Guideline on Clinical Development of New Drug of Traditional Chinese Medicine Compound Preparations Based on Human-use Experience

(Final)

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1. Overview

Traditional Chinese medicine (TCM) compound preparations are generally derived from TCM clinical practice and have the support and guidance of TCM theory. On the basis of summarizing individual medication experience, the applicable population, medication dose, efficacy characteristics and clinical benefits are gradually clarified in clinical practice to form a fixed formula and develop new TCM drugs suitable for group medication.

In order to promote the essence inheritance and innovation of TCM, to accelerate the construction of "Evidence System for TMC Registration and Review Combining Traditional Chinese Medicine Theory, Human-use experience and Clinical Trials" (hereinafter referred to as " Triple combined" evidence system for review), and to guide the new drug research and development of TCM compound preparations based on the rules and characteristics of TCM research and development, the Guideline is hereby formulated.

TCM theory is an important basis for the use of TCM compound preparations in clinical practice, mainly reflecting the formula's reasonable explanation of the proposed major functions, that is, the rationality of "Theory-Diagnosis-Formula-Medicine". The TCM compound preparations to be developed should be supported by TCM theory.

Human-use experience contains the understanding and summary of the target population, dosage, efficacy characteristics, and clinical benefits of TCM formulas /preparations accumulated during clinical medication. The process of obtaining human-use experience is the process of gradually exploring and clarifying the efficacy, safety and clinical benefits of TCM compound preparations, and is also an important stage in the research and development process of TCM compound preparations, and its study

can run through the whole process of development.

Clinical trials should combine the above TCM theory basis and summaries of human-use experience to carry out studies on efficacy and safety issues not yet clarified. Different research and development strategies and flexible and diverse trial designs can be adopted as needed.

Combining TCM theory, human-use experience and clinical trials, an evidence system supporting the marketing application of TCM compound preparations is formed.

The research and development of new drugs of TCM compound preparations shall be patient-focused, clinical value-oriented, reflect the drug action characteristics of TCM, take the clinical advantages of TCM, carry out in various ways such as the combination of diseases and syndromes, specialized medicine for specific diseases or syndrome TCM, and clarify the clinical benefits of patients.

The sources of TCM compound preparations include not only TCM formula from clinical experience, preparation from medical institution, addition or subtraction of ancient classical formulas, but also scientific formulas based on modern studies, with multi-path characteristics for research and development. This guideline focuses on the collection of human-use experience and how evidence to support regulatory decisions can be generated based on human-use experience. This guideline is applicable to clinical research and development of new drug of TCM compound preparations based on human-use experience. With the update of relevant regulations and the accumulation of practical experience, this guideline will also be updated and improved.

2. General Principles

(1) The information of human-use experience discussed in this guideline is formed in the process of clinical practice of fixed TCM formulas or TCM compound preparations supported by TCM theory, after the formula ingredients (including base, medicinal site, preparation, etc.), dosage, clinical positioning are basically clear, accumulated by a longer period of time and/or a larger population range of clinical use, including formula source (and evolution), key pharmaceutical data, clinical use, clinical practice data, and

other clinical study data, etc., and used to support the research and development decision or registration application of new p0drugs of TCM compound preparations. (2) Except for approved preparations (such as TCM preparations in medical institutions), the preparation process shall be a traditional process that can reflect the actual situation of clinical practice of TCM.

(3) Human-use experience study can run through the whole process of studies and development of new drugs of TCM compound preparations, especially for new TCM drugs with human-use experience based on ancient classical formulas, distinguished veteran TCM doctor's experience formulas, medical institution preparations, etc. The information generated in the process of TCM clinical diagnosis and treatment practice can be reasonably utilized through pre-specified study design to further explain their clinical application population, efficacy characteristics, etc., and provide support for researchers to develop strategies for drug research and development, as well as provide references for researchers to develop protocols for non-clinical and clinical studies.

(4) If human-use experience meets the relevant requirements for data curation and data evaluation with reasonable and sufficient analysis of human-use experience data and correct result interpretations, it can be used as evidence to support registration application. For the research and development of new drugs of TCM compound preparations based on human-use experience, the clinical benefits, target population, dosage and efficacy characteristics can be preliminarily determined through human-use experience, and therefore non-clinical pharmacodynamic studies are usually not required. If it is necessary to carry out clinical trials, it is necessary to reasonably design subsequent clinical trials according to the formula characteristics and the support of human-use experience. It is feasible to adopt randomized controlled clinical trial (RCT) design or adopt real world study designs such as pragmatic clinical trial (PCT).

(5) According to different application categories and situations of human-use experience of TCM compound preparations, different research and development paths of new TCM drugs may be selected. In the actual application process, applicants may

communicate with CDE according to the specific varieties.

3. Scope of Application

This guideline is applicable to clinical research and development of new drugs of TCM compound preparations based on human-use experience, such as Class 1.1 TCM compound preparations, Class 3.2 other TCM compound preparations derived from ancient classical formulas etc.

4. Information on Human-use Experience

4.1 Source and evolution of formula

The source and evolution of formulas of TCM compound preparations include the source of formulas, the TCM theory on which they are based, formula ingredient's dosage, dosage form, intended functional indication scope, applicable population, dosage and administration, course of treatment, whether they contain toxic herbs or contain TCM incompatibilities. If the formula is based on addition or subtraction of ancient classical TCM formulae, the corresponding changes and their rationale should also be provided. For more specific content and requirements, see the Guideline for Writing Application Dossier of Traditional Chinese Medicine Theory for New Drug of Traditional Chinese Medicine Compound Preparations (Final).

4.2 Key pharmaceutical information

Including but not limited to: formula ingredients (including base, application site, preparation methods, etc.), dosage form and preparation process and its changes and evolution (if any). See relevant guidelines for specific requirements.

4.3 Clinical use

The complete clinical use of TCM compound preparations from the original formula to the preparation under application and its evolution (if any), including the medical institutions (name, grade, region) where it is used in clinical practice, initial year and month, departments, major population, number of patients and doses, adverse reactions, etc. If there is a break in clinical use, the reason should be provided.

4.4 Clinical practice data

The source data of clinical practice data are mainly the original records of clinical practice stored in hospital information system and medical records database, including structured and unstructured data, digital and non-digital medical records. Clinical practice data may also be derived from previous clinical studies.

4.4.1 Medical records

Medical records are the primary source of clinical practice data. The vast majority of current medical records are electronic, but may also be paper-based records. In any form, data curation is required to meet the quality requirements for subsequent analysis and meet the submission standards for registration application.

In general, outpatient and emergency medical records are less informative and have more missing out-of-hospital data, especially for clinical outcome variables, which directly affect the integrity of individual's longitudinal data. These data should be used with great caution in clinical studies. The integrity of outpatient and emergency medical records should be improved by informatization technology tools to improve the quality of data, so as to support the clinical studies and development of TCM.

4.4.2 Clinical study data

For previous clinical studies of TCM compound preparations, whether prospectively or retrospectively observational, or randomized controlled, their data quality is generally better than that of medical records in routine clinical practice. There may be multiple clinical studies for the same TCM compound preparation, and there may be multiple types of study designs. For example, there may be retrospective studies and prospective studies, observational studies and interventional studies. If a unified data standard is not implemented for these studies , or the standards used do not meet the requirements of registration studies, it is necessary to unify and standardize the data from these studies before it may be applicable to subsequent data analysis for the purpose of registration and marketing. In addition, clinical study data shall be traceable to the original medical records or the independent source database of the projects in which data were independently collected and entered.

For data from multiple clinical studies conducted with the same fixed TCM formula or TCM compound preparation, if a combined analysis (e.g., meta-analysis) is required, it is encouraged that the analysis be based on individual level data from each study rather than on summary statistics extracted from study reports.

5. Strategies for Clinical Researchand Development of New Drugs of TCM Compound Preparations Based on Human-use Experience

Following the "Three combinations" evidence system for review, provided that sufficient TCM theory is available, human-use experience can be used to support studies and development decisions or registration applications for new drugs of TCM compound preparations. The clinical research and development strategy based on human-use experience is illustrated in Figure 1.

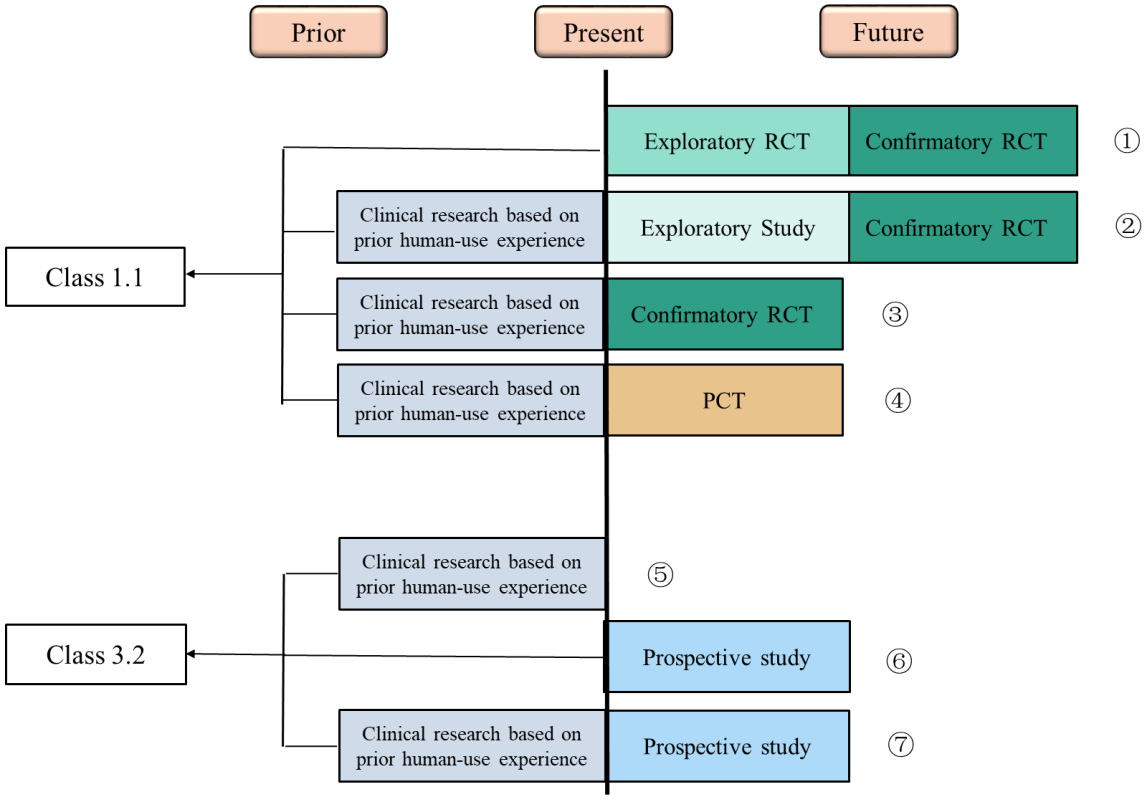

Figure 1 Clinical research and development strategy for TCM compound preparations based on human-use experience *

* Cut-off points for "present": for path ① and ③ it is the time of obtaining clinical trial license; for path ② and ④ it is the time of obtaining clinical study license or the

time of reaching consensus after communication with regulatory agencies; for path ⑤ it is the time of submitting marketing application; for path ⑥ and ⑦ it is the time of reaching consensus after communication with regulatory agencies.

According to the timing of data acquisition, this guideline classifies studies into two categories: clinical studies based on data from historical human-use experience and prospective studies. Data from historical human-use experience can be either source data from medical records or data from previously conducted clinical studies, which may be retrospective or prospective observational studies, or retrospective and prospective observational studies, or RCT or PCT. For historical data, both source data from medical records and data obtained from different clinical studies, unified data curation should be performed to make the study data meet the requirements for analysis. Prospectively collected data are data from prospective studies, including RCT, PCT, and prospective observational clinical studies.

Historical data and prospectively collected data are separated by the "present" cut point. Depending on the type of submission, "present" may be the time when a marketing application is submitted, or when a clinical study (including clinical trials and real-world studies) is licensed, or when a consensus has been reached after communications with regulatory agencies (see note to Figure 1).

Evidence based on human-use experience to support the marketing of a new drug is broadly categorized into two categories: direct support for marketing and laying the foundation for subsequent clinical studies.

(1) Evidence based on human-use experience to support registration

For previously obtained human-use experience data, through good study design, standardized data curation, and adequate and reasonable statistical analysis, if the analytical results can provide sufficient evidence of efficacy and safety within the proposed functional indication scope as well as dosage and administration, it can be used directly as the key evidence to support the marketing registration of the product after communication with regulatory agencies, as shown in Figure 1 for Class 3.2 the

research and development path ⑤ for other TCM compound preparations derived from ancient classical formulas.

(2) Further clinical studies based on human-use experience

If the results of the above-mentioned studies based on human-use experience are not yet sufficient to support the drug efficacy and safety and cannot completely and accurately answer the scientific questions in support of marketing, further clinical studies are needed to obtain more substantial clinical evidence to support the marketing of new drug.

If human-use experience is used to support the design of subsequent clinical studies, some key elements can be identified through the analysis of human-use experience data, such as target population and functional indication scope, drug dosage and administration, primary endpoint, observation period and follow-up nodes, and specific parameters or effect size parameters required for sample size estimation. Furthermore, if the human-use experience data are of good quality and in sufficient quantity, the analysis results and subsequent clinical study results can be used simultaneously as evidence for regulatory decisions.

The type of clinical studies to be followed should be determined on a case-by-case basis. If high-quality human-use experience data are available, and the study results are positive or show a clear positive trend, then a confirmatory RCT or a PCT can be conducted directly. Otherwise, exploratory clinical studies are still need first. Such exploratory studies can be interventional or observational, and then on this basis, whether to conduct further confirmatory clinical trials can be evaluated.

It needs to be noted that clinical research and development of TCM compound preparations should still follow the conventional pathway if there is no foundation of human-use experience-based studies.

Different research and development pathways are described below according to the submission categories. It needs to be emphasized that the research and development pathways shown in Figure 1 does not represent all possible research and development

pathways and that the applicant can choose the appropriate pathway based on their categories or communicate fully with regulatory agencies on their research and development strategy.

5.1 Class 1.1 TCM Compound Preparations

Paths ① to ④ mainly aim at Class 1.1 TCM compound preparations.

Path ①: Without any human-use experience, the conventional clinical trial pathway should be followed, i.e., a sequence of exploratory and confirmatory RCTs.

Path ②: Clinical studies based on previous human-use experience data have weak evidence but may inform the design of subsequent clinical studies, then subsequent exploratory studies (either interventional or observational) is required before conducting confirmatory RCTs.

Path ③: With high quality human-use experience data and positive study results or clear positive trends, confirmatory RCTs can be conducted directly afterwards.

Path ④: With high-quality human-use experience data and positive study results or clear positive trends, confirmatory PCTs can be conducted directly afterwards.

5.2 Class 3.2 Other TCM compound preparations derived from ancient classical formulas

Paths ⑤ to ⑦ mainly aim at class 3.2 other TCM compound preparations derived from ancient classical formulas.

Path ⑤: Use evidence from clinical studies based on historical human-use experience data to support registration.

Path ⑥: Use evidence obtained from prospective studies to support registration. Prospective studies can be interventional or observational.

Path ⑦: Insufficient evidence from a clinical study based on historical human-use experience data is not yet available to support registration. The strength of evidence needs to be improved through prospective studies.

6. Curation and Evaluation of Clinical Practice Data of Human-use experience

Clinical data from human-use-experience-based TCM clinical research and development are generally obtained from previous or historical sources, whether from medical records or from previous clinical studies. Since these data are often incomplete, their data standards/models and description methods are not consistent, and hardly can directly meet the requirements for analysis purposes, these data must be subject to a standardized curation process to meet the requirements for generating clinical evidence and meet the data submission standards.

6.1 Data curation

The curation of previous clinical data mainly includes but is not limited to: data security (desensitization) processing, data extraction (including multiple data sources), data cleaning (logic check and processing of abnormal data and missing data, etc.), data conversion (data standard, common data model, normalization, natural language processing, medical coding, derived variable calculation, etc.), data transfer and storage, and data quality control, etc.

6.2 Data quality evaluation

The quality evaluation of historical clinical data is generally divided into two steps. Firstly, whether the source data meet the basic analysis requirements is preliminarily evaluated; whether the use of data complied with ethical review regulatory requirements and data security and privacy protection requirements, whether the data are accessible, the completeness of key variables (e.g., outcome variables, exposure/intervention variables, demographic variables and important covariates, etc.), and whether a sufficient sample size can be ensured after curation are mainly evaluated. Secondly, the fitness of the data after curation is evaluated, mainly from two aspects: relevance and reliability. The relevance focuses on the coverage rate of key variables, the accuracy defined by exposure/treatment and clinical outcomes, the representativeness of the target population and the fusion of multiple source heterogeneous data; the reliability mainly includes several aspects such as the completeness, accuracy, transparency, quality control and quality assurance of the data.

Please refer to “Guideline on Using Real-World Data to Generate Real-World Evidence (Final)” for detailed requirements for data curation and quality evaluation, and refer to “Guideline for Clinical Trial Data Submission (Final)” for relevant data submission standards.

7. Clinical Study Design Based on Human-use experience

As described in Section 5 " Strategies for Clinical Research and Development of TCM Compound Preparations Based on Human-use experience", it is divided into clinical study design based on data from historical human-use experience, and prospective study design based on prospective collection of clinical data.

7.1 Design of clinical study based on historical human-use experience data

7.1.1 Study objectives

The objectives of the study should be clearly defined, and the scientific questions to be answered in the clinical study should be addressed around the target population, treatment or exposure, and effect measurement. In addition to the primary objective, secondary and exploratory objectives can also be set.

7.1.2 Target population and clinical positioning

The target population and clinical positioning of clinical studies should be consistent with TCM theory and TCM diagnosis and treatment practice, and consistent with the study objectives. The inclusion and exclusion criteria should be set depending on the objectives of the study, and can be appropriately relaxed if a wider range of indications are desired for the drug. If more focus is on the confirmation of the study conclusions, the inclusion and exclusion criteria can be relatively strict. The diagnostic criteria (if any) on which the study population is based should be described in detail or its source should be provided. The efficacy characteristics and advantages of TCM should be fully considered for clinical positioning and its functional indication scope should be clarified.

7.1.3 Choice of controls

Active control or standard of care (SOC) control is usually selected for clinical studies based on human-use experience. Attention should be paid to the comparability of TCM with control drugs in their major functional indications. If active control is selected, it should be an established treatment method or treatment strategy with clear efficacy in current clinical practice. Evidence to support regulatory decision-making may also be provided by well-designed, placebo-controlled randomized clinical trials that were conducted in the past.

7.1.4 Outcome variable and other study variables

Outcome variables (indicators) are usually divided into primary endpoints and secondary endpoints. The choice of primary endpoints is a core issue in study design and should correspond to their clinical positioning. Widely accepted outcome variables or their surrogates should be adopted, including disease recovery or delayed progression, disease status or symptom improvement, etc. At the same time, attention should be paid to the use of patient-focused clinical outcome assessment (COA) variables, such as patient-reported outcomes (PRO), etc. For specific content, please refer to “Guideline on Using Patient-Reported Outcomes in Drug Clinical Trial (Final)”. Variables (indicators) directly or indirectly related to the study should be collected as far as possible. In addition to study variables (indicators), at least the following should also be included: treatment/exposure, demographic data, medical history, treatment regimen (dosage form, dosage form, course of treatment, etc.), concomitant therapies, various investigations, time points of collection of each variable, etc. Important baseline variables that may have an impact on clinical outcomes should be defined from the variables mentioned above.

7.1.5 Data source and curation plan

The data source should be preliminarily specified, and the data curation plan should be developed in detail. If there are extensive contents in the data curation plan, it can be presented as an appendix to the study protocol.

7.1.6 Statistical analysis plan

The statistical analysis plan shall be developed in detail. If there are extensive contents in the statistical analysis plan, it can also be presented as an appendix to the study protocol, but it must be pre-specified in parallel with the protocol. The analysis plan should focus on statistical assumptions and analysis models for the primary analysis.

The sample size estimation should take into account the number of covariates in the primary analysis model, which involves causal inference methods, and their relationship to the treatment/exposure factors, as well as the proportion of remained available data after data curation. In principle, it is encouraged to include all eligible patients according to the inclusion and exclusion criteria after meeting the minimum sample size required for the study. If not, to avoid selection bias, rules for inclusion should be specified and justified, e.g., random sampling of all eligible patients, or selection of patients in the latest period.

7.1.7 Bias Control

The potential impact of various biases on study results should be fully considered and countermeasures should be proposed. In this regard, it is necessary to focus on data selection bias, confounding bias and result-driven bias, etc., and their countermeasures may be reflected in the data curation plan and statistical analysis plan, as well as corresponding major modifications plans of protocol during implementation.

If a study based on human-use experience is only to provide a basis for the design of a subsequent clinical study, its study design will be appropriate as long as it can achieve exploratory objectives.

7.2 Prospective clinical study design

If the results of studies based on historical human-use experience are insufficient to support marketing of a new TCM drug, further prospective clinical studies are required to form substantial clinical evidence to support the marketing application. In this regard, the results of previous studies can provide the basis for subsequent study design (see the above Section 5).

In principle, the subsequent clinical study shall be interventional prospective study, such as RCT, PCT, or single-arm trial in special circumstances.

For RCT please refer to relevant international and domestic guidelines.

With respect to PCT, it differs mainly from RCT in the extent to which it is close to real medical practice. In terms of design, PCTs should be as close as possible to the real medical practice, and wider inclusion and exclusion criteria should be used to make the study population more representative. The interventions can be standard or implemented according to the diagnosis and treatment routinely. Generally, active control or standard of care control should be selected, and placebo control should not be encouraged. Randomized design should be used as far as possible, and if its implementation is difficult then non-randomized design can also be used. Blinding method should be used as far as possible, but open design considered based on practical factors may also be accepted. In addition, the effect assessment of PCTs is usually not limited to clinical efficacy, but focuses more on the overall effectiveness that can reflect the characteristics of TCM treatment, such as the improvement of quality of life, etc. The primary analysis should control the influence of potential confounding factors as much as possible, especially for non-randomized designs. Influence and control of various biases should also be fully considered.

Regarding single-arm trials, which are mostly used for rare and critical diseases, the comparability between the test group and external controls should be focused on, and the control of bias (e.g., selection bias, survivor bias, etc.). External controls can be either historical or parallel, and parallel external controls are encouraged. If target value controls are used, the determination of the target value should be well justified.

8. Evaluation of Clinical Studies Based on Human-use experience

8.1 Efficacy assessment

The efficacy evaluation of TCM shall reflect the characteristics of its clinical application and efficacy of TCM. Studies of efficacy evaluation indicators, evaluation tools and evaluation methods with clinical meaning that can reflect the clinical efficacy

of TCM according to the dominant diseases and clinical positioning of TCM treatment is encouraged. If new tools and new methods are used to evaluate the efficacy, their rationality and scientific basis should be provided, and the clinical meaning and clinical benefits they reflect should be explained.

8.1.1 Adequacy of information on human-use experience and fitness of clinical data

Information on human-use experience should contain at least the source and evolution of the formula (if any), the underlying TCM theory, clinical positioning, dosage form, preparation process and its changes (if any), and clinical data. If there are other clinical and/or non-clinical data relevant to it, they should also be provided as far as possible, such as external control data, basic study data, etc.

The evaluation of the fitness of the clinical data should satisfy the requirements for relevance and reliability and ensure data traceability (see Guideline on Using Real-World Data to Generate Real-World Evidence (Final)).

8.1.2 Reasonability, integrity and consistency of implementation of clinical study protocols

The clinical study protocol shall be scientific and rational, complete in content, operable and shall be specified prior to the initiation of the study. In addition to the general design principles, the clinical study protocol should also elaborate the methods and measures for bias control, data curation plan and statistical analysis plan. If the data curation plan and the statistical analysis plan are not to be developed in detail in the protocol, they may be presented as an addendum to the protocol, but they must be synchronized with the protocol. In order to ensure the transparency of the study, the study protocol shall be registered on the clinical study registration platform in advance. If the protocol is significantly changed, it shall also be timely updated in the registration system.

The conduct of the study should be consistent with the protocol. If during the implementation process, requires adjustment of data curation plan resulting in major changes in the nature or number of the target analysis population, or if the primary

analysis plan needs to be adjusted, these shall all be major changes to the protocol, requiring re-ethical review and communication with regulatory agency for agreement. These are also necessary to ensure the transparency of study.

8.1.3 Integrity, correctness, and sufficiency of the study report

The study report should be integral, correct and sufficient. In addition to the main report, it is encouraged to provide other relevant independent study reports. The study report should reflect the evaluation of the study designs, the stringency of the quality control of the study, the transparency of the study process (including the data extraction and data curation process, changes in the data curation plan and statistical analysis plan), the robustness of the analysis results under different assumptions, and the appropriateness of the data analysis methods and the interpretation of the analysis results.

8.2 Safety assessment

The adequacy of information and fitness of data for human-use experience involved in safety assessment, as well as the rationality of the study protocol and the consistency of its implementation, are similar to efficacy assessment. Adverse reactions and serious adverse events in the clinical use of TCM compound preparations should be reported in detail and relevant analysis should be performed.

The identification of risk signals should focus on whether the formula contains toxic or known toxic compositions, or a combination that suggests the possibility of synergistic increased toxicity according to TCM theory. If relevant toxic reactions are identified in non-clinical studies, the ability of the target population to tolerate this risk should be assessed based on the characteristics of the toxic reaction (including target organs, time of appearance, dose relevance, reversibility, species variations, etc.) as well as whether there are sensitive monitoring indicators in human body, in combination with the safety profile in human-use experience, to provide a basis for the development of relevant risk control measures to adequately protect the safety of subjects/patients .

8.3 Benefit-risk evaluation

Synthetically assess whether the results of clinical studies can answer the scientific questions of the product as a marketable drug, including aspects but not limited to: ① clear functional scope and characteristics of the applicable population, such as age, disease severity, characteristics of the symptoms, subgroups of people at risk of use; ② clear, clinically realistic method of administration, including dose, duration of treatment, etc.; ③ clear advantages of clinical application; ④ can bring definite clinical benefits for patients, and the benefits outweigh the risks.

9. Communication with Regulatory Agency

Careful and rigorous study design, good quality control during the conduct of the project (particularly data quality control), correct statistical analysis, and reasonable interpretation of the results are necessary to ensure the reliability of the study conclusions. Applicants are encouraged to communicate with regulatory agency at key time points of their studies and development. For details, please refer to the Guidelines for Communication Under the "Triple-Combined" Evidence System for Registration Review.

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Glossary

Observational Study: studies of natural or clinical subjects that explore the causal relationship between exposure/treatment and outcome with respect to specific study questions, without active intervention.

Retrospective Observational Study: An observational study that identifies the target population at the start of the study and is based on historical data (data collected before the study initiation).

Retrospective and Prospective Observational Study: Identify the target population at the start of the study, identify the exposure/treatment and outcome data to be collected prior to the start of the study, and conduct the observational study based on historical data (data generated prior to the start of the study) and prospectively collected data.

Clinical Trial: An interventional clinical study in which one or more interventions (which may include placebo or other controls) are prospectively assigned to human subjects to assess their impact on health-related biomedical or behavioral outcomes.

Prospective Observational Study: An observational study in which the target population is identified at the start of the study and exposure/treatment and outcome data to be collected are identified prior to the start of the study.

Pragmatic Clinical Trial (PCT): sometimes called a practical clinical trial, for which the design and conduct of trial are as close as possible to the real-world clinical practice. The PCT is a type of clinical studies that are between traditional RCTs and observational studies.

Data Curation: refers to the curation of the source data for the purpose of statistical analysis of specific clinical study questions. Data curation includes the following aspects: data acquisition (including multiple data sources), data safety processing, data cleaning (logical judgment and outliers processing, data completeness processing), data input and structuring (CDM, normalization, natural language processing, medical coding, derived variable calculation), data transmission, etc.

Real-World Data (RWD): Data derived from various sources reflecting patient's

health status and/or diagnosis and health care that are collected in routine practice. Not all real-world data can be used to generate real-world evidence and only real-world data that satisfies fit-for-purpose requirements can potentially be used to generate real-world evidence.