Selecting Alternative Treatment Methods through Assessment</td><td colspan="3">使用蔚通胶囊治疗

Treatment with Vibrabot Capsule</td></tr>
<tr><td colspan="3">患者填写问卷，收集数据

Patients Complete Questionnaires to Collect Data</td><td colspan="3">沪惠保优惠或其他渠道购买

Purchase through Shanghai-Huibo Health Benefits or Other Channels</td></tr>
<tr><td>不同使用频次

Different Frequency of Use</td><td>不同疗程

Different Treatment Duration</td><td>与其他方法联合治疗

Combination Treatment with Other Methods</td><td>不同严重程度

Various Severity Levels</td><td>对比其他方法治愈

Comparing Treatment Efficacy with Other Methods</td><td>.....</td></tr>
<tr><td colspan="3">各中心医生端数据共享

Data Sharing among Medical Centers</td><td colspan="3">定期学术会议讨论

Regular Academic Meetings for Discussion</td></tr>
<tr><td colspan="3">蔚通治疗方法不断优化，形成专家共识

Continuous Optimization of the Vibrabot Treatment Method, Leading to Expert Consensus</td><td colspan="3">完成总结报告、科技论文，研究生培养

Completion of Summary Report, Scientific Paper, and Training of Graduate Students</td></tr>
</table>

7.1.2 Visit Content

Each patient will undergo a series of study visits, including screening, treatment visit, and follow-up visit. The visit process is briefly described as follows:

Visit 1 (0 ~ 1 day) - Baseline/Screening Period:

This visit includes:

The patient will sign an informed consent form;

Set the inclusion/exclusion criteria;

Guide patients to fill out the questionnaire using the Official Account and complete the *Baseline Period Questionnaire* in the Official Account.

Prescription Vibrabot capsule treatment or other treatment options.

Visit 2 (Week 2 ±3 days) - Treatment Period 1:

This visit includes:

Fill out the *Daily Bowel Movement Questionnaire* in the WeChat Official Account every day, take Vibrabot capsules on time or opt for other treatment plans;

Fill out the *Constipation Symptom Self-Assessment Scale* and *Assessment Scale for Quality of Life with Constipation* in the Official Account every 2 treatment weeks.

Record adverse events and concomitant treatments;

Prescription Vibrabot capsules or other treatment options.

Visit 3 (Week 4±3 days) - Treatment Period 2

This visit includes:

Fill out the *Daily Bowel Movement Questionnaire* in the WeChat Official Account every day, take Vibrabot capsules on time or opt for other treatment plans;

Fill out the *Constipation Symptom Self-Assessment Scale* and *Assessment Scale for Quality of Life with Constipation* in the Official Account every 2 treatment weeks.

Record adverse events and concomitant treatments;

Prescription Vibrabot capsules or other treatment options.

Visit 4 (Week 6 ±3 days) - Treatment Period 3

This visit includes:

Fill out the *Daily Bowel Movement Questionnaire* in the WeChat Official Account every day, take Vibrabot capsules on time or opt for other treatment plans;

Fill out the *Constipation Symptom Self-Assessment Scale* and *Assessment Scale for Quality of Life with Constipation* in the Official Account every 2 treatment weeks.

Record adverse events and concomitant treatments.

Visit 5 (Week 10±3 days) - Follow-up Period:

This visit includes:

Fill out the *Daily Bowel Movement Questionnaire* in the WeChat Official Account every day;

Fill out the *Constipation Symptom Self-Assessment Scale* and *Assessment Scale for Quality of Life with Constipation* in the Official Account every 2 treatment weeks;

Record adverse events and concomitant treatments.

7.2 Effectiveness Evaluation Methods

7.2.1 Primary Efficacy Endpoints

After treatment, whether the response rate of patients using the Vibrabot vibrating capsules alone reaches 50%.

The definition of the responder is a patient with an average weekly increase of ≥1 complete spontaneous bowel movement (CSBM) compared to the baseline.

7.2 Secondary Efficacy Endpoints

1) Proportion of constipated patients who use/do not use other constipation treatment methods during treatment and after the vibrating capsule treatment and at the end of follow-up;

2) Proportion of patients with an average increase of ≥1 CSBMs per week compared to the baseline period;

3) Proportion of respondents with an average of ≥3 SBMs per week during the treatment period;

4) Proportion of subjects with ≥3 SBMs per week and an increase of ≥1 CSBMs during at least 4 weeks of treatment compared to baseline;

5) Proportion of patients with an average increase of ≥1 CSBMs per week during the follow-up phase compared to the baseline period;

6) Proportion of patients with an average of ≥3 SBMs per week during the follow-up phase;

7) Proportion of patients with a reduction of ≥1 point in total PAC-QOL and PAC-SYM scores after treatment compared to the baseline period;

8) Proportion of patients with a reduction of ≥1 point in total PAC-QOL and PAC-SYM scores after follow-up compared to the baseline period;

9) Time of first use of laxative or enema after a course of vibrating capsule treatment (6 weeks);

10) Proportion of constipated patients (including different constipation types, occupations, age groups, BMI, gender, and baseline treatment status) responding to vibrating capsule treatment and at the end of follow-up.

7.3 Safety Evaluation Method

The safety is evaluated by the occurrence of device-related adverse events (AEs) and device-related serious adverse events (SAEs) throughout the study period.

7.4 Criteria and Procedure for Stopping the Trial/Treatment

1. The patient or their representative requests to withdraw from the clinical trial;
2. The subject fails to follow the requirements of the standard operating protocol of the trial and seriously violates the protocol so that the data of this subject are unreliable.
3. An AE or SAE occurs, rendering the patient unfit to continue in this clinical trial.
4. Lost to follow-up;
5. Those who, in the investigator's opinion, are unfit to continue participating in this clinical trial.

7.5 Expected Overall Duration of Clinical Trial and Reasons for Determination

The overall duration of the clinical trial includes the signing of the clinical trial protocol for all participating hospitals, ethical review meetings and post-meeting correction as per comments, trial initiation, patient enrollment and follow-up time, as well as the collection, statistics, and summary report writing time for trial data. It is expected to be from September 2023 to October 2025.

Reason: The estimated overall duration of this trial is approximately 2 years, based on the number of outpatient visits required for the application of test products in each hospital, the scheduling of patient follow-up times, and the process systems of various hospitals.

8. Statistical Considerations

8.1 Statistical Analysis of the Population

Sample Size Calculation

H0: The effectiveness rate of vibrating capsule treatment for constipation ≤50%

H1: The effectiveness rate of vibrating capsule treatment for constipation >50%

In a single-group design, if the study goal is to evaluate the effectiveness of vibrating capsule

treatment for constipation and compare it with the expected 50% effectiveness rate, then a one-sample proportion test can be considered for sample size calculation.

Sample size calculation formula for single sample proportion test is:

$$n = \frac{\left[Z_{1-\alpha}\sqrt{P_0(1-P_0)} + Z_{\beta}\sqrt{P_T(1-P_T)}\right]^2}{(P_T - P_0)^2}$$

Where:

(1) p is the overall expected success rate (here it is estimated that the effectiveness of treating constipation with vibrating capsules is 50%);

(2) p0 is the success rate under the null hypothesis (assuming a 40% success rate under the null hypothesis);

(3) The probability of Type I error α is set to 0.05, and the probability of Type II error β is set to 0.2 (i.e., the statistical power is 1−β=0.8);

At least 191 participants are needed for this study. Assuming a 20% loss to follow-up, the final sample size required is 239. Considering this is a real-world study and taking into account the outpatient volume of the participating center, it is planned to enroll 300 patients who will take vibrating capsules for 6 weeks, and at the same time, include ≥300 patients undergoing constipation treatment during the same period.

(1) Full Analysis Set (FAS) is the set of patients that is as close as possible to the ideal implied by the Intention-to-Treat principle. Specifically, in this trial, the FAS is the data set of all patients with baseline evaluation who take at least one capsule treatment/other treatment option. Missing data for primary efficacy endpoints in the FAS will be imputed according to certain rules while missing data for secondary efficacy endpoints will not be imputed.

(2) Per Protocol Set (PPS) is a subset of the FAS and refers to the set of subjects who meet the inclusion criteria, do not meet the exclusion criteria, complete the treatment, and have no protocol violations. Specifically, in this trial, the PPS includes the patients in the FAS who:

a) complete the full treatment,

b) meet the inclusion criteria and do not meet the exclusion criteria,

c) have good compliance with capsule administration/other treatment, and

d) have a complete evaluation of the primary efficacy endpoints.

The PPS is a secondary population for efficacy analysis and is used for sensitivity analysis during efficacy analysis.

(3) Safety Data (SS) includes all randomized patients. It is the primary population for safety analysis.

8.2 Statistical Analysis Principle

SAS (version 9.2 or above) or R is used in this study for statistical analysis. Measurement data are presented as the number of cases, mean±standard deviation, median, minimum, maximum, and quartiles. Count data are presented as frequencies and percentages. Parametric methods are first considered for statistical tests, and non-parametric methods are used if the data distribution differs significantly from the distribution assumed by the statistical test.

A two-sided hypothesis test is used for difference test, and the alpha level is set to 0.05 (two-sided); that is, if the p-value is<0.05, the difference is considered statistically significant.

8.3 Statistical Procedure for all Data

The investigators should submit completed case report forms to the CRA in a timely manner. The CRA should check the case report forms, verify the original records, and check for any omissions or errors. After ensuring there are no errors, the CRA should deliver the forms to the principal investigator. If there are any questions about the case report forms, the CRA should ask the investigators, who should respond promptly and make any necessary data modifications and confirmations.

Do not fill in missing data.

8.4 Procedure for Handling Deviation of Report from the Original Statistical Plan

Any changes to the original statistical plan should be explained and justified in the protocol and/or in the final report.

9 . Risk-Benefit Analysis

9.1 Benefits of the Study

During the trial period, the collected information can help doctors better assess patients' constipation conditions and treatments, so the patients can know their health status. Important information obtained from this study may provide information for future patients and medical staff who use such device, helping to increase their own or other patients' treatment options.

9.2 Risks of the Study

The risk of using the Vibrabot capsule during treatment is relatively low, with capsule retention being the most concerning adverse event. The current systematic review reported in international authoritative journals mentions that the retention rate of capsule devices is about 0.73% (95% confidence interval: 0.59-0.89%). There has not been a single case of capsule-related death since the use of capsule devices. Even if capsule retention occurs clinically, it can indirectly prompt patients to receive early diagnosis and treatment, and the benefits to patients are greater than the risks. If the capsule is not expelled after 14 days, an abdominal upright X-ray is required to confirm whether the capsule is retained and its approximate location. Retention is not a complication caused by the capsule but is due to the patient's hidden condition, not the quality of the capsule itself. The current methods for removing retained capsules include spontaneous expulsion, drug treatment, surgery, or endoscopic removal. Drug treatment can alleviate intestinal mucosal edema and inflammatory response, which

may cause the inflammatory stricture to recede and the retained capsule to pass spontaneously.

During the capsule vibration process, you may experience symptoms such as bloating, abdominal pain, and diarrhea. If serious adverse events occur, you can contact the investigator immediately for appropriate treatment.

10. Feasibility Analysis of the Trial

1) The Vibrabot capsule has been approved by the National Medical Products Administration (NMPA), and its safety and efficacy have been verified by registered clinical trials.

2) The common risk of capsule devices is capsule retention. In this study, the study physician has excluded subjects with contraindications to the Vibrabot capsule according to the exclusion criteria to avoid capsule retention, and the dosage of similar products approved by the FDA is five capsules/week, it is safe for the subjects in this trial to take five capsules per week.

3) Shanghai Changhai Hospital is a is a tertiary hospital with medical device clinical trial qualification and sufficient patient sources. The co-investigators have rich clinical experience and received GCP and related training. The investigators will be trained on the protocol and product details prior to the study implementation to ensure that they can strictly follow the protocol for examination and treatment, and the subjects will be required to strictly follow the physician's advice.

11. Quality Control of the Clinical Trial

Investigator’s Qualification: Investigators participating in this clinical trial are qualified and have the professional background and ability to conduct this trial.

Investigator training: Prior to the start of the clinical trial, all investigators will be trained to have a full understanding of the clinical trial protocol and the specifics of each indicator.

Informed consent will be carefully executed by the investigators so that the subjects fully understand the requirements of the trial.

Clinical trial monitoring: The sponsor will appoint a CRA to pay regular monitoring visits on the implementation of the clinical trial. The CRA will check the completeness of medical records and the correctness of case report forms and verify the trial data.

Data Management: During the entire test, the main tool used is the "Vibrabot Health" electronic questionnaire to collect patients' treatment information. Patients are required to record their test data completely, truthfully, clearly, and objectively. The electronic questionnaire can directly store test data, avoiding errors from secondary transcription.

12. Ethical Issues and Informed Consent

12.1 Ethical Considerations

12.1.1 Ethics and Regulations

This trial complies with the requirements of the Declaration of Helsinki, the *Good Clinical Practice for Medical Devices*, and other applicable national laws and regulations.

12.1.2 Medical Ethics Committee

Prior to the clinical trial, the investigator submits the trial protocol, ICF, and other relevant documents to the EC of the clinical trial site and obtains EC’s approval before the trial can be conducted. Any modification of the trial protocol must be approved by the EC before implementation. SAEs during the trial shall be submitted to the EC in writing in a timely manner.

12.2 Informed Consent Process

Before enrollment, the investigator must explain to the subject or his/her guardian the details of the clinical trial, including the nature, purpose, content, expected efficacy, possible AEs and countermeasures of the trial, and answer questions from the subject. Subjects are enrolled after they fully understand the trial and sign the ICF. The ICF shall be signed by the investigator and the subject or his/her guardian in duplicate, and each party keeps one copy.

13. Provisions for Reporting Adverse Events and Device Defects

13.1 Definition of Adverse Events and Reporting Requirements

Definition: An AE is any untoward medical occurrence in a clinical trial, whether or not considered device-related.

13.1.1 Severity of Adverse Events

Mild AE: Event results in perceptible signs or symptoms, not requiring discontinuation of the device and treatment;

Moderate AE: Event results in tolerable signs and symptoms, requiring treatment; does not interfere with daily activities;

Severe AE: Event results in intolerable symptoms and signs, requiring discontinuation of the device and treatment; interferes with daily activities.

Note: AE severity is used to describe the intensity of an event. An event is not necessarily an adverse event.

13.1.2 Event Relationship to the Investigational Device

Definitely related: the use of the device and the reaction occurrence follow a reasonable temporal sequence; the reaction stops, rapidly relieves, or reduces after

stopping using the device; the reaction recurs or significantly gets worse after using the device again; supported by literature; and the influence of other factors, such as underlying diseases, have been excluded.

Probably related: no repeated device use and other criteria are the same as "definitely related"; or although other devices or drugs have been used in combination, the possibility of the reaction resulting from using concomitant devices or drugs can be excluded.

Possibly related: the time of the occurrence of the reaction is closely related to the use of the device; supported by the literature; however, more than one device or drug, in this case, result in the adverse reaction, or other factors, such as underlying diseases, cannot be excluded.

Unlikely related: the time of the occurrence of the reaction is not closely related to the use of the device; the reaction does not belong to the known adverse reactions to the device, and the development of the underlying disease may have similar clinical reactions.

Unrelated: the use of the device and the reaction occurrence do not follow a reasonable temporal sequence; the reaction is not the type of adverse reaction to the device; the reaction can be explained by the patient's clinical status or other reasons; the reaction relieves or disappears after excluding the clinical symptoms or other reasons.

13.1.3 Adverse Event Record

All AEs that occur during the study must be truthfully recorded on the adverse event form. The investigator shall give targeted treatment for the AE and follow up until the symptoms are stable or disappear.

13.2 Device Defects

Device defects are unreasonable risks that may endanger human health and life in the normal use of medical devices during clinical trials, such as labeling errors, quality

problems, malfunctions, etc.

13.3 Definition of Serious Adverse Events

Serious adverse events are events that occur during the clinical trial that result in death; serious deterioration in the health of the patient, user, or others, including life-threatening illness or injury, permanent impairment of a body structure or a body function, requiring inpatient hospitalization or prolongation of existing hospitalization, requiring medical or surgical intervention is required to avoid permanent impairment of a body structure or a body function; resulting in fetal distress, fetal death or congenital anomalies/birth defects.

13.4 Reporting Procedures and Contact Information

13.4.1 SAE Reporting Procedure

In case of any SAE in the clinical trial, the investigator shall immediately take appropriate therapeutic measures for the subject, report the SAE in writing to the medical device clinical trial management department of the clinical trial site, and notify the sponsor in writing via the management department. The management department shall report in writing to the competent EC within 24 hours. In the case of death, the clinical trial site and the investigator shall provide all the information required to the EC and the sponsor.

13.4.2 Device Defect Reporting Procedure

The investigator shall record the device defects found during the clinical trial, analyze the cause of the defects with the sponsor, form a written analysis report, and put forward the opinion to continue, suspend or terminate the trial. The medical device clinical trial management department of the clinical trial site shall report them to the EC for review.

The sponsor shall report the SAEs and device defects that may lead to SAEs to other

clinical trial sites and investigators of the trial, and its medical device clinical trial management department shall promptly notify the EC of the SAEs and device defects.

14. Deviations from the Clinical Trial Protocol and Provisions for Modification of the Protocol

14 Deviations from the Clinical Trial Protocol

The investigator shall not alter or deviate from the trial protocol except in emergencies to protect the lives and safety of the subject. If the investigator deviates from the trial protocol in an emergency to protect the life and safety of the subject, he or she shall notify the sponsor and the EC (if applicable) of such deviation and the deviations that impact the scientific validity of the clinical study.

All protocol deviations and their causes and dates of occurrence must be documented and reported to the sponsor. The sponsor shall timely review and evaluate the deviations and take necessary corrective and preventive actions, including, but not limited to, notifying the center to do retraining or close the center. Protocol deviations may include, but are not limited to:

Enrolled patients do not meet the inclusion criteria, or they meet the exclusion criteria;

Failure to perform or failure to correctly perform the tests and/or assays specified in the clinical trial protocol;

Failure of the investigator to report AEs or device defects within the period specified in the clinical trial protocol;.

Patients are enrolled during the lapse in EC approval.

14 Provisions for Modifications of the Clinical Trial Protocol

In general, clinical trial protocols shall be strictly implemented once they are approved by the EC. If supplements or revisions to the protocol are necessary after the

trial has started, the protocol can only be revised with the mutual agreement of the investigator and the sponsor and be submitted to the EC for approval before the revised one can be implemented. The modification of the protocol shall be recorded in detail, and the record shall include the specific contents and reasons for the modification, the correspondence letter submitted to the EC for re-approval, and the approval document of the EC.

15. Direct Access to Source Data and Files

The investigator/site allows direct access to raw data/information to relevant personnel for trial-related monitoring, verification, EC evaluation, and regulatory inspections.

By signing the ICF, the patient grants the sponsor or the sponsor's designee access to information in his or her medical record that is relevant to the trial. As part of the informed consent, the investigator obtains the patient's permission to allow the CRA or regulatory agency to review any records identifying the patient in this clinical trial at the trial site, but they must keep such records confidential. The sponsor shall not disclose the patients' personal information under local data protection laws.

16. Contents Covered by the Clinical Trial Report

The investigator shall follow the clinical trial protocol to verify the efficacy and safety of the experimental treatment plans and complete the clinical trial report. The clinical trial report shall be signed and dated by the investigator, reviewed, dated, and affixed with a seal by the medical device clinical trial management department of the clinical trial site, and then it shall be submitted to the sponsor.

17. Confidentiality

The contents of this clinical trial and all accompanying information are confidential

and belong exclusively to the sponsor. The investigator shall keep confidential the patent applications, manufacturing processes, and unpublished data provided by the sponsor, which shall not be disclosed to any third party except with the consent of the sponsor, and such confidentiality obligations shall survive the termination or completion of this trial.

18. Agreement on Publication of Trial Results

The investigator has the right to write papers, reports, etc., on this trial, but is required to notify the sponsor in writing prior to publication and shall not violate the confidentiality obligations specified in this protocol.

19. References:

[1] Chinese Medical Association, et al. Guidelines for the Diagnosis and Treatment of Chronic Constipation in Primary Care (2019). Chinese General Practitioner Magazine, 2020. 19(12): Pages 1100-1107.

[2] Scott S M, Simrén M, Farmer A D, et al. Chronic constipation in adults: Contemporary perspectives and clinical challenges. 1: Epidemiology, diagnosis, clinical associations, pathophysiology and investigation[J]. Neurogastroenterology & Motility, 2021, 33(6): e14050.

[3] Chinese Expert Consensus on Chronic Constipation (2019, Guangzhou) [J]. Chinese Journal of Digestion, 2019(09):577-598.

[4] Li Junxiang, Chen Ju, Ke Xiao. Consensus on the combined diagnosis and treatment of functional constipation in traditional Chinese and Western medicine (2017)[J]. Chinese Journal of Integrated Traditional and Western Medicine on Digestion, 2018, 26(01): 18-26.

[5] Camilleri, M., Kerstens, R., Rykx, A., & Vandeplassche, L. (2008). A placebo-controlled trial of prucalopride for severe chronic constipation. The New England journal of medicine, 358(22), 2344–2354.

[6]Zhu, J. H., Qian, Y. Y., Pan, J., He, C., Lan, Y., Chen, W. N., Wang, B. M., Zhao, W., Li, J. N., Li, X. Q., Lv, B., Fan, Y. H., Zuo, X. L., Li, Z., Zou, D. W., Li, Z. S., & Liao, Z. (2022). Efficacy and safety of vibrating capsule for functional constipation (VICONS): A randomised, double-blind, placebo-controlled, multicenter trial. EClinicalMedicine, 47, 101407.

Investigator's Statement:

I will:

1. Conduct this clinical trial in strict compliance with the Declaration of Helsinki, existing Chinese laws and regulations, and this trial protocol.

2. Record all required data accurately in the case report form and complete the clinical trial report on time.

3. Use the investigational device only for this clinical trial, accurately and completely record the receipt and usage of the investigational device during this clinical trial and keep the records.

4. Cooperate with the CRA and verifiers authorized or assigned by the Sponsor, and regulatory authorities to monitor, verify, and inspect this clinical trial.

5. Strictly adhere to the terms of the clinical trial contract/agreement signed.

I have thoroughly read this clinical trial protocol, including the above statements, and I agree to all of the above.

Investigator's Opinion Signature YYYY/MM/DD

Opinion of the Medical Device Clinical Trial Site Signature (Seal) YYYY/MM/DD