A Prospective Single-arm Feasibility Clinical Study of Huangqi Yangyuan Formula for Capecitabine-Induced Adverse Reactions in Patients with Advanced Colorectal Cancer

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1. Background

Colorectal cancer is a highly prevalent gastrointestinal malignant tumor in China. Patients with locally-advanced or advanced colorectal cancer frequently present with lymph-node or distant metastasis, carrying substantially elevated risks of disease recurrence and tumor progression. Domestic and international guidelines recommend single-agent oral capecitabine chemotherapy for this patient population to control tumor progression, reduce recurrence and metastasis risk, and prolong survival.

Capecitabine is an oral fluoropyrimidine chemotherapy with convenient administration; nevertheless, prominent toxicities remain common in clinical practice, mainly including hand-foot skin reaction, diarrhea, persistent fatigue, myelosuppression, nausea and vomiting, decreased appetite, oral mucositis, etc. Pooled safety data from international phase III registration trials of capecitabine for first-line single-agent treatment of metastatic colorectal cancer demonstrated a permanent treatment discontinuation rate of 13 % due to drug-related adverse events; grade 3-4 hand-foot skin reaction and diarrhea constituted the most frequent severe toxicities. Clinical observations in East-Asian populations indicate that, influenced by ethnicity, age and underlying comorbidities, Chinese patients with advanced colorectal cancer receiving single-agent capecitabine chemotherapy face higher risks of adverse events such as hand-foot skin reaction compared with Western registration-trial populations. Real-world studies report wide variability in rates of dose reduction and cycle delay, and no universally accepted reference values are available. These toxicities may compromise chemotherapy completion, potentially impair anti-tumor efficacy and deteriorate patients' quality of life during treatment.

From the perspective of traditional Chinese medicine (TCM), the core pathogenesis

in patients with advanced colorectal cancer is spleen-kidney deficiency intermingled with damp-heat, stasis and toxin. Chemotherapy agents are categorized as "medicinal toxin" in TCM theory, which continuously consumes spleen-kidney qi-blood and injures yin-fluid, further aggravating physical debilitation. Insufficient healthy qi impairs clearance of cancer toxin and raises long-term recurrence risk.

Huangqi Yangyuan Formula is an empirical formula for supporting healthy qi and anti-cancer. Astragali Radix and Rehmanniae Radix are employed as monarch herbs, combined with ingredients for invigorating spleen-qi, nourishing blood-yin, detoxifying and dissipating masses. The whole formula exerts therapeutic effects of invigorating spleen and consolidating origin, tonifying healthy qi, eliminating cancer toxin and resolving stasis-masses. On one hand, it reinforces spleen-kidney healthy qi, repairs viscera-qi-blood injury induced by chemotherapy, mitigates severity of chemotherapy-related toxicities and improves treatment tolerance. On the other hand, it detoxifies and dissipates residual tumor toxin, generating synergistic anti-tumor effects when combined with capecitabine to achieve toxicity-reduction and efficacy-enhancement.

Pharmacological evidence shows active components in Huangqi Yangyuan Formula (e.g. astragalus polysaccharides, icariin, lycium barbarum polysaccharide, dioscorea opposita polysaccharide) can inhibit colon cancer cell proliferation, regulate host immunity and alleviate chemotherapy-related myelosuppression and gastrointestinal mucosal injury. However, no prospective clinical trials have yet confirmed the safety and clinical benefits of this formula in advanced colorectal cancer patients receiving capecitabine-based chemotherapy.

2. Study Objectives

Thirty-five patients with advanced colorectal cancer will be enrolled to receive combined intervention of Huangqi Yangyuan Formula and capecitabine. This study aims to evaluate clinical implementation feasibility and chemotherapy completion rate of the combined regimen, and preliminarily explore potential signals of alleviating chemotherapy-related adverse reactions and improving quality of life. There is no confirmatory hypothesis for anti-tumor or toxicity-reduction efficacy.

Sample size is insufficient for testing anti-tumor endpoints, and progression-free survival will only be observed descriptively. This feasibility study will provide protocol basis, sample-size reference and clinical evidence for subsequent large-sample randomized controlled confirmatory trials.

Sample-size rationale: This is a feasibility clinical study. Feasibility studies generally enroll 20-50 subjects to assess recruitment feasibility, medication adherence, follow-up accessibility and adverse-event profiles, without formal confirmatory hypothesis testing. Considering the annual volume of advanced colorectal cancer patients receiving capecitabine chemotherapy in our center, the planned total sample size is set to 35 patients.

Project timeline: Rolling enrollment will be adopted; subjects will not be enrolled synchronously. Enrollment start date: January 1, 2027; overall project completion date: December 31, 2029; total project duration: 36 months (3 years). The enrollment window is 12 months: all 35 subjects shall be screened and enrolled between Jan 1 2027 and Dec 31 2027. Each subject receives 6-month intervention, followed by 3-month post-chemotherapy follow-up; total individual observation period is 9 months. Under rolling enrollment design, the 9-month observation and follow-up for the last enrolled subject will be completed before the overall project deadline December 31 2029.

3. Study Design and Principles

3.1 Study Design

Single-center, prospective, single-arm feasibility clinical study. Primary purpose: feasibility assessment.

3.2 Study Site

Hebei Provincial Hospital of Traditional Chinese Medicine.

4. Study Population

Subjects are in-hospital and out-hospital patients diagnosed with stage IIIB-IV colorectal adenocarcinoma with TCM spleen-kidney deficiency syndrome at Department of Oncology 2, Hebei Provincial Hospital of Traditional Chinese

Medicine.

4.1 Western-medicine Diagnostic Criteria

Refer to CSCO Colorectal Cancer Diagnosis and Treatment Guidelines (2026 edition): confirmed stage IIIB-IV colorectal adenocarcinoma.

4.2 TCM Diagnostic Criteria

TCM spleen-kidney deficiency syndrome is diagnosed referring to Guiding Principles for Clinical Research of New Chinese Medicines (Trial). Core symptoms include lassitude, shortness of breath, soreness and weakness of waist and knees, poor appetite, pale tongue with white coating, weak pulse, etc. Patients who meet ≥ 2 core symptoms will be diagnosed as spleen-kidney deficiency syndrome.

4.3 Inclusion Criteria

(1) Aged 18-80 years old;
(2) Stage IIIB - IV colorectal adenocarcinoma unresectable by surgery, or with recurrence/metastasis after radical resection;
(3) Eligible for initiation or ongoing single - agent capecitabine chemotherapy per domestic and international colorectal-cancer guidelines;
(4) Expected overall survival ≥ 6 months;
(5) Eastern Cooperative Oncology Group (ECOG) performance status 0-2;
(6) Baseline hematologic, hepatic and renal function satisfying clinical tolerance criteria for capecitabine chemotherapy;
(7) Capable of continuously taking Huangqi Yangyuan Formula orally, completing scale assessments, regular laboratory re-examinations and imaging evaluations;
(8) Fully understands trial content and voluntarily provides written informed consent.

4.4 Exclusion Criteria

(1) Pregnant or lactating women;
(2) History of other malignant tumors within past 5 years or gastrointestinal carcinoma in-situ;
(3) Severe underlying organic diseases of heart, liver, kidney, respiratory or hematopoietic system;
(4) Baseline persistent severe diarrhea, hand - foot ulcer, severe malnutrition

precluding chemotherapy tolerance;

(5) Conscious disturbance or psychiatric disorders precluding independent scale completion and follow-up;

(6) Documented allergy to any herbal component of Huangqi Yangyuan Formula or to capecitabine;

(7) Regular intake of anti-tumor Chinese patent medicine, anti-tumor TCM decoction, long-term anti-tumor acupuncture/moxibustion or anti-tumor health-care products within 2 weeks prior to enrollment and failure to complete wash-out period. Wash-out period for anti-tumor TCM interventions is set as 2 weeks according to metabolic characteristics of TCM decoctions and conventions for feasibility oncology TCM studies;

(8) Received radiotherapy, other chemotherapy agents, targeted therapy or immunotherapy within 1 month before enrollment;

(9) Currently receiving dual-agent chemotherapy or immunotherapy;

(10) Refusal to discontinue other anti-tumor TCM interventions or failure to truthfully report concomitant medications.

4.5 Subject Drop-out and Management

4.5.1 Definition of drop-out

Subject will be judged as drop-out and TCM intervention terminated if any of following occurs:

(1) Self-discontinuation of Huangqi Yangyuan Formula for more than 14 consecutive days;

(2) Voluntary withdrawal from trial or loss-to-follow-up;

(3) Severe intolerable chemotherapy-related adverse events leading to permanent capecitabine discontinuation;

(4) Tumor recurrence or distant metastasis detected during follow-up requiring switch to second-line anti-tumor regimen;

(5) Unauthorized long-term combined use of anti-tumor TCM preparations constituting major protocol violation.

4.5.2 Management of drop-out subjects

(1) For subjects withdrawing or lost-to-follow-up, researchers shall actively

attempt contact via home visits, telephone or mail to document last treatment timepoint, accomplish final assessments whenever feasible and analyze clinical outcomes.

(2) Subjects withdrawing due to allergic reactions, adverse events or treatment ineffectiveness shall receive appropriate clinical management according to individual condition.

(3) Drop-out reasons and trial conclusions shall be fully documented in case report forms (CRFs).

(4) Dataset definition:

- Intention-to-treat (ITT) set: all enrolled subjects who have received at least one dose of Huangqi Yangyuan Formula. Screen-failure subjects without any study drug exposure are excluded from ITT set.

- Per-protocol (PP) set: subjects completing interventions per protocol without major protocol violations and without unauthorized anti-tumor TCM use.

- Drop-out subjects will be included in ITT set and safety analysis set.

4.6 Termination of individual subject participation

(1) Occurrence of allergic reaction or serious adverse event judged by investigator to warrant trial discontinuation.

(2) Subject refuses or becomes unable to continue trial participation for any reason.

(3) Subject declines further treatment or assessments without explicit written withdrawal statement.

4.7 Trial Procedures

Patients will be screened based on medical history, imaging and pathological results. Eligible subjects will sign informed consent, then receive baseline examinations including blood routine, hepatic - renal function, tumor biomarkers, imaging assessments and scale evaluation. Qualified subjects will be enrolled. Each subject receives combined capecitabine chemotherapy plus Huangqi Yangyuan Formula for 6-month intervention period followed by 3-month post-chemotherapy follow-up (total 9-month observation). Clinical data, adverse events, quality-of-life scores, TCM constitution scores and peripheral-blood T-lymphocyte subset indicators will be collected at the end of cycle 4, end of cycle 8 and follow-up timepoints. Changes

in chemotherapy completion rate, chemotherapy-related toxicities, immune status and quality of life will be analyzed to evaluate clinical feasibility and safety of combined regimen and preliminarily explore potential toxicity-reduction signals.

Biological-sample management: Peripheral blood will be collected for flow-cytometry detection of T-lymphocyte subsets. Residual blood specimens will be destroyed immediately after testing, without long-term storage or usage for research purposes outside this study. This content will be clearly described in informed-consent documents.

5. Treatment Regimens

This is a single-center, open-label, non-randomized, single-arm prospective feasibility trial. All enrolled subjects receive capecitabine standard chemotherapy combined with synchronous Huangqi Yangyuan Formula. There is no concurrent control arm. Published capecitabine monotherapy literature serves only as descriptive background reference; no formal statistical hypothesis testing against external historical control data will be performed.

5.1 Capecitabine Chemotherapy Regimen

Oral capecitabine: 1250 mg/m^2 twice daily, 30 minutes after meals, swallowed with water; 14-day on-treatment followed by 7-day rest; 21 days constitutes one chemotherapy cycle. Standard planned total treatment course: 8 cycles. Capecitabine dose will be adjusted according to blood routine, hepatic-renal function and hand-foot-syndrome grading following colorectal-cancer guidelines.

Operational definition for primary endpoint chemotherapy completion rate:

(1) Completion of 8 standard chemotherapy cycles: accomplishment of all planned 8 capecitabine cycles. Guideline-permitted dose reduction and cycle delay are allowed. Permanent capecitabine discontinuation due to tumor progression or intolerable adverse events counts as failure to complete 8 cycles.

(2) Completion of 4 standard chemotherapy cycles: accomplishment of first 4 capecitabine cycles. Guideline-permitted dose reduction and cycle delay are allowed. Permanent capecitabine discontinuation due to tumor progression or intolerable adverse events counts as failure to complete 4 cycles.

5.2 Huangqi Yangyuan Formula Intervention

Dosage form: TCM decoction uniformly prepared by pharmacy decoction room of Hebei Provincial Hospital of Traditional Chinese Medicine; 150 mL per bag. Administration: one bag twice daily, taken 0.5 h apart from capecitabine.

Huangqi Yangyuan Formula will be initiated synchronously on day 1 of capecitabine cycle 1. TCM decoction will be paused for one week at end of chemotherapy cycle 4 (This one-week temporary interruption is set according to local clinical experience for TCM gastrointestinal tolerance optimization, without interfering with capecitabine chemotherapy schedule); capecitabine chemotherapy will continue per original schedule without interruption. Total planned TCM intervention duration is 6 months.Basic formula composition:

Astragali Radix 20 g, Rehmanniae Radix 10 g, Lycii Fructus 10 g, Dioscoreae Rhizoma 15 g, Poria Cocos 10 g, Epimedii Folium (honey-processed) 10 g, Spatholobi Caulis 10 g, Angelicae Sinensis Radix 10 g, Galli Gigerii Endothelium Corneum 5 g.

5.3 Observation Time-points

(1) Baseline period: within 1 week before initiation of chemotherapy plus TCM intervention; complete baseline assessments, scales, laboratory and imaging examinations.
(2) Treatment-period endpoints: repeat all evaluation indicators at end of cycle 4 and end of cycle 8.
(3) Long-term follow-up: 3 months after chemotherapy completion; record adverse events, tumor recurrence and distant-metastasis status.

5.4 Concomitant-medication regulations

Symptomatic treatment for comorbidities may be administered according to clinical conditions; medications for chronic diseases (coronary heart disease, diabetes, hypertension etc.) will follow relevant guidelines. Drug name, manufacturer, batch number, dosage and administration shall be fully documented.

6. Outcome Measures

6.1 General documentation items

Trial site, subject name (or phonetic initials), trial start date, residential address,

contact information, occupation, collected at enrollment.

6.2 Primary Outcome Measures

Completion rate of 4-cycle and 8-cycle standard capecitabine chemotherapy, which is used to evaluate treatment-related feasibility including medication adherence and chemotherapy completion of the combined regimen. Recruitment and follow-up situation will be summarized as descriptive background information.

6.3 Secondary Outcome Measures

(1) Severity of chemotherapy-related adverse events (CTCAE Version 5.0): the incidence of adverse events at each grade, focusing on grade ≥ 3 events. Incidence rates and two-sided 95 % confidence intervals will be reported. Only descriptive comparison against published literature will be performed, without formal statistical hypothesis testing. It is used to preliminarily explore potential toxicity-reduction signals and provide effect-size reference for subsequent confirmatory trials.

(2) Quality of life for cancer patients will be assessed by Chinese version of EORTC QLQ-C30 questionnaire at baseline, end of cycle 4 and end of cycle 8. Higher scores in functional domains indicate better quality of life; higher scores in symptom domains indicate more severe discomforts.

(3) Changes of TCM constitution will be evaluated by standardized Body-Constitution Questionnaire (BCQ) to assess scores of qi-deficiency, blood-deficiency and yang-deficiency constitution. Constitution distribution and score changes before and after intervention will be compared. All physicians participating in BCQ scale assessment receive unified training to guarantee evaluation consistency.

(4) Anti-tumor objective efficacy: progression-free survival will be recorded at 3-month follow-up after chemotherapy completion. Given limited sample size of this study, this indicator is for descriptive observation only and cannot confirm synergistic anti-tumor effect.

(5) Immune-function related indicators: proportions of peripheral-blood $CD3^+$, $CD4^+$, $CD8^+$ T-lymphocyte subsets will be detected by flow cytometry to evaluate immune function status.

(6) Safety indicators: blood routine, hepatic-renal function and electrolytes will be re-examined at baseline and every two chemotherapy cycles. Laboratory indicators (AST, ALT, BUN, creatinine, GFR, white blood cell, neutrophil, hemoglobin, platelet) at baseline will be compared with those at end of cycle 4 and cycle 8. All adverse events potentially related to Huangqi Yangyuan Formula will be documented throughout the study to evaluate hepatic and renal toxicity of this formula.

6.4 Observation and Summary

Unified forms will be used for detailed documentation according to study design. Statistical processing and correlation analysis will be performed after observation completion.

7. Assessment Tools and Testing Standards

(1) CTCAE Version 5.0 Common Terminology Criteria for Adverse Events: all chemotherapy-related adverse events will be graded from grade 0-5 by trained oncologists.

(2) Chinese version of EORTC QLQ-C30 quality-of-life questionnaire: filled out independently by patients, collected and checked by researchers.

(3) TCM Body-Constitution Questionnaire (BCQ): scored by uniformly-trained TCM physicians to determine biased-constitution types and scores.

(4) Laboratory tests: hepatic-renal function and blood routine will be measured by automatic biochemical analyzer and hematology analyzer.

(5) Tumor efficacy assessment: contrast-enhanced chest-abdomen-pelvis CT and tumor biomarkers (CEA, CA19-9) will be re-examined every 3 chemotherapy cycles; imaging evaluation will be performed 3 months after chemotherapy completion.

8. Statistical Methods

(1) Statistical software: SAS 9.4; significance level $\alpha = 0.05$.

(2) Scale reliability analysis: Cronbach's α coefficient of QLQ-C30 before and after intervention will be calculated to evaluate internal consistency.

(3) Within-group pre-post comparison: normality test will be performed for quantitative data. Paired t-test will be applied for normally-distributed scale scores and laboratory indicators at baseline versus treatment endpoints; Wilcoxon signed-rank test will be used for non-normal distribution.

(4) Count data (adverse-event grading, chemotherapy completion rate, constitution distribution) will be described by case number and percentage.

(5) Stratified analysis: secondary endpoints will be compared stratified by whether short-term symptomatic TCM interventions are applied. Descriptive analysis will also be performed for confounding factors including tumor progression and dose adjustment, to distinguish different causes for chemotherapy non-completion.

(6) Dataset definition: ITT set includes all enrolled subjects receiving at least one dose of Huangqi Yangyuan Formula. PP set includes subjects completing interventions as-per-protocol without major protocol violations and unauthorized anti-tumor TCM usage. Drop-out and protocol-violation subjects are kept in ITT set for analysis. Screen-failure subjects without study-drug exposure are excluded from ITT set.

(7) Effect size and statistical power will be calculated after trial completion, providing sample-size basis for subsequent large-sample randomized controlled trials.

Incidence rates and two-sided 95 % confidence intervals will be calculated for chemotherapy completion rate and adverse-event incidence. Quantitative data will be presented as mean ± standard deviation or median (inter-quartile range). This is a feasibility exploratory study; no formal hypothesis testing will be performed against external historical control data. Effect estimates generated from this study will provide reference for sample-size design of subsequent confirmatory clinical trials. All within-group pre-post statistical comparisons for secondary endpoints are exploratory descriptive analyses. No formal hypothesis testing for confirmatory purpose will be performed. P-values are presented for exploratory reference only; no multiplicity adjustment will be applied. Findings shall not be interpreted as confirmatory clinical conclusions.

9. Adverse-Event Observation and Analysis

9.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject administered a study drug; it does not necessarily imply causal relationship with the investigational product. An AE may be new disease, worsening of concomitant disease, effect of comparator drug, event unrelated to trial participation, or combination of multiple factors. "Adverse event" does not equate causal association with study treatment.

A serious adverse event (SAE) is any adverse event occurring at any dose or during any observation period that results in death; is immediately life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; occurs after overdose; induces malignancy; or is medically important (events not immediately life-threatening, not leading to death or hospitalization, yet may endanger patients or require intervention to prevent above-mentioned outcomes).

Adverse drug reaction means harmful and unintended reaction occurring under normal dosage, which has causal relationship with study drug. Causal association between adverse events and study interventions will be assessed in clinical research.

9.2 Expected Adverse Events of Study Treatment

Expected TCM-related adverse events mainly include diarrhea, constipation, abdominal distension and others.

9.3 Causal-Relationship Assessment Between Adverse Events and Study Therapy

Five dimensions will be evaluated:

(1) Whether reasonable temporal sequence exists between medication start and AE onset;
(2) Whether AE is consistent with known safety profile of study drug;
(3) Whether AE can be explained by subject's underlying disease, concomitant medications or prior therapies;
(4) Whether AE subsides or alleviates after drug discontinuation or dose reduction;
(5) Whether identical AE recurs upon re-exposure.

Investigators will evaluate possible association between adverse events and study drugs / concomitant medications according to 5‑grade classification: definitely related, probably related, possibly related, probably unrelated, unrelated.

Causality	Reasonable temporal sequence	Consistent with known AE profile	Explainable by other factors	Improved after de-challenge	Positive re-challenge
Definitely related	+	+	–	+	+
Probably related	+	+	–	+	–
Possibly related	+	+	±	?	–
Probably unrelated	±	–	+	?	–
Unrelated	–	–	+	–	–

Note: "+" = yes; "–" = no; "±" = uncertain; "?" = unknown.

9.4 Management and Reporting of Adverse Events

9.4.1 Observation and Documentation

Adverse‑event record forms shall be filled truthfully during trial. Researchers shall instruct subjects to truthfully report changes in disease status; suggestive questioning should be avoided. While observing efficacy, close attention shall be paid to adverse events or unexpected toxicities (symptoms, signs, laboratory findings). Whether related to study intervention or not, all events shall be documented in detail, causes analyzed, correlation evaluated, with symptoms, severity, onset time, duration, management measures, clinical course and outcome recorded. Investigators shall sign and date the documentation.

9.4.2 Management of Subjects with Adverse Events

Upon occurrence of adverse events, principal investigator shall decide clinical management and whether to discontinue trial observation according to clinical conditions. Mild adverse events generally do not require special management or only symptomatic treatment without threatening subject safety. Moderate adverse events require trial discontinuation and targeted management. Severe life‑

threatening adverse events require immediate trial termination and emergency rescue according to institutional emergency protocols. Research monitors shall be notified and adverse-event report forms filled. Subjects withdrawing due to adverse reactions shall be followed-up, with management course documented. If adverse events remain unresolved upon study end, subjects will be followed-up until recovery or stable condition.

9.4.3 Reporting

This is an investigator-initiated trial (IIT). If any serious adverse event occurs during trial, it shall be promptly reported to institutional ethics committee, research administration department and principal investigator, and reported within time limit specified by ethics committee. This study does not require 24-hour reporting to national drug regulatory authority as for registrative clinical trials. Hebei Provincial Hospital of Traditional Chinese Medicine will strictly follow local SAE reporting regulations for investigator-initiated clinical research.

10. Quality Control

Quality-control system will be strictly implemented, standard operating procedures (SOPs) formulated, and project personnel specially trained to improve subject adherence.

10.1 Formulation of Standard Operating Procedures

Study site and collaborative units will strictly follow project manual and SOPs for laboratory indicators to guarantee data accuracy. SOPs for laboratory tests (blood, urine, stool routine, hepatic-renal function etc.) shall be implemented in participating laboratories. Local laboratory reference ranges shall be submitted to project team and biostatisticians.

10.2 Unified Training and Consistent Methodology

Before study initiation, project personnel including laboratory staff will receive unified training covering study protocol, project manual and SOPs. TCM physicians will receive special training for BCQ scale assessment to guarantee scoring consistency. Laboratory operators shall hold relevant professional qualifications.

10.3 Strict Implementation of Quality-Control System

Monitors and auditors will supervise SOP compliance, verifying authenticity, accuracy and completeness of trial documentation and reports.

10.4 Improvement of Subject Adherence

Diagnostic accuracy shall be guaranteed; inclusion/exclusion criteria shall be strictly implemented. Subject contact information shall be fully recorded. Regular follow-up via telephone and short messages will enhance subject persistence in trial participation.

10.5 Quality-Control and Quality-Assurance System

Project coordination group, quality-control group, finance-management group and data - management group will be established for project coordination, guidance, supervision and quality control.

11. Clinical Data Management

11.1 Establishment of Data-Management Group

Data - management SOPs will be formulated for data inspection, verification and entry. In collaboration with biostatistical team, study database will be built and data quality controlled.

11.2 Definition of Source Data

Study subjects are in - hospital and out - hospital patients from Department of Oncology 2. Source data include clinical research medical records and original laboratory test reports, which must be traceable.

11.3 Regulations for Clinical-Data Documentation

Study source data will be documented in Case Report Forms (CRFs), with corresponding electronic database established. Before study initiation, investigators will receive training covering study protocol, SOPs and CRF completion requirements.

11.3.1 CRF Completion

Researchers shall guarantee timely, complete, accurate and truthful documentation. CRFs shall be filled within 24 hours after required assessment time - points. All mandatory items shall be filled; reasons shall be noted for blank items. CRF entries must be consistent with source documents; fabrication of data is strictly prohibited.

11.3.2 CRF Correction

Any correction on CRFs shall be performed by strikethrough original value, adding corrected value nearby, with investigator signature and date. Erasure or covering original records is forbidden.

11.3.3 Laboratory Report Attachment

Original or copied laboratory reports shall be pasted on designated attachment pages; laboratory results shall be transcribed into CRF laboratory sections.

11.3.4 All Study Cases

Whether completing trial or not, study medical records shall be filled accurately for every enrolled subject.

11.3.5 Clinical-Data Collection

Data collection will strictly comply with study protocol and SOPs.

11.4 Data Reporting

11.4.1 CRF Submission

Upon completion of observation for each subject, investigators shall submit completed CRFs to site principal investigator for review and signature within 3 working days; identified queries shall be resolved and documented timely.

11.4.2 CRF Filing and Preservation

After review, CRFs will be submitted to sponsor site for archiving. Electronic files including database, inspection program, analysis program, output reports and codebooks shall be backed-up on multiple storage media. All source documents shall be preserved in compliance with national administrative requirements for clinical research.

11.5 Data Verification

11.5.1 Query Checking

Data verifiers will perform completeness and logic check item-by-item for submitted CRFs. Data query forms will be generated for identified problems and fed back to clinical investigators. Responses shall be returned within 48 hours; overdue queries will be escalated to site principal investigator.

11.5.2 Data Entry

Qualified CRFs will be double-entered independently by two data entry operators

into two separate databases. Data entry queries will be documented and fed back to investigators for resolution.

11.5.3 Data Consistency Check

After double entry, automated consistency comparison will be performed between two databases and discrepancy report generated.

11.5.4 Database Revision

Discrepancy reports will be printed. Based on source CRF records, identified errors in primary database will be corrected, with signature on printed discrepancy report.

11.5.5 Visual Database Inspection

Key statistical variables will be sorted to identify outlier values and generate visual inspection report. Suspicious outliers will be cross-checked against source CRFs; if not entry error, outlier query forms will be created and fed back to clinical sites.

11.5.6 Sampling Audit

More than 10 % of CRFs will be randomly sampled by independent staff and cross-checked against database records. Sampling-audit report will be generated after passing verification.

11.5.7 Data-Quality Review

Database quality will be jointly reviewed by biostatisticians, data managers and database developers, generating formal data-quality review report.

11.5.8 Database Locking

After blind review, database will be locked under joint supervision of biostatisticians and data managers, with database-locking report completed.

11.5.9 Database Hand-over for Analysis

Locked database will be handed over to biostatistical team with signed hand-over document.

11.6 Data Query and Response

Laboratory values deviating more than 20 % from clinical acceptable reference range (hepatic - renal function in adverse - event monitoring) shall be verified with necessary explanation from clinical investigators. Inconsistent pulmonary-function data and economically unreasonable drug-cost records shall also be verified with investigator explanation.

All identified data queries will be recorded on query forms with query labels attached to original CRF pages for easy location. Queries will be delivered to clinical monitors for investigator resolution with specified time limit. Investigators shall reply and resolve queries within one week upon receipt of query forms; overdue items will be escalated to site principal investigator.

12. Ethical Principles

12.1 Ethical-Review System

This study will comply with ethical principles for clinical research to guarantee subject rights and safety.

(1) The study protocol must be reviewed and approved by Medical Ethics Committee of Hebei Provincial Hospital of Traditional Chinese Medicine prior to study initiation.

(2) Participating site ethics committees will review local feasibility including investigator qualification, experience and facility conditions.

(3) Upon occurrence of serious adverse events, site ethics committees will convene timely review meetings and communicate conclusions to sponsor - site ethics committee and study investigators.

(4) Written recommendations for protocol modification issued by ethics committees for subject protection shall be transmitted to principal investigator. Sponsor-site will implement revisions uniformly to guarantee consistency across all participating sites.

(5) Ethics-committee meeting minutes will be fully documented for audit purpose; frequency of continuing review will be determined by ethics committee based on risk magnitude.

12.2 Risk-Benefit Assessment

Subject benefit: This is a single-arm feasibility exploratory trial; clinical benefit is not guaranteed for every participant. During study participation, subjects will receive standardized systematic disease assessment; clinical records can serve as reference for routine clinical management. Subjects will obtain more regular disease follow-up and medical consultation. No free TCM decoction is provided. All medications,

laboratory and imaging examinations specified in protocol are routine clinical services, and relevant costs shall be borne by subjects themselves.

Risk: Huangqi Yangyuan Formula is commonly used TCM adjuvant anti-cancer formula in clinical practice; main herbal ingredients include Astragali Radix, Rehmanniae Radix, Lycii Fructus, Dioscoreae Rhizoma, Poria Cocos, Spatholobi Caulis, Angelicae Sinensis Radix, etc. No obvious severe adverse reactions have been reported so far. Capecitabine is standard first-line chemotherapy for advanced colorectal cancer; potential toxicities include hand-foot skin reaction, diarrhea, myelosuppression, nausea-vomiting, fatigue, hepatic-renal function abnormality, etc. Adverse-event manifestations vary individually. Treatment may be ineffective, and tumor recurrence or metastasis may occur due to disease progression. Strict confidentiality measures will be implemented for subject personal privacy information.

Risk classification: greater-than-minimal risk; corresponding clinical management measures are available for all identified risks.

Compensation for subject harm: If physical harm is definitely caused directly by study intervention, medical institution will provide corresponding medical treatment. No special compensation fund is available for this study. Harm caused by underlying disease progression, intrinsic adverse reactions of routine drugs or non-study-related factors will not be compensated. Above content will be fully specified in informed-consent documents.

12.3 Informed Consent

Prior to enrollment, investigators shall fully introduce study purpose, procedures, risks and benefits to subjects or their authorized representatives via written documents. Subjects shall be informed of the right to withdraw at any time without penalty to routine clinical care. Each subject shall receive a copy of signed informed-consent form, with adequate time for question-asking and consideration before signature. Informed-consent documents shall cover biological-sample management, self-paid study-related costs, harm-compensation clauses and subject-reimbursement rules. Signed informed-consent forms will be preserved as essential source documents.

12.4 Subject Recruitment

Recruitment is the initial step of informed consent and subject screening, respecting subject autonomy and privacy.

All recruitment materials must be reviewed and approved by ethics committee. Any revision of recruitment materials requires additional ethical review. Ethical considerations for subject recruitment include respect for privacy and voluntary participation; exaggeration of potential benefit or underestimation of risk is forbidden to avoid undue inducement.

No free drug or free examination is provided as recruitment incentive. Subjects will be recruited from clinical outpatient/in‑patient population and via ethically‑approved recruitment posters. Attending physicians (who are also study investigators) will identify potentially eligible patients and invite participation.

Reimbursement principle: reasonable reimbursement for subject time and transportation cost is allowed; excessive inducement is prohibited.

Subject withdrawal and reimbursement: subjects withdrawing due to study‑related intolerable adverse events will obtain corresponding transportation subsidy proportional to actual participation duration. Subjects withdrawing for other reasons will receive pro‑rated subsidy according to actual participation. Investigators may deduct partial or all subsidy for subjects eliminated due to intentional non‑compliance with protocol.

12.5 Subject Medical Care and Protection

(1) Study investigators are attending‑physician level or above with ≥ 3‑year professional experience in oncology. Site investigators are responsible for subject medical care and clinical decisions related to trial.

(2) Interventions used in this study are routine clinical regimens; participation will not delay standard clinical treatment.

(3) Subjects voluntarily withdrawing from study will still receive appropriate clinical management according to clinical condition.

(4) Timely and appropriate medical treatment will be provided for adverse events occurring during study. Medical rescue will be performed for serious adverse events definitely related to study intervention according to institutional IIT

management procedures. No compensation will be offered for non-study-related adverse events.

(5) No free medication or free examinations are supplied in this study. All drugs, laboratory and imaging examinations specified in protocol are routine clinical services and should be paid by subjects.

(6) Subject privacy will be strictly protected; access permissions for personal medical records and biological specimens will be defined to guarantee information security and confidentiality.

13. References

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