

# Exploring the Safety, Effectiveness, and Cost-Effectiveness of a Chinese Patent Medicine (Fufang E'jiao Syrup) for Alleviating Cancer-Related Fatigue: A Protocol for a Randomized, Double-Blinded, Placebo-Controlled, Multicenter Trial

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## Abstract

**Objective:** To provide higher level evidence on the benefits of a Chinese patent medicine (CPM) (Fufang E'jiao Syrup, FFEJS) for alleviating cancer-related fatigue (CRF), this article describes a protocol for a randomized controlled trial. **Methods/design:** We designed a double-blind, placebo-controlled stratified permuted block randomization clinical trial on CRF among 3 types of cancer in China. Participants will be equally allocated to FFEJS group or placebo group according to the randomization sequence and the hospitals they were enrolled at. Each patient will receive 20 ml of either the study formula FFEJS or a placebo formula, 3 times a day for 6 weeks. The follow-up period will be another 4 weeks for safety evaluation. The primary outcome is the difference in improvement of fatigue as measured with the Revised Piper Fatigue Scale-Chinese Version (RPFS-CV). Secondary outcomes include change in fatigue (measured by routine blood panel and hormones in peripheral blood) and QoL (measured by Edmonton symptom assessment scale and Functional Assessment of Cancer Therapy). Patient safety will be measured by liver, renal or cardiac damage, and the risk of FFEJS having a tumor promotion and progression effect will be monitored throughout this study. Cost-effectiveness will also be evaluated mainly by incremental cost per each quality-adjusted life year gained. **Discussion:** This article describes the study design of a CPM for CRF in patients with advanced cancer through exploring the effectiveness, safety, and cost-effectiveness of FFEJS. **Trial registration:** ClinicalTrials.gov, NCT04147312. Registered on 1 Sep 2019.

## Keywords

cancer-related fatigue, Fufang E'jiao syrup, traditional Chinese medicine, Chinese patent medicine, randomized-controlled trial, multicenter

Submitted February 8, 2021; revised February 8, 2021; accepted February 25, 2021

## Introduction

Cancer-related fatigue (CRF) is a distressing feeling of tiredness or exhaustion induced by cancer or cancer treatments, commonly experienced by cancer patients.<sup>1</sup> Approximately 70% to 90% of patients with advanced cancer frequently suffer from CRF, while 60% to 100% of patients receiving either chemotherapy or radiotherapy also experience CRF.<sup>2-4</sup> Studies showed that CRF is associated with poor quality of life (QoL) and functional status, which results in less compliance with conventional therapies and

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reduced self-efficacy.<sup>5</sup> At present, the etiology and underlying mechanisms of CRF are not fully understood. In addition to its association with adverse effects of cancer and cancer therapy, comorbid conditions including anemia, cachexia, sleep disorders, and depression are also reported to be associated with CRF.<sup>6-8</sup> Currently, there is limited evidence to support specific pharmacological treatments for the management of CRF.<sup>9</sup> Several complementary and alternative medicine (CAM) approaches such as yoga, exercise, psychosocial interventions, massage, and acupuncture have been reported to achieve efficacy in alleviating CRF when used as an adjuvant therapy.<sup>10-14</sup>

As a preeminent CAM therapy, Chinese herbal medicine (CHM) is widely used in clinical practice in China for the management of CRF. According to traditional Chinese medicine (TCM) theory, Qi refers to the energy flow within the body, while Blood refers to the source of physiological nourishment. Within the conceptual framework of TCM, deficiency of Qi and Blood are considered the main pathogenic factors that cause CRF.<sup>15</sup> In a single arm clinical trial, the CHM formula Ren Shen Yang Rong Tang (RSYRT) was reported to reduce fatigue level from 7.06 to 3.30 on a numerical scale with a range from 0 to 10, without adverse events or toxicity.<sup>16</sup> In a randomized controlled trial (RCT) conducted by a Korean team on 40 patients, the CHM formula Bojungikki-tang (also known as Bu Zhong Yi Qi Tang, BZYQT) was also reported to improve CRF and QoL in cancer patients.<sup>17</sup> Currently, there is an ongoing RCT study which was designed to investigate a CHM formula's (Jianpi Shengsui, JPSS) effect on improving CRF only among non-small cell lung cancer (NSCLC) patients with relatively small sample size ( $n=50$ ).<sup>18</sup> While existing studies indicate that CHM might be effective to improve CRF as a potential therapeutic modality, specifically targeted to patients with TCM pattern diagnosis of deficiency of Qi and Blood syndrome, the evidence is still preliminary and insufficient.

Fufang E'jiao syrup (FFEJS, Supplemental File 1) is a National Medical Products Administration (NMPA) approved Chinese patent medicine (CPM) that has been marketed and utilized for the treatment of fatigue and anemia in China for approximately 40 years.<sup>19</sup> It had been shown to be effective for alleviating cancer-related or chemotherapy-induced anemia, as well as for the improvement of fatigue and QoL in cancer patients with randomized trials of small sample size.<sup>20-22</sup> Current studies of FFEJS have primarily focused on anemia as a primary outcome, and fatigue has only been assessed as a component within the measures of QoL as a secondary outcome. Moreover, the research findings have been limited by the design of existing studies, without strict eligibility criteria for inclusion of specific cancer types or therapies, and have been limited by small sample sizes, with recruitment drawn from only 1 or 2 centers. A phase II study of 73 patients including 7 cancer

types showed that FFEJS effectively alleviated CRF (remission rate 89.19 vs 61.11), and improved QoL and myelosuppression.<sup>23</sup> The 2 main components of FFEJS, Radix Ginseng, and Colla Corii Asini (Supplemental File 2), are commonly used among patients with CRF in both China and the United States as natural products respectively to tonify Qi and Blood.<sup>24-26</sup> FFEJS may be a potential therapeutic medicine for CRF, however there is currently insufficient higher level evidence to support its clinical application.

To explore the safety, effectiveness, and cost effectiveness of FFEJS for alleviation of CRF in advanced cancer patients, we designed a randomized, double-blind, placebo-controlled, and multicenter trial in China. Through this study, we hope to provide more evidence of CHM for alleviation of CRF.

## Methods and Design

### Study Setting

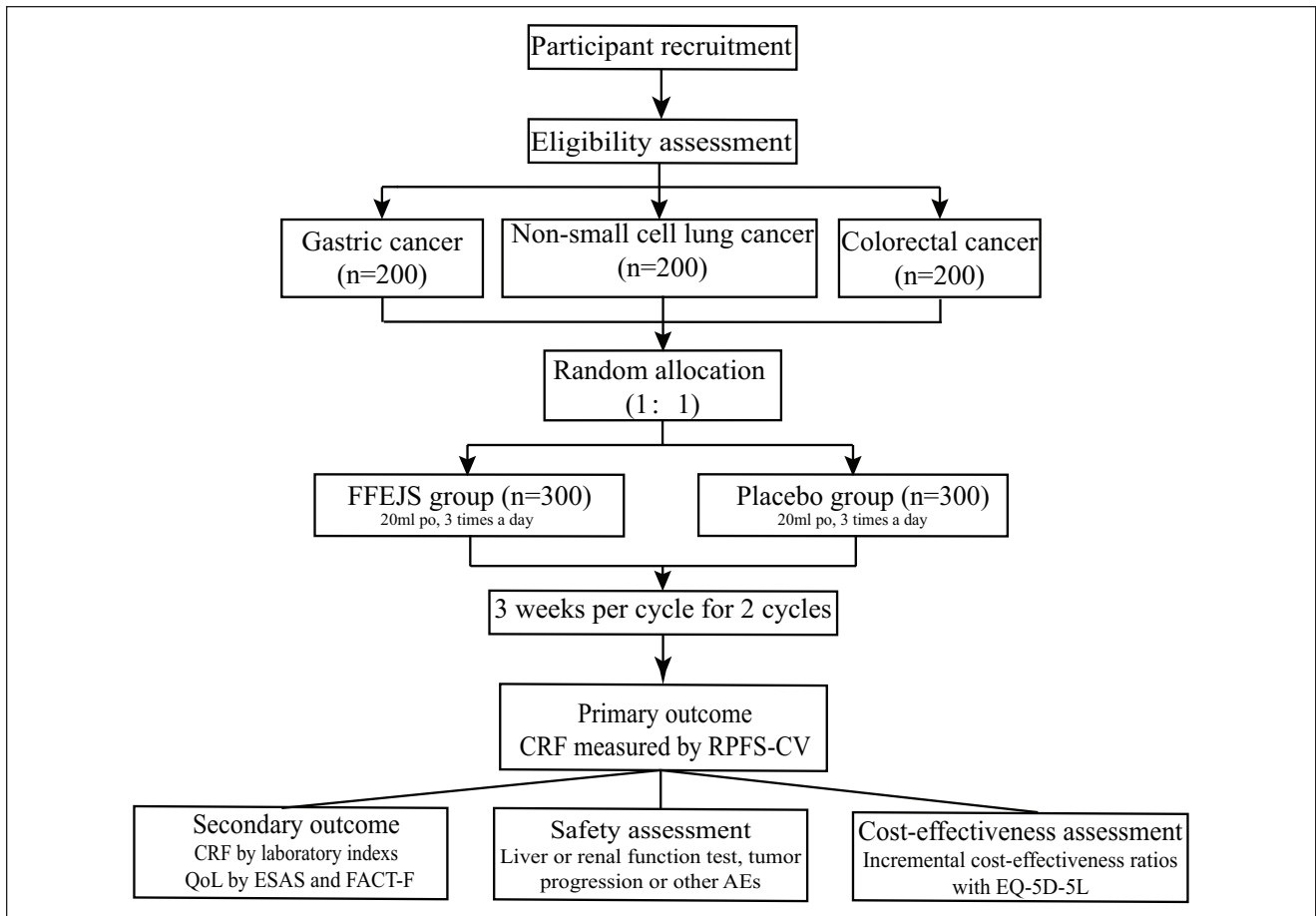
This study is a prospective, multicenter, double-blinded, placebo-controlled trial with stratified permuted block randomization, as shown in Figure 1. Eligible participants, as those with a diagnosis of CRF and the TCM pattern diagnosis of deficiency of Qi and Blood syndrome will be randomized according to a 1:1 ratio to receive either FFEJS or placebo for 6 weeks. Participants will be monitored and assessed for safety during an additional follow-up period of 4 weeks after the intervention.

This trial has been approved by the Ethics Committee of Xiyuan Hospital, China Academy of Chinese Medical Science (No. 2019XLA028-3) and registered at ClinicalTrials.gov (NCT04147312). The protocol and informed consent forms will also be approved by the institutional ethics committees at each of the participating clinical centers before the commencement of participant recruitment.

### Participants

We plan to enroll CRF patients with NSCLC, colorectal cancer, and gastric cancer from both outpatient and inpatient settings of 20 participating hospitals located in 9 provinces in China from October 2019 to December 2021 (Supplemental File 3). Participants will be recruited through advertisements and referrals starting from 31 October 2019. Recruitment advertisements will include the use of social media, and the placement of posters, and flyers in hospital and public areas, such as the cancer center and outpatient waiting halls.

The diagnosis of NSCLC, colorectal cancer, and gastric cancer for this trial is based on NCCN guidelines. TNM staging is according to the eighth staging standard of American Joint Committee on Cancer (AJCC).<sup>27</sup> The



**Figure 1.** Flow chart of the trial procedure.

Abbreviations: FFEJS, Fufang E'jiao syrup; CRF, cancer related fatigue; RPF5-CV, revised piper fatigue scale of Chinese version; QoL, quality of life; ESAS, edmonton symptom assessment scale; FACT-F, functional assessment of cancer therapy; AEs, adverse events; EQ-5D-5L, Euroqol scale of 5 dimensions at 5 levels.

diagnosis for CRF is proposed by the 10th revision of the International Classification of Diseases (ICH10).<sup>28</sup> For this trial, we have designed a procedure to determine the TCM pattern diagnosis of deficiency of Qi and Blood syndrome, introduced in Supplemental File 4.

### Eligibility Criteria

**Inclusion criteria.** (1) Age between 18 and 75 years; (2) Presence of moderate to severe CRF according to the diagnostic criteria proposed by ICH10; (3) Pathologically diagnosed with NSCLC, colorectal cancer or gastric cancer; (4) TNM stage for NSCLC is IIIB-IV, colorectal cancer is IV, and gastric cancer is IV according to the eighth staging standard of AJCC; In addition, all patients should have tumor burden, without the possibility of radical resection; (5) For patients who are receiving chemotherapy, regimens should be those listed in Table 1; (6) Patients not receiving chemotherapy should be evaluated to ensure no rapid tumor progression within approximately 30 days, and able to tolerate

intravenous targeted therapy for the treatment of potential rapid tumor progression within the following 3 months; (7) According to the approved instructions, FFEJS is prescribed for patients with the TCM pattern diagnosis of "Deficiency of Qi and Blood Syndrome." Therefore, eligible patients should also meet a diagnosis of deficiency of Qi and blood syndrome matching with the following symptoms in accordance with TCM theory: fatigue, pale or sallow complexion, hard breath, dizziness, spontaneous sweating, palpitations, specified tongue, and weak pulse.

**Exclusion criteria.** (1) Received immunotherapy or radiotherapy during the study; (2) Suffered significant surgery or traumatic injuries within the past 1 month; (3) Received erythropoietin or blood transfusion within the past 1 month; (4) Presence of hypersplenism, hyperthyroidism, connective tissue diseases, tuberculosis, or other diseases that have not completely controlled; (5) Comorbidities such as serious cerebrovascular, heart, kidney, or liver disease; (6) A history of hypersensitivity to the components of the trial

**Table 1.** Specified Chemotherapy Regimens.

Tumor types	Chemotherapy regimens
NSCLC	Containing platinum chemotherapy plan, 21 d/cycle
Colorectal cancer	CapeOX: Oxaliplatin 130 mg/m <sup>2</sup> , ivgtt, d1; Capecitabine 1000 mg/m <sup>2</sup> , oral, bid half an hour after meal, d1-14, 21 d/cycle. Xeliri: Irinotecan 180 mg/m <sup>2</sup> , ivgtt, d1; Capecitabine 1000 mg/m <sup>2</sup> , oral, bid, half an hour after meal, d1-14, 21 d/cycle.
Gastric cancer	Sox: Oxaliplatin 130 mg/m <sup>2</sup> , ivgtt, d1; S-1 60 mg, oral, bid, half an hour after meal, d1-14, 21 d/cycle. Capeox: Oxaliplatin 130 mg/m <sup>2</sup> , ivgtt, d1; Capecitabine 1000 mg/m <sup>2</sup> , oral, bid, half an hour after meal, d1-14, 21 d/cycle.

Abbreviation: NSCLC, non-small cell lung cancer.

medication; (7) Consumed Colla Corii Asini products within the past 2 weeks; (8) Unable to understand or complete the self-rating scales and informed consent forms; (9) Other conditions that were considered inappropriate as determined by the investigators.

**Withdrawal criteria.** (1) Change in the established chemotherapy regimen during the intervention process, which may affect the evaluation of efficacy and safety; (2) More than 3 episodes of transfusion during the intervention process; (3) Withdrawal of consent for any reason; (4) Not willing to receive the intervention and non-compliance with intervention follow-up although consent has not been withdrawn.

### Randomization and Allocation Concealment

This trial adopts a stratified permuted block randomization method, where each cancer type serves as a stratification factor, regardless of whether participants are or are not receiving chemotherapy. A random sequence with a permuted block size of 4 is generated by a computerized random number generator from an independent data management institute. Each hospital will have at least 1 complete block group. Participants of each cancer type will be randomized into FFEJS group or placebo group at a 1:1 ratio according to the sequence and hospitals they were enrolled at.

The random sequences are sealed in opaque envelopes and kept by the sponsor, and will not be available to patients or investigators during the study. In addition, the placebo was manufactured and tested as having no difference to the FFEJS formula in terms of appearance, flavor, and scent. The manufacturing company provided the code labeling assigned to the study intervention and to the placebo, and a third-party agent matched the random number assigned to each participant to the code assigned to the study intervention and placebo. Only in the case of a medical emergency, the individual's randomization code and group allocation can be identified as described previously.<sup>29</sup>

### Interventions

All eligible participants will be randomly assigned to receive either FFEJS or placebo. The experimental medicine of FFEJS and placebo are both manufactured specifically by Dong-E-E-Jiao Co., Ltd (Production batch number: 1910063). Eligible patients may either receive chemotherapy or not receive chemotherapy, in accordance with their physician's treatment plan. For patients that are receiving chemotherapy, the chemotherapy regimen will meet the conditions as stated in the eligibility inclusion criteria above. During the statistical analysis, the difference in change in fatigue between FFEJS and placebo group will be adjusted for whether patients have or have not received chemotherapy. The administration of FFEJS would be executed as described in Table 2. The different interventions administered to the 2 groups are as follows.

**FFEJS group.** The participants in the FFEJS group will be administered with FFEJS, an oral liquid preparation, the same original marketed patent medicine (20 ml per bottle), 3 times per day for a total of 6 weeks. Each bottle of FFEJS contains donkey-hide gelation (Colla Corii Asini, 870 mg), red ginseng (Radix Ginseng Rubra, 435 mg), prepared rehmannia root (Radix Rehmanniae Preparata, 3043 mg), dang shen (Radix Codonopsis, 3043 mg), and hawthorn fruit (Fructus Crataegi, 1304 mg). The quality test report was conducted in accordance with the manufacturing enterprise registration standards as determined by the Chinese Pharmacopoeia, and confirms that the FFEJS formulation contains glycine, L-hydroxyproline, Panaxatriol, Radix Codonopsis, and Fructus Crataegi.

**Control group.** The participants in the control group will be administered with a placebo formula. The placebo formula (20 ml per bottle) will be administered 3 times per day for a total of 6 weeks. Each bottle of placebo will contain a syrup of a similar consistency to the FFEJS preparation, that comprises 5% of the original FFEJS patent medicine, with added caramel and steviol glycoside to adjust for color and

**Table 2.** Measurement Items and Point of Data Capture.

Study period	Screen			Intervention				Follow-up	
	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Day -7 to 0	Day 7 ± 2	Day 14 ± 2	Day 21 ± 2	Day 28 ± 2	Day 35 ± 2	Day 42 ± 2	Close-out day	Day 70 ± 2
Enrolment									
Eligibility criteria	×								
Informed consent	×								
Urine pregnancy test	×								
Routine urine and stool test	×						×		
Observational indicators									
Physical examination	×			×			×		
Vital sign	×			×			×		
Piper (RPFS-CV)	×	×		×			×		
Routine blood panel	×	×		×			×		×
Serum hormone	×						×		
FACT-F	×			×			×		
ESAS	×	×		×			×		
Safety assessment									
Liver and kidney function	×						×		
ECG	×						×		
Tumor markers	×						×		
Imaging examination	×						×		
Other AEs	×	×		×			×		
Cost-effectiveness assessment									
EQ-5D-5L	×	×		×			×		
Costs		×		×			×		
Drug administration									
Distribute drugs	×	×		×			×		
Recover drugs									

Abbreviations: FACT-F, functional assessment of cancer therapy; ESAS, edmonton symptom assessment scale; ECG, electrocardiogram; AEs, adverse events; EQ-5D-5L, euroqol scale of 5 dimensions at 5 level.

taste. An evaluation of similarity has confirmed and approved the placebo as similar to the FFEJS preparation in terms of appearance, flavor, and scent. The quality test report conducted in accordance with the manufacturing enterprise registration standards as determined by the Chinese Pharmacopoeia, confirms that the placebo formulation does not contain glycine, L-hydroxyproline, Panaxatriol, Radix Codonopsis, and Fructus Crataegi.

## Outcomes

**Primary outcome.** The primary outcome is difference in severity of fatigue as measured by the Revised Piper Fatigue Scale-Chinese Version (RPFS-CV) between the 2 groups from baseline to week 6. RPFS-CV<sup>30</sup> is a self-rating scale and a multidimensional assessment tool that has been widely used to measure CRF. It comprises 24 questions assessing total CRF, as well as a subscale assessment of behavioral, affective, sensory, and cognitive/mood attributes of fatigue. Each question is given a score of 0 to 10, where a higher score indicates greater symptom severity. According to the calculation of sample size, efficacy of FFEJS will be determined as a decrease in the average score by at least 1 point compared to the placebo group. RPFS-CV will be measured in both groups during treatments at baseline, week 1, week 3, week 4, and week 6.

**Secondary Outcomes.** The secondary outcomes include objective measures of fatigue with serum indices<sup>31</sup> and by assessment of QoL of patients measured with the Edmonton Symptom Assessment Scale (ESAS) and Functional Assessment of Cancer Therapy (FACT-F).

*Fatigue will be measured with serum indices including routine serum pathology assessment of red blood cells, white blood cells, neutrophils, platelets, and hemoglobin.* For all participants, routine serum pathology assessment will be conducted at baseline, week 3, week 6, week 10 during the intervention. For participants that are receiving chemotherapy, routine serum pathology assessment will be conducted at 2 additional timeframes, at week 1 and week 4. Myelosuppression and anemia will be assessed according to serum indices at week 3, week 6, and week 10. The total time period of myelosuppression, salvage therapy, incidence, and duration of severe myelosuppression among chemotherapy patients will be recorded and calculated at the end of the study. Fatigue will also be measured by hormone presence in peripheral blood at baseline and week 6 timepoints during the intervention, of aldosterone, insulin-like growth factor, cortisol, growth hormone, triiodothyronine, free triiodothyronine, bound thyroxine, free thyroxine, and thyroid stimulating hormone.

*Assessment of QoL will be measured with edmonton symptom assessment scale (ESAS).*<sup>32</sup> ESAS is a screening tool generally used to measure 11 common symptoms (pain, fatigue, nausea, sadness, anxiety, drowsiness, shortness of breath, appetite, sleep problems, feeling of well-being, and pruritus). Symptom intensity is rated on a scale of 0 to 10, where 0=no symptoms and 10=worst possible symptoms. ESAS is measured at baseline, week 1, week 3, week 4, and week 6 during the intervention.

*Assessment of QoL will be measured with functional assessment of cancer therapy (FACT-F).*<sup>33</sup> FACT-F is a screening tool generally used to investigate physical wellbeing (7 items), social and family wellbeing (7 items), emotional wellbeing (6 items), and functional wellbeing (7 items), with 13 fatigue-related questions. Each question is scored as 5 levels, where a higher score connotes a higher health status. FACT-F is measured at baseline, week 3 and week 6 during the intervention.

**Safety evaluation.** Safety evaluation will be primarily measured with liver function test, renal function test, and electrocardiographs (ECGs). To assess whether CHM may promote tumor progression, tumor markers, and computed tomography (CT) or (magnetic resonance imaging) MRI will be evaluated to determine tumor site progression. Assessment of tumor markers, CT, or MRI evaluation will be conducted at baseline and week 6. Adverse events (AEs) (except for myelosuppression and anemia) during the study will be classified according to the National Cancer Institute, Common Terminology Criteria for Adverse Events v4.03 (NCI-CTCAE v4.03). Any incidence of AEs will be monitored, timely managed and recorded in detail in accordance with the Management Measures for Adverse Drug Reaction Reporting and Monitoring, China (Order No. 81 of the Ministry of health of China).<sup>34</sup> Incidence of AEs (except for myelosuppression and anemia), percentage of patient dropouts due to serious AEs as determined in accordance with the CTCAE v4.03, and risk of the promotion of tumor progression caused by the FFEJS formulation will be analyzed between the 2 groups.<sup>35</sup>

**Cost-effectiveness evaluation.** Cost-effectiveness will be evaluated by incremental cost-effectiveness ratios (ICERs). All costs that incur during the entire trial duration will be recorded, including direct costs and indirect costs at each visit. Direct costs refer to expenses related to relevant medical services, such as inpatient fee, nursing fee, and transportation fee for patients. Indirect costs refer to the expenses related to the time and material required for relevant medical visits, such as the number of days of leave taken by patients or their families, the number of assistant escorts required, and any transportation expenses. The

Numeric Results for Two-Sample T-Test									
Null Hypothesis: Mean 1 = Mean 2. Alternative Hypothesis: Mean 1 ≠ Mean 2									
The standard deviations were assumed to be unknown and unequal.									
	Allocation								
Power	N1	N2	Ratio	Alpha	Beta	Mean1	Mean2	S1	S2
0.90066	77	77	1.000	0.05000	0.09934	3.2	4.2	1.9	1.9

**Figure 2.** Two-sample *T*-test power analysis.

quality-adjusted life years (QALYs) will be calculated according to the Chinese population-based preference scores for EQ-5D-5L utility value integration system.<sup>36</sup> Cost-effectiveness analysis will be evaluated as incremental costs per incremental QALY. Findings of increased QALY and decreased incremental costs in the FFEJS group compared to the placebo group will indicate that FFEJS group has absolute advantage in cost-effectiveness. Findings of decreased QALY and increased incremental costs in the FFEJS group compared to the placebo will indicate that FFEJS is not only ineffective but also associated with higher cost. If both incremental costs and QALY are found to be increased in both groups, ICERs will be calculated to determine further analysis of cost-effectiveness.<sup>37</sup>

### Sample Size

The sample size calculation was based on a meta-analysis that was conducted. According to the meta-analysis, following the change in RPFS-CV score before and after TCM intervention, the mean and standard deviation of RPFS-CV were  $3.2 \pm 1.9$  and  $4.2 \pm 1.9$  for the experimental group and the placebo group.<sup>38</sup> For this study, the sample size was calculated based on the mean change in RPFS-CV score for CRF measured in 3 different cancer types. Using a 0.05 significance level, 90% power, it was determined that 77 cases were needed for each group of 3 different cancer types, as shown in Figure 2, according to the sample size calculation using 2 sample *T*-Test power analysis with PASS software. We defined the final sample size as 600 for all 3 different cancer type subgroups in consideration of 20% of the participants who may drop out and be lost to follow-up.

### Data Management and Monitoring

The original data collected by trained researchers will be recorded in the case report, and then uploaded onto the electronic data capture system (EDC) within 2 weeks of collection. A contract research organization will serve as the second quality controller, to manage and monitor the study through regular contact and visits with the researchers. The Institute of Clinical Medicine, Chinese Academy of Chinese Medical Sciences will serve as the third quality controller to supervise the entire trial process. All researchers will be trained and compliant with Good Clinical Practice (GCP)

regulations. Relevant documents will be archived by the presider and the manager. The data will be maintained in storage for a period of 3 years after study completion. Blood samples will be collected in a timely manner and stored at the general clinical laboratory of each of the study centers. Each stored sample will be coded with a unique participant number. Date and time of sampling will be recorded on the samples. Any change in the study protocol or for the management of AEs will first be immediately reported to the presider and approved by the Ethics Committee of this trial, and all investigators will be subsequently informed.

### Statistical Analysis

The detailed statistical analysis plan was formulated by a statistician and determined with the principal investigator before the implementation of this trial. Statistical analysis will be completed by an independent statistician. Software of SPSS 22.0 for Windows will be used. Differences were considered statistically significant if the *P* value was lower than .05 with both sides being examined. Three analysis sets will be used for assessment of this trial: the intention-to-treat set (ITT), the per-protocol analysis set (PPS), and the safety analysis set (SS). ITT and PPS will be used to appraise the effectiveness of FFEJS. In the case of any missing data on critical variables, the last recorded observation will be used as the final result. After completion of the main analysis, a sensitivity analysis will also be performed on each dataset to evaluate the impact of missing data on the study results. The primary efficacy analysis will measure the average efficacy of FFEJS for alleviation of CRF in the 3 cancer types, and a subgroup analysis will be performed for each cancer type.

The baseline characteristics between 2 groups including sex, age, histopathological type, differentiation degree, TNM stage, gene detection, combined diseases, and therapeutic history, will be described with descriptive statistical analysis and compared using Pearson's chi-squared test. For quantitative data, the mean, median, standard deviation (SD), minimum and maximum variables will be reported. The primary objective is to investigate whether there is improvement in CRF in patients receiving FFEJS vs placebo from baseline to the endpoint of the study. A repeated-measures analysis of variance (ANOVA) will be used to analyze score change in RPFS-CV. If the data is normally distributed, ANOVA will be used to analyze the scores for the ESAS and FACT-F; a paired *t* test will be used to analyze change in fatigue for laboratory indices including routine blood panel and hormones. If the data is non-normally distributed, the Wilcoxon signed rank test will be used for RPFS-CV, ESAS, FACT-F, and laboratory indices for fatigue evaluation. The difference in change in fatigue between FFEJS and placebo group before and after the intervention will be adjusted by whether participants have

or have not received chemotherapy. The safety evaluation including incidence of AEs, percentage of patient dropouts and risk of tumor growth promotion will be analyzed with descriptive statistical analysis and a paired *t* test. Cost effectiveness evaluation will calculate the confidence interval of incremental cost-effectiveness ratio (ICER) and the influence of main parameters on the evaluation indices respectively, by non-parametric bootstrap and sensitivity analysis, and then analyzed with a paired *t*-test.

## Discussion

At present, while the trend of research suggests that CHM may improve the management of CRF, its therapeutic potential remains understudied in rigorous and large sample clinical trials. The protocol design of randomized, double-blinded, placebo-controlled RCT study with a 600-participant sample size aims to explore the benefits of CHM for improvement of CRF. The protocol was designed and developed according to the Standard Protocol Items for Clinical Trials (SPIRIT) statement and corresponding extension requirements.<sup>39,40</sup>

FFEJS was developed based on the classical TCM formula with a more than 400-year old recorded history, Liangyi Ointment, which is designed to invigorate Qi and nourish Blood. FFEJS comprises of the Chinese medicine Colla Corii Asini, Radix Ginseng Rubra, Radix Rehmanniae Preparata, Radix Codonopsis, and Fructus Crataegi.<sup>41,42</sup> FFEJS is indicated to treat the main pathogenic factors that are considered to cause CRF in TCM theory. This study is designed to investigate the use of FFEJS in cancer patients with a TCM diagnosis of deficiency of Qi and Blood syndrome to better understand its therapeutic potential in targeted populations of CRF. Based on previous studies and our clinical experience, we hypothesized that FFEJS may improve CRF in advanced cancer patients, improve QoL, and is a safe and cost effective therapy.

Several design measures were implemented to control potential bias. As indicated by existing research, different cancer types and cancer treatment therapies are associated with different severities of CRF. To reduce potential confounding, this study will limit participant eligibility to 3 types of tumors including NSCLC, colorectal cancer, and gastric cancer, which are the most frequently diagnosed cancers in China. Other cancer types were excluded, such as liver cancer due to its known poor prognosis, breast cancer as the associated fatigue is closely related to its management therapeutics, and any other cancers with special factors. The eligibility criteria includes patients that are not receiving chemotherapy and those that are receiving chemotherapy, where chemotherapy regimens are specifically defined according to the new guidelines. Given that intravenously administered targeted therapy plays a very small role among combinations with chemotherapy and as it is widely used, patients receiving this combination of treatment were

also included in the eligibility criteria. To reduce potential confounding, the following characteristics were listed in the exclusion criteria: received radiotherapy, and received orally administered targeted therapy or immunotherapy. To ensure the rigor of the disease condition, this trial limits eligibility to include patients with moderate to severe CRF, and excludes patients with mild CRF, which may not require medical intervention, and those with severe CRF where symptoms affect consciousness. To control confounding caused by anemia, CRF patients with severe anemia by bleeding, hypersplenism, connective tissue diseases, or bone marrow metastases, and that received erythropoietin or blood transfusion were also excluded from the study. Anemia is reported to be greatly associated with CRF, and FFEJS has been shown to alleviate CRF by improving anemia conditions.<sup>22,43,44</sup> To avoid the exposure of the placebo, due to the highly recognizable and distinct flavor and scent of Colla Corii Asini, this study adopted a placebo that contained 5% of the original FFEJS patent medicine. Studies show that placebos of CHM formulae with a content lower than 10% of original formula can meet the placebo effect.<sup>45</sup> To ensure that the results of the study are comprehensive and objectively, both subjective and objective instruments were used to measure fatigue. For the primary outcome of this study, fatigue is measured by a subjective fatigue scale, while as secondary outcomes, laboratory indices including routine blood panel and hormones were used to measure fatigue, to ensure more objective results as well as to investigate the possible mechanisms of FFEJS for the management of CRF.<sup>46</sup> To improve research rigor, all the selected outcome measurement scales used in this trial are recognized internationally and have also been shown to have good internal consistency with the Chinese versions. Researchers were trained in the use of the measurement scales, and competency in understanding and completing the scale was one of the criterium for participant eligibility. Moreover, to further ensure research rigor, an independent agency was invited to participate in the randomization, management, and analysis of data.

There are some limitations to this study. Firstly, the concurrent usage of other CHM formulations in addition to FFEJS will not be a condition for exclusion from participant eligibility, as in China the majority of cancer patients will use CHM formulations and components in addition to prescribed care. However, the concurrent usage of specific CHM formulations that contain either the specific ingredients of FFEJS (Colla Corii Asini, Radix Rehmanniae Preparata), specific ingredients indicated as prohibited to be used in conjunction with FFEJS (Veratrum, Faeces Trogopterori, Gleditsia Sinensis), or ingredients with similar effects (Angelica Sinensis), in accordance with TCM theory,<sup>47</sup> is a listed exclusion criteria. Secondly, although FFEJS is a marketed patent medicine which has been widely used in China, its pharmacological mechanisms are complex and still not comprehensively understood. Thirdly, the



purpose of this study is to explore the efficacy of FFEJS on CRF, limited to patients with advanced cancer and not generalized to all cancer survivors. Fourthly, as both patients receiving chemotherapy and patients not receiving chemotherapy will be included in this study, the distribution of participants between the 2 subgroups will need to be assessed and adjusted for during the statistical analysis. Fifthly, this study shares a common limitation to many TCM trials; there is no current standardized validated TCM diagnostic scale against which the eligibility criteria for a concurrent TCM diagnosis of deficiency of Qi and Blood syndrome and CRF is determined. To address this limitation, before the trial's commencement, the project team used the Delphi process to conduct a series of interviews with experts to establish a unified diagnostic criteria for the TCM diagnosis of deficiency of Qi and Blood syndrome. All study investigators were trained in the use of the established diagnostic criteria to ensure its consistent application. During COVID-19 pandemic, the recruitment and follow-up for the current study could be affected to a certain extent due to restriction of hospitalization and clinic visits.<sup>48</sup> Nevertheless, we managed to put up more recruitment advertising and increase screening work to accelerate patients' enrollment and utilized online remote techniques to communicate with patients and express delivered their research materials to reduce the risk of lost follow-up.<sup>49-51</sup>

In conclusion, the results of this study will provide more evidence for the therapeutic potential, safety and cost-effectiveness of FFEJS for alleviation of CRF. We hope this study will help to provide a better understanding of CHM's role in the management of CRF and the improvement of QoL in advanced cancer patients.

### Abbreviations

CRF: Cancer-related Fatigue; FFEJS: Fufang E'Jiao Syrup; QoL: quality of life (QoL); TCM: Traditional Chinese Medicine; CAM: Complementary or alternative medicine; CHM: Chinese herb medicine; RSYRT: Ren Shen Yangrong Tang; BZYQT: Bojungikki-tang (Buzhongyiqi tang); JPSS: Jianpishengsui; AJCC: American Joint Committee on Cancer; ICH10: 10th revision of the International Classification of Diseases; NSCLC: non-small cell lung cancer; NCCN: National Comprehensive Cancer Network; GMP: good manufacturing practice; RPPS-CV: Revised Piper fatigue scale of Chinese Version ESAS; edmonton symptom assessment scale; FACT-F: functional assessment of cancer therapy; QALM: quality-adjusted life months; AEs: adverse events; CTCAE: common terminology criteria for adverse events; GCP: Good Clinical Practice; ITT: intention-to-treat set; PPS: per-protocol analysis set; SAS: safety analysis set; ANOVA: analysis of variance; ICER: incremental cost-effectiveness ratio; ECG: electrocardiogram.

### Acknowledgments

The authors thank the Institute of Basic Theory for Chinese Medicine, China Academy of Chinese Medicine Science for

leading undertaking this project; thank the Ministry of Science and Technology of the People's Republic of China (MSTPRC) for supporting the project; and give heartfelt thanks to all participants in this trial and the independent statistician.

### Authors' Contributions

YX presided this study, ZS, LS, HL drafted the protocol, YX, XZ, and YW revised the protocol. NC, LS, QL, ZS, and SG recruited the patients. All of authors participated in the design and read, approved the final manuscript.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study is sponsored by the National Key Research and Development Program of China (Research Project of Modernization on TCM, Grant number: 2018YFC1707406), funded by the MSTPRC. During the entire research process, the research was partially funded by MSTPRC, while the remainder of the research was self-funded.

### Role of Study Funders

This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

### Consent for Publication

All participants have provided consent to share their individual medical information.


### Trial Sponsor

Ministry of science and technology of China.

### Trial Status

The trial was approved by the ethical committee of Xi Yuan Hospital of China Academy of Chinese Medical Sciences (Approval Number: 2019XLA028-3). Patient recruitment began in October 2019 and is expected to be completed in December 2021. At the time of October 28, 2020, 209 patients have been recruited and 20 sub-centers have recruited patients. Currently, we are still recruiting participants.

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### Supplemental Material

Supplemental material for this article is available online.

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