

## **Attachment**

### **Technical Guidance on Clinical Evaluation of Medical Devices**

#### **I. Purpose**

The clinical evaluation of medical devices is the assessment procedure conducted by registration applicants to validate whether the application requirements or intended use of the target medical device(s) can be achieved based on a comprehensive analysis of clinical literatures, clinical experience data and information gathered from the clinical trial(s). This guidance is intended for providing technical guidance to registration applicants for conducting clinical evaluation and to food and drug administrative authorities for reviewing the clinical evaluation report and related data.

#### **II. Legal Basis**

- (1) “Regulations for the Supervision and Administration of Medical Devices” (State Council Decree No. 650)
- (2) “Provisions for Medical Device Registration” (Decree No. 4 by China Food and Drug Administration)
- (3) Relevant provisions on clinical trial quality control of medical devices

#### **III. Scope of Application**

This guidance is applicable to the clinical evaluation for registration application of Class II and Class III medical devices, and is not applicable to the clinical evaluation of in-vitro diagnostics administrated as medical devices. If there is technical guidance on clinical evaluation of specific medical device product available, the specific guideline should be followed for the clinical evaluation of the corresponding product.

#### **IV. Basic Principles**

The clinical evaluations should be thorough and objective. Corresponding data should be collected by multiple means including clinical trial(s). Clinical performance and safety data collected during clinical evaluation (including both favorable and unfavorable data) should be included in the analysis. The depth and extent of clinical evaluation, and required data type and volume should be flexible and appropriate to the product design features, critical technologies, intended use, and risks of the device as well as the depth and extent of the non-clinical studies.

A clinical evaluation should verify the clinical claims made about the device, such as intended purpose and application of the device (e.g., target treatment group, the site of application to/in the body, method of contact with human body, indications, severity and state of the disease, application requirements and operation environment, etc.), method of deployment, contraindications, precautions, and warnings.

The registration applicant should be able to reach the following conclusions through clinical evaluation: the product can achieve the expected performance in normal use conditions; the product risks are acceptable balanced with expected benefits; clinical performance and safety of the product are both supported by sufficient evidence.

#### **V. The Requirements of Clinical Evaluation for the Products Listed in “The**

## **Catalogue of Medical Devices Exempted from Clinical Trial”**

For the clinical evaluation of products listed in “The Catalogue of Medical Devices Exempted from Clinical Trial” (hereinafter referred to as “the Catalogue”), the registration applicant should submit the comparison summary of relevant information of the device under application with the corresponding information in the Catalogue, and the comparison description of the device under registration to the equivalent product listed in the Catalogue which has already obtained domestic registration approval. The clinical evaluation to be submitted should include the following information:

(1) Comparison between the device under application and corresponding information in the Catalogue.

(2) Comparison between the device under application and an equivalent device in the Catalogue which has obtained domestic registration approval. The comparison description should include ‘comparison table between the device under application and an equivalent device which has obtained domestic registration approval’ (see Annex 1) and relevant supporting documents.

The above submissions should be able to prove equivalence between the device under application and the corresponding device listed in the Catalogue. If this is not the case, the application procedures should be followed according to other relevant requirements defined in this guidance.

## **VI. Requirements for Clinical Analysis and Evaluation Based on Data from Clinical Application or Clinical Trial(s) of the Equivalent Medical Device**

### **(I) Equivalent Medical Devices**

#### **1. Definition of Equivalent Medical Device**

The equivalent medical device refers to the device product which has obtained domestic registration approval and is substantially equivalent to the registration device in aspects of basic principle, structure composition, manufacturing material (manufacturing material in contact with the human body for active device), manufacturing process, performance requirements, safety evaluation, conformed national /industry standards and intended use.

The registration device could be viewed as substantially equivalent with the equivalent device in case that the differences between the two devices do not cause any negative impact on the safety and effectiveness of the device.

#### **2. Determination of Equivalent Medical Device**

If the registration applicant would like to prove the safety and effectiveness of the registration device utilizing the data from the clinical application experience or clinical trial(s) of the equivalent device, the applicant needs to compare the registration device with one or more equivalent device(s) and prove the substantial equivalence between the devices

The comparison items with the equivalent device shall include, but be not limited to the items listed in Annex 2, including the qualitative and quantitative data, the verification and validation results. The similarities and differences between the two products should be described in details. Whether the differences will result in any negative impact on the safety or effectiveness of the registration device should be verified and/or confirmed based on the data of the registration device, such as data

obtained from its non-clinical study, clinical literature, clinical experience, and clinical trials conducted in China to address any difference. Collection, analysis, and evaluation of the relevant data should meet the requirements defined in sections (III) and (IV) and corresponding annexes. The clinical trials should meet clinical trial quality management regulations.

The registration applicant should provide comparative information in tabular form (see Annex 3 for the format). For specific products with inapplicable items, the justification should be provided.

## **(II) Evaluation Path**

See Annex 4 for the details of evaluation path.

## **(III) Collection of Data from Clinical Experience or Clinical Trial(s) of Equivalent Medical Device**

The clinical experience or trial(s) data (hereinafter abbreviated as clinical data) can be obtained from public scientific literature released in China and/or overseas and legally obtained data, including clinical literature data and clinical experience data. The registration applicant can select the appropriate data sources and collection methods based on the specific requirements of the products.

### **1. Collection of Clinical Literature Data**

When collecting the literature data for clinical evaluation, the reliability, comprehensiveness of the literature search should be guaranteed. The recommended literature search and screening elements are in Annex 5. Before literature search, the literature search and screening protocol should be formulated (the content and format are in Annex 6). After the literature search and screening, the report on literature search and screening must be prepared (the content and format are in Annex 7). The clinical literature search and screening should have repeatability. The personnel in charge of literature search and screening should have appropriate professional knowledge and practical experience.

### **2. Collection of Clinical Experience Data**

Collection of clinical experience data should include collection of data from completed clinical trials, adverse events, and corrective measures related to clinical risks.

#### **(1) Collection of Data from Completed Clinical Trials**

According to the design of the clinical study, clinical studies can be divided into prospective study, retrospective study, random control study, nonrandom control study, single arm study and case report.

The registration applicant should collect and provide the opinion of Ethics Committee (if applicable), clinical study protocol and clinical study report.

#### **(2) Collection of Adverse Events Data**

The registration applicant should collect the corresponding adverse event data from the complaints and adverse events database established by the applicant, and the adverse events database issued by the regulatory authorities of various countries, such as the “Medical Device Adverse Events Bulletin” and “Alert Newsletter of Medical Devices” issued by China Food and Drug Administration, the Manufacturer and User

Facility Device Experience Database (MAUDE) of U.S. Food and Drug Administration and the British Medical Device Alert (MDA).

The registration applicant should provide the following information related to the equivalent device: number of complaints and adverse events, classified reasons of complaints and adverse events, number of complaints and adverse events in different classified reasons, the relationship of the adverse events with the product. For serious adverse events, the specific information such as event description, cause analysis, and corrective action should be summarized in tabular form.

For the product under application, specific information such as the time on market in different countries, accumulated sales and outcome of serious adverse events should also be provided.

### (3) Data Collection of Corrective Measures Associated with Clinical Risks

The specific information of corrective measures associated with clinical risks (such as recall, announcements, warnings, etc.) of the equivalent device and adopted risk control measures should be collected and provided by the registration applicant.

## **(IV) Analysis and Evaluation of Clinical Data from Equivalent Medical Device**

### 1. Quality Evaluation of Data

The registration applicant should classify the data to be analyzed in accordance with generally accepted evaluation criteria of clinical evidence level (such as the evaluation criteria of clinical evidence level developed by the Oxford Center of Evidence Based Medicine). For some clinical data that are not applicable for product performance evaluation, if applicable they may be still applied to the safety evaluation of the product.

### 2. Establishment of Data Sets

The collected clinical data can be grouped into several data sets according to their different data type and data quality. The registration applicant may also establish data sets according to different evaluation purposes, for example, if the clinical performance and/or safety of certain products have ethnic differences, the Chinese subgroup data sets can be established for evaluating the safety and /or efficacy of the product in Chinese population.

### 3. Statistical Analysis of Data

The appropriate data analysis methods should be adopted to conduct statistical analysis in different data sets. For the data sets with multiple study results, the analysis method should include the qualitative analysis and quantitative analysis.

### 4. Data Evaluation

Based on the analysis results of different data sets, the applicant should evaluate whether the registration device could reach the expected performance in normal conditions of use, and whether the risks are acceptable balanced with the expected benefits.

## **(V) Clinical Evaluation Report**

A clinical evaluation report should be prepared (see Annex 7 for the format) after completion of the clinical evaluation, and should be submitted as a part of the clinical evaluation materials during registration application.

## **VII. Requirements for Clinical Trials**

For medical devices with clinical trials conducted in China, such trials should be conducted by a qualified clinical trial organization according to clinical quality management regulations of medical device. The registration applicant should submit clinical trial protocol and report during registration submission.

For imported medical devices with clinical trials conducted overseas, if such trials comply with relevant Chinese regulations, and requirements defined in technical guidance for registration such as sample size, control group selection, evaluation endpoints and criteria, and efficacy evaluation endpoints, the registration applicant can submit the clinical trial data provided to corresponding foreign medical device administration authorities during its marketing approval. Such data should at least contain opinions of the ethics committee, clinical trial protocol, and clinical trial report. The applicant also needs to provide supporting documents that demonstrate any ethnic difference of the product concerning clinical performance and/or safety.

For medical devices included in Category III Medical Devices Subject to Clinical Trial Approval, clinical trials in China are required.

### List of Annexes

Annex 1 Comparison Table of Device under Application and Equivalent Device in the Catalogue Which has Obtained Domestic Registration Approval

Annex 2 The Comparison Items of Device under Application and the Equivalent Device

Annex 3 The Format of Comparison Table of Device under Application and the Equivalent Device

Annex 4 Clinical Evaluation Path Based on the Clinical Experience or Trial(s) Data of the Equivalent Device

Annex 5 Requirements of Literature Search and Screening

Annex 6 Literature Search and Screening Protocol

Annex 7 Literature Search and Screening Report

Annex 8 Clinical Evaluation Report Based on the Clinical Trial / Application Data of the Equivalent Device



## Annex 1

### Comparison Table of Device under Application and Equivalent Device in the Catalogue which has Obtained Domestic Registration Approval

Comparison item	Medical Device in the catalogue	Device under application	Difference	Overview of Supporting material
Basic principles (operation principles/mechanism)				
Structural composition				
Manufacturing materials or manufacturing materials in contact with human body				
Performance requirements				
Disinfection / sterilization method				
Intended Use method of application				
.....				

Note: The comparison items can be added according to actual needs.

## Annex 2

### The Comparison Items of Device under Application and the Equivalent Device

(Non-Active medical devices)

	Comparison item
Non-Active medical devices	1. Basic principle
	2. Structural composition
	3. Manufacturing process
	4. Manufacturing material (such as material mark, animal-derived material, allograft material, ingredient, pharmaceutical ingredient, bioactive substance, conformed standard etc.)
	5. Performance requirement
	6. Safety evaluation (such as biocompatibility, biosafety, etc.)
	7. Conformed national/ industry standards
	8. Intended Use (1) target treatment group (2) the site of application to/in the body (3) Contact mode with human body (4) Indications (5) the state and severity of the applicable disease (6) Operation environment
	9. Application method
	10. Contraindications
	11. Precautions and warnings
	12. Delivery status
	13. Sterilization/disinfection mode
	14. Packaging
	15. Labeling
	16. Instruction for use (Product Insert)

## The Comparison Items of Device under Application and the Equivalent Device

(Active medical devices)

	Comparison item
Active medical devices	1. Basic principle (1) Principle of operation (2) Action mechanism
	2. Structural composition: (1) Product composition (2) Core component
	3. Manufacturing process
	4. Manufacturing material in contact with human body (such as material mark, animal-derived material, allograft material, ingredients, pharmaceutical ingredients, bioactive substance, conformed standard, etc.)
	5. Performance requirement (1) Performance parameters (2) Function parameters
	6. Safety evaluation (such as biocompatibility, biosafety, electrical safety, radiation safety, etc.)
	7. Software core functions
	8. Conformed national/ industry standards
	9. Intended Use (1) target treatment group (2) the site of application to/in the body (3) Contact mode with human body (4) Indications (5) the state and severity of the applicable disease (1) (6) Operation environment
	10. Application method
	11. Contraindications
	12. Precautions and warnings
	13. Sterilization/disinfection mode
	14. Packaging
	15. Labeling
	16. Instruction for use (Product Insert)

### Annex 3

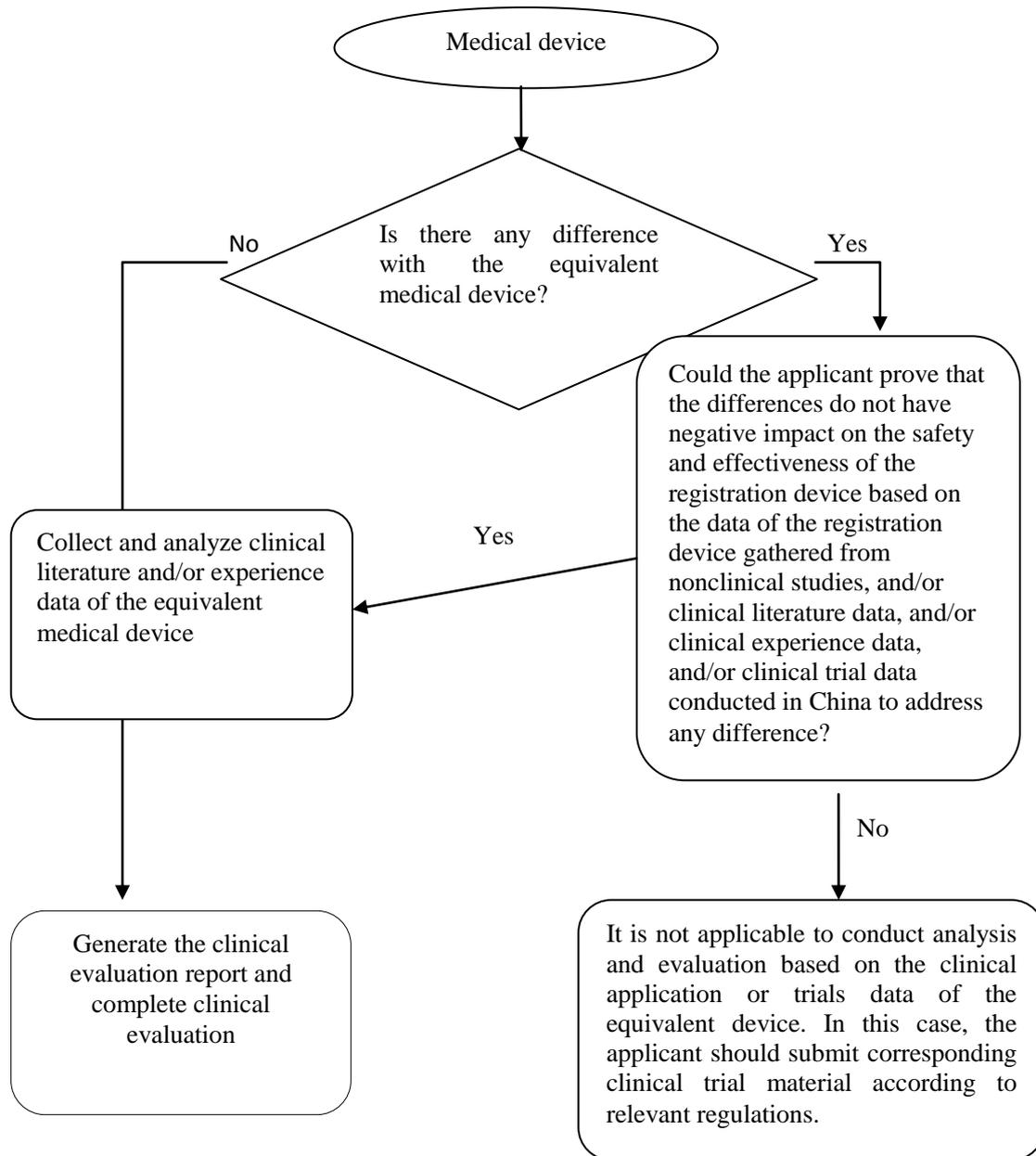
#### The Format of Comparison Table of Device under Application and the Equivalent Device

Comparison item	Equivalent medical device	Device under application	Difference	Overview of supporting material
Basic principle				
Structural composition				
.....				
.....				
.....				

Note: The comparison items should at least contain all items listed in Annex 2.

## Annex 4

### Clinical Evaluation Path Based on the Clinical Experience or Trial(s) Data of the Equivalent Device



## **Annex 5**

### **Requirements of Literature Search and Screening**

#### **I. Search Database**

The registration applicant should select the search database based on the specific characteristics of device under application/ the equivalent device (such as design features, intended use, etc.) and provide the justification of the selection. The selection of database should be comprehensive and below are some examples of the databases:

1. Science database: such as the China Academic Journal Databases, “Index Medicus” (Medline) of the United States and “EMBASE” (EM) of Netherlands, etc.
2. Clinical trials database: such as Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, etc.
3. Database of systematic reviews: such as the Cochrane Library.
4. Professional database: such as MEDION and osteoarticular registration database.

#### **II. Search Means, Search Terms and Logical Relationship of Search Terms**

In order to complete the clinical literature of products under application/ the equivalent device comprehensively and accurately, the selection of search paths, search terms and the logical relations among search terms should be considered for working out the scientific search strategy. The common search means include subject words search, keywords search, abstract search and full text search. Search terms should be adapted to the chosen search means, and factors for consideration include common name, commercial name, manufacturer, basic principles, structural composition, manufacturing materials, design features, key technology and intended use of the product. When conducting the logical matching of search terms, the proper logical operators should be adopted for expressing the logical relationship between the search terms, such as the logical OR to expand the search range and the logical AND to limit search range. The selection reason for the search means, search terms and logical relation of search terms should be expounded in the search protocol.

#### **III. Procedure and Criteria of Literature Screening**

For the further screening of searched literatures, the steps as specified in Diagram 1 should be followed. Registration applicant should screen the literatures which could possibly satisfy the requirements according to the titles and abstracts of literatures; and screen the literatures to be included in the analysis according to the full text of literature; if it is still impossible to determine whether to include the literatures in the analysis according to the full text, the author should be contacted for further judgment or the literature can be excluded directly.

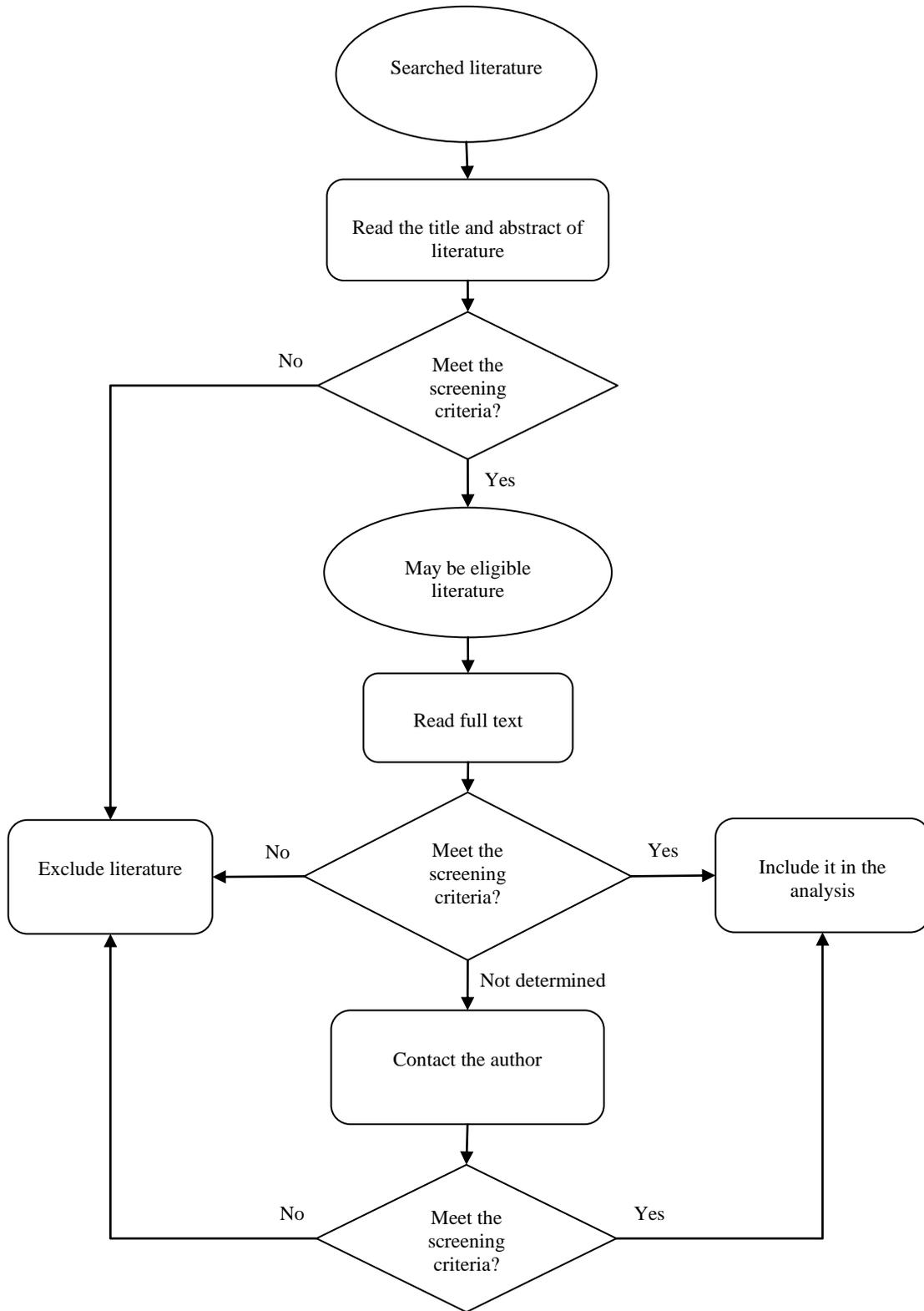
The screening criteria of literature, namely the inclusion and exclusion criteria of literature should be explicit and operable.

#### **IV. The Output of Literature Search and Screening Results**

The output of literature search and screening results should be in the form of reference with consistent format. The document reference forms include author, title, journal

name, publication year, volume (issue) number, and page number. The literature included in clinical evaluation after screening should be provided in full text.

Diagram 1. Literature Screening Procedure



## **Annex 6**

### Literature Search and Screening Protocol

Device name:

Model and specification:

Time period of search:

Search database:

Selection reason for search database:

Search means:

Search terms:

Logical matching of the search terms:

Determination reason of search means, search terms and logical matching of search terms

Output format of search results:

Literature screening procedure:

Literature screening criteria:

Justification for literature screening criteria:

Output format of literature screening results:

Name(s) of personal for literature search and screening:

## **Annex 7**

### Literature Search and Screening Report

Device name:

Model and specification:

Time period of search:

Search database:

Search means:

Search terms:

Logical matching of the search terms:

Output of search results:

Description, causes of search deviation and impact on the results:

Literature screening procedure:

Literature screening criteria:

Excluded literature:

Exclusion reasons:

Output of literature screening results:

Description, causes of screening deviation and impact on the results:

Note: all searched and screened literature need to be listed in the consistent format. It is suggested to include such information as “author, title, journal name, year of publication, volume (number), and page”.

Personal signature for literature search and screening:

Date:

## **Annex 8**

### **Clinical Evaluation Report Based on the Clinical Trial / Application Data of the Equivalent Device**

Product name:

Model and specification:

Signature of responsible personnel:

Completion time:

## **I. Determination of the Equivalent Medical Device**

For the format of comparison items and comparison table for the product under application and the equivalent device, see Annexes 2 and 3.

## **II. Evaluation Path**

Describe the evaluation path.

## **III. Analysis and Evaluation**

The registration applicant should select applicable clauses according to the specific situation of the product under application.

### **(I) The equivalence of the Product under Application and the Equivalent Medical Device**

The equivalence should be demonstrated.

### **(II) Supporting Documents (Including Non-clinical Study, Clinical Literature, and Experience Data of the Product under Application) Showing that Differences Between the Product under Application and the Equivalent Medical Device do not Result in any Negative Impact on Safety or Effectiveness of the Product 1.**

Non-clinical study data:

(1) Study overview;

(2) Non-clinical study report, provided as annexes.

#### **2. Collection and Analysis of Clinical Literature and Data for the Production under Application**

Select the appropriate data sources and collection methods according to the specific condition of the product. Group the collected data into different data sets for analysis and evaluation according to different data types, data quality and evaluation purposes. Provide the complete information of various data in accordance with relevant requirements of this Guidance and submit them in the form of annex. See the examples as below:

##### **(I) Data Sets of Clinical Study**

General description of data: such as data source, data type, data quality and other information;

Analysis method: clarify the specific analysis methods and reasons for selection;

Data analysis: including data summarization, analysis process and analysis results;

Explanation and evaluation for analysis results:

Annex: such as related full text of literature, opinions of ethics committee (if applicable), clinical study protocol and clinical study report.

##### **(2) Data Sets of Complaints and Adverse Events**

General description of data:

Analysis method: clarify the specific analysis methods and reasons for selection

Data analysis: including data collection, analysis process and analysis results;

Explanation and evaluation for analysis results:

Annex: time on market in different countries, accumulated sales, number of complaints and adverse events, classified reasons of complaints and adverse events, number of complaints and adverse events in different classified reasons, relationship of complaints and adverse events with the products. For serious adverse events, the specific information of event description, cause analysis, corrective action and results should be provided in the tabular format.

### (3) Data Sets of Corrective Measures Associated with Clinical Risks

General description of data

Analysis and evaluation of data:

Annex: specific information of corrective measures associated with clinical risks (such as recall, announcements, warnings, etc.) and adopted risk control measures.

### (4) Data Sets of Chinese Population

General description of data: such as data source;

Analysis method: clarify the specific analysis methods and reasons for selection;

Data analysis: including data summarization, analysis process and analysis results;

Explanation and evaluation for analysis results:

Annex: the complete information about all types of data.

Note: the number of data sets is unlimited and prepared by the registration applicant in accordance with the actual condition.

### (5) Comprehensive Evaluation and Conclusion of Multiple Data Sets

Study overview;

Literature search, screening protocol and report;

Experience data collection and analysis report.

## 2. Data of Clinical Trials Conducted in China to Address Differences

(1) Trial overview;

(2) Clinical trial protocol and clinical trial report.

3. Other supporting documents:

(1) Document overview;

(2) Full text of the documents.

## I. 4. Conclusions

### **IV. Analysis of Clinical Trial(s) or Application Data of the Equivalent Medical Device**

Select the appropriate clinical literature and experience data sources and collection methods according to the specific condition of the equivalent medical device. Group the collected data into different data sets for analysis and evaluation according to different data types, data quality and evaluation purposes. Provide the complete information of various data in accordance with relevant requirements of this guidance and submit them in the form of annex. See the examples as below:

#### 1. Data Sets of Clinical Study

General description of data: such as data source, data type, data quality and other information;

Analysis method: clarify the specific analysis methods and reasons for selection;

Data analysis: including data summarization, analysis process and analysis results;

Explanation and evaluation for analysis results:

Annex: such as related full text of literature, opinions of ethics committee (if applicable), clinical study protocol and clinical study report.

## (2) Data Sets of Complaints and Adverse Events

General description of data

Analysis method: clarify the specific analysis methods and reasons for selection;

Data analysis: including data summarization, analysis process and analysis results;

Explanation and evaluation for analysis results:

Annex: time on market in different countries, accumulated sales, number of complaints and adverse events, classified reasons of complaints and adverse events, number of complaints and adverse events in different classified reasons, the relationship of the complaints and adverse events with the product. For serious adverse events, the specific information of event description, cause analysis, and corrective action should be provided in the tabular format.

## 3. Data Sets of Corrective Measures Associated with Clinical Risks

General description of data

Analysis and evaluation of data:

Annex: specific information of corrective measures associated with clinical risks (such as recall, announcements, warnings, etc.) and adopted risk control measures.

## 4. Data Sets of Chinese Population

General description of data: such as data source and other information;

Analysis method: clarify the specific analysis methods and reasons for selection;

Data analysis: including data summarization, analysis process and analysis results;

Explanation and evaluation for analysis results:

Annex: the complete information about all types of data.

Note: the number of data sets is unlimited and prepared by the registration applicant in accordance with the actual condition.

## 5. Comprehensive Evaluation and Conclusion of Multiple Data Sets

Study overview;

literature search and screening protocol and report;

Experience data collection and analysis report.

## 6. Conclusion

## **V. Conclusion**

## **VI. Other Issues to be Clarified (If Applicable)**