Annex

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 device(s) under application can be achieved based on clinical literatures, clinical experience data and information gathered from the clinical trial(s). This Guidance is to provide technical guidance to registration applicants for conducting clinical evaluation and to food and drug administrative authorities for reviewing the clinical evaluation data.

II. Legal Basis

I. Regulation on the Supervision and Administration of Medical Devices (Decree of the State Council No. 650);

II. Measures for the Administration of Registration of Medical Devices (Decree No. 4 of China Food and Drug Administration); and

III. Related provisions on clinical trial quality control of medical device.

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. In case there is technical guidance on clinical evaluation of specific medical device product available, it should be followed for the clinical evaluation of the corresponding product.

IV. Basic Principles

The clinical evaluation 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 non-clinical studies, and required data type and volume should be appropriate to the product design features, critical technologies, intended use, and risks of the device.

A clinical evaluation should verify the clinical claims made about the device, including the 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 application, contraindications, precautions, and warnings, etc.

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 acceptably 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 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 application to the equivalent medical device listed in the Catalogue which has already obtained domestic registration approval. Specific data for the clinical evaluation should include:

I. Comparison between the device under application and corresponding information in the Catalogue;

II. Comparison between the device under application and an equivalent medical device in the Catalogue that has obtained domestic registration approval. The comparison description should include *Comparison Table of the Device under Application and an Equivalent Medical Device Listed in the Catalogue that has Obtained Domestic Registration Approval (see Annex 1)* and relevant supporting documents.

The above submitted documentation 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 Obtained from Clinical Trial(s) or Clinical Application of the Equivalent Medical Device

I. Equivalent Medical Device

1. Definition of Equivalent Medical Device

The equivalent medical device refers to the device that has obtained domestic registration approval and is substantially equivalent to the device under application in aspects of basic principles, structural composition, manufacturing materials (manufacturing materials that come into contact with the human body for active devices), manufacturing process, performance requirements, safety evaluation, conformed national /industry standards and expected use.

The device under application can be considered as substantially equivalent with

the equivalent medical device in the case that no adverse effects on the safety and effectiveness of the device are caused by the differences between the two devices.

2. Determination of Equivalent Medical Device

In order to prove the safety and effectiveness of the device under application utilizing the data from the clinical application experience or clinical trial(s) of the equivalent medical device, the applicant needs to compare the device under application with one or more equivalent medical device(s) and prove the substantial equivalence between the devices

The items involved in the comparison with the equivalent medical device shall include, but be not limited to those listed in Annex 2, including the qualitative and quantitative data, and the verification and validation results. The similarities and differences between the two products should be described in detail. It shall be verified and/or confirmed based on the data of the device under application whether the differences will result in any negative impact on the safety or effectiveness of the device. This data includes that obtained from its non-clinical study, clinical literature, clinical experience, and clinical trials conducted in China to address any differences. The collection, analysis, and evaluation of the relevant data should meet the requirements specified in sections (III) and (IV), as well as the corresponding annexes. Clinical trials should be consistent with relative requirements of Quality Management Practices.

The applicant should provide comparative information in the form of a table (see Annex 3 for the format). For specific products with inapplicable items/ items that do not apply, reasons should be provided.

II. Evaluation Path

See Annex 4 for the details of evaluation path.

III. Collection of Data from Clinical Trial(s) or Clinical Application of Equivalent Medical Device

The data from clinical trial(s) or clinical application (hereinafter abbreviated as clinical data) can be obtained from public scientific literature released in China and/or overseas and other relative data acquired legally, including clinical literature data and clinical experience data. The registration applicant can select the appropriate data sources and methods of collection according to the characteristics of the product.

1. Collection of Clinical Literature Data

During the collection of clinical literature data, the accuracy and comprehensiveness of the literature should be guaranteed. The recommended literature search and screening elements are in Annex 5. The literature search

and screening protocol should be prepared prior to any literature search (see Annex 6 for the content and format). After the literature search and screening, a report on the literature search and screening must be compiled (see Annex 7 for the content and format). The clinical literature search and screening should be repeatable. The personnel in charge of literature search and screening should be equipped with 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 studies, adverse events, and corrective action related to clinical risks.

1) Collection of Data from Completed Clinical Studies

As far as design is concerned, clinical studies can be divided into prospective study, retrospective study, randomized controlled trials, non-randomized controlled trials, single-arm studies and case reports, etc.

The applicant is required to collect and submit the opinions from Ethics Committee (if applicable), the clinical research plan and the clinical research 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 himself, and the adverse events database issued by the regulatory authorities of all nations, 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 medical device: number of complaints and adverse events, reasons classification of complaints and adverse events, number of complaints and adverse events classified by different reasons, and the relationship of the adverse events with the product. For serious adverse events, the specific information such as event description, cause analysis, and corrective solutions should be summarized in the form of a table.

For the device 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 Related to Clinical Risks

The applicant should collect and provide specific information on corrective measures associated with clinical risks of the equivalent medical device (e.g. recall, announcements, warnings, etc.), and the risk control measures that have been taken.

IV. Analysis and Evaluation of Clinical Data from Equivalent Medical Device

1. Quality Evaluation of Data

The registration applicant should classify the data involved in the analysis in accordance with generally accepted evaluation criteria of clinical evidence level (e.g. the Evaluation Criteria of Clinical Evidence level established by Oxford Center for Evidence-based Medicine). The clinical data found to be unsuitable for validity evaluation can be applied to the safety evaluation of the device if applicable.

2. Establishment of Data Sets

The collected clinical data can be grouped into several data sets based on their different data type and data quality. The registration applicant may also create data sets according to different evaluation purposes. For example, if ethnic differences exist within the clinical performance and/or safety of certain products, 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 device under application could reach the expected performance in normal conditions of use, and whether the risks are acceptable compared to the intended benefits.

V. Clinical Evaluation Report

A clinical evaluation report should be prepared after completion of the clinical evaluation (see Annex 8 for the format), 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, these trials should be conducted by a qualified clinical trial institution in accordance with Quality Management Regulations for Clinical Trial(s) of Medical Devices. When applying for registration, the registration applicant

should submit clinical trial protocol and report.

For imported medical devices with clinical trials conducted overseas, the registration applicant can submit the clinical trial data provided to foreign authorities on medical devices during its marketing approval, as long as such trials comply with relevant Chinese regulations and requirements defined in technical guidance for registration, e.g. sample size, control group selection, evaluation indexes and principles, and efficacy evaluation indexes. Such data should at least contain opinions of the ethics committee, clinical trial protocol, and the 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 listed in Category III Medical Devices Subject to Clinical Trial Approval, clinical trials in China are required.

List of Annexes:

Annex 1. Comparison Table of the Device under Application and an Equivalent Medical Device Listed in the Catalogue that has Obtained Domestic Registration Approval

Annex 2. Items Compared between Device under Application and the Equivalent Medical Device

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

Annex 4. The Analysis and Evaluation Path Based on Data from Clinical Trials or Clinical Application of Equivalent Medical Devices

Annex 5. Requirements of Literature Search and Screening

Annex 6. Literature Search and Screening Protocol

Annex 7. Literature Search and Screening Report

Annex 8. The Analysis and Evaluation Report Based on Data from Clinical Trials or Clinical Application of Equivalent Medical Devices

Annex 1

Comparison Table of the Device under Application and an Equivalent Medical Device Listed in the Catalogue that has Obtained Domestic Registration Approval

Items	Medical Devices in the Catalogue	Device under Application	Differences	Summary of Supporting Data
Basic Principles (Working Principles / Mechanism of Action)				
Structural Composition				
Manufacturing materials or Manufacturing materials in contact with human body				
Performance Requirements				
Sterilization / Disinfection Methods				
Scope of Application				
Method of Application				
……				

NOTE: More items can be added to the table based on the actual situation.

Annex 2

Items Compared between Device under Application and the Equivalent Medical Device (Passive Medical Devices)

	Items
Passive Medical Devices	1.Basic Principles
	2.Structural Composition
	3.Manufacturing Process
	4. Manufacturing materials (including material grades, animal-derived materials, allograft materials, ingredients, pharmaceutical ingredients, bioactive substances, and required standards, etc.)
	5. Performance Requirement
	6. Safety Evaluation (e.g. biocompatibility, biological safety, etc.)
	7. Conformed National /Industry Standards
	8.Scope of Application: （1）Target Treatment Group （2）Site of Application to/in the Body （3）Mode or Method of contact with the Human Body （4）Indication （5）Stage and Severity of Disease （6）Operational Environment
	9. Method of Application
	10.Contraindications
	11. Precautions and Warnings
	12. Delivery Status
	13. Sterilization / Disinfection Methods
	14. Packaging
	15. Label
	16. Product Specification

Items Compared between Device under Application and the Equivalent Medical Device
(Active Medical Devices)

	Items
Active Medical Devices	1. Basic Principles （1）Working Principles （2）Mechanism of Action
	2.Structural Composition （1）Product Composition （2）Core Components
	3. Manufacturing Process
	4. Manufacturing materials in contact with human body (including material grades, animal-derived materials, allograft materials, ingredients, pharmaceutical ingredients, bioactive substances, and required standards, etc.)
	5. Performance Requirement （1）Performance Parameters （2）Function Parameters
	6. Safety evaluation (e.g. biocompatibility, biological safety, electrical safety, radiation safety, etc.)
	7. Core Function
	8.Conformed National /Industry Standards
	9.Scope of Application: （1）Target Treatment Group （2）Site of Application to/in the Body （3）Methods Contacting with Human Body （4）Indications （5）Stage and Severity of Disease （6）Operational Environment
	10. Method of Application
	11. Contraindications
	12. Precautions and Warnings
	13. Sterilization / Disinfection Methods
	14. Packaging
	15. Label
	16. Product Specification

Annex 3

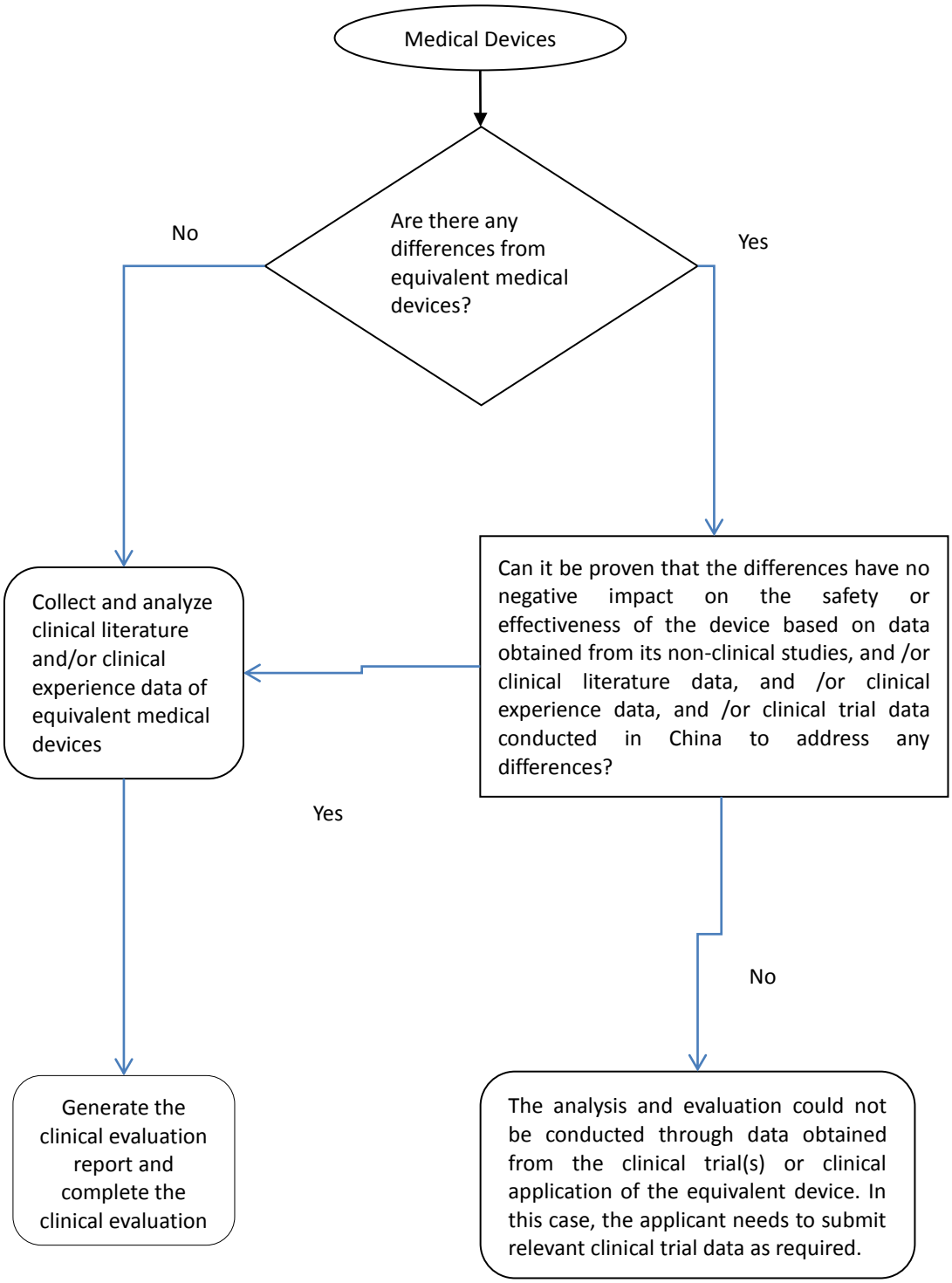
Format of Comparison Table of Device under Application and the Equivalent Medical Device

Items	Equivalent Medical Devices	Device under Application	Difference	Summary of Supporting Data
Basic Principles				
Structural Composition				
……				
……				
……				

NOTE: All the items listed in Annex 2 should be included.

Annex 4

The Analysis and Evaluation Path Based on Data from Clinical Trials or Clinical Application of Equivalent Medical Devices



Annex 5

Requirements of Literature Search and Screening

I. Search Database

The registration applicant is required to choose a search database based on the specific characteristics of the device under application/ the equivalent medical device (e.g. design features, scope of application, etc.), and discuss his reasons in the protocol. The selection of the database should be comprehensive, and below are some examples of database types:

1. Science database: such as the Chinese Journal Full-text Database, *Index Medicus* (Medline) of the United States and *EMBASE* (EM) of Netherlands, etc.;
2. Clinical Trial Database: such as Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, etc.;
3. Database of Systematic Reviews: such as the Cochrane Library, etc.;
4. Professional Database: such as MEDION and osteoarticular registration database, etc.

II. Search Methods, Search Terms and Logical Relationship of Search Terms

In order to find comprehensive and accurate clinical literature of the device under application/ the equivalent medical device, the selection of search paths, search terms and the logical relations among search terms should be considered when developing the scientific search strategy. The common search methods include subject words search, keywords search, abstract search, and full text search. Search terms should be adapted to the selected search methods, and factors such as common name, commercial name, manufacturer, basic principles, structural composition, manufacturing materials, design features, key technology and scope of application shall be considered. When conducting the logical matching of search terms, the proper logical operators should be chosen to express the logical relationship between the search terms, such as using the logical word "OR" to expand the search range and "AND" to narrow it. The selection reason for the search methods, search terms and logical relationship of search terms should be explained in the search protocol.

III. Procedure and Criteria of Literature Screening

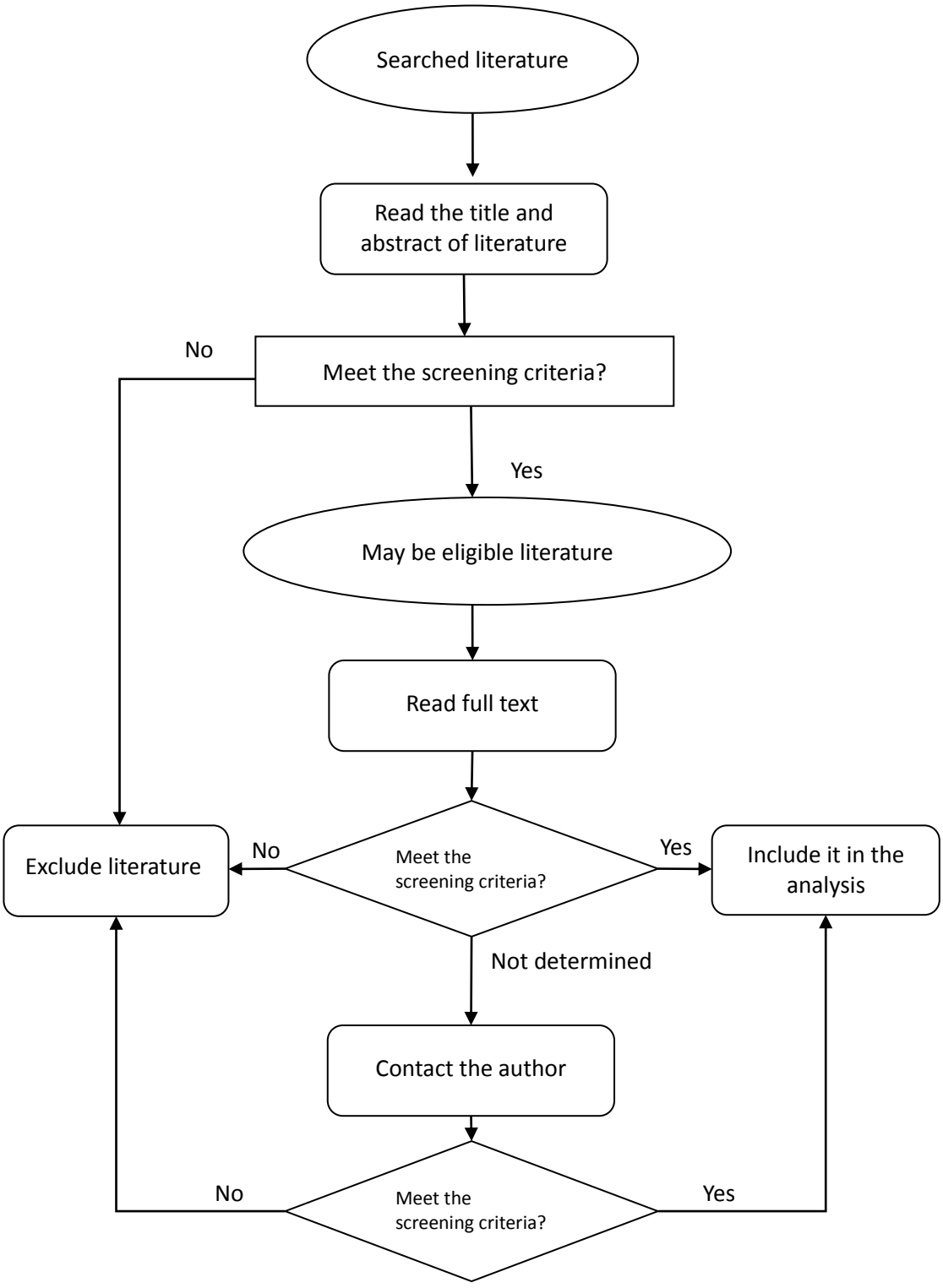
For the further screening of searched literatures, the steps as specified in Diagram 1 should be followed. The registration applicant, based on the titles and abstracts of literatures, shall screen the literatures that possibly satisfy the requirements, and screen the literatures to be included in the analysis according to the full text of the literatures; in case it is still impossible to determine whether to include the literatures in the analysis with the full text or not, he should contact the author for further judgment or exclude the literature directly.

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

IV. The Output of Literature Search and Screening Results

The output of the literature search and screening results should be in citation form, using a consistent format. The citation form includes the author, title, journal name, publication year, number of volumes (issues), 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 range of search:

Search database:

Selection reasons for search database:

Search methods:

Search terms:

Logical matching of the search terms:

Determination reasons of search methods, 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 personnel for literature search and screening:

Annex 7

Literature Search and Screening Report

Device name:

Model and specification:

Time range of search:

Search database:

Search methods:

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:

Reasons of exclusion:

Output of literature screening results:

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

Note: All searched and screened literature needs to be listed in a consistent format. It is suggested to include such information as “author, title, journal name, year of publication, number of volumes (issues), and page number”.

Personnel signature for literature search and screening:

Date:

Annex 8

The Analysis and Evaluation Report Based on Data Obtained from Clinical Trials or Clinical Application of Equivalent Medical Device

Product Name:

Model and Specifications:

Signature of Responsible Personnel:

Time Completed:

I. Determination for Equivalent Medical Device

Refer to Annexes 2 and 3 for the format of comparison items and comparison table on the device under application and the equivalent medical device.

II. Evaluation Path

Describe the path for evaluation.

III. Analysis and Evaluation

The registration applicant should select applicable provisions in accordance with the specific circumstances of the device under application.

I. The Device under Application and Equivalent Medical Device Have No Differences.
Discuss the equivalence of both.

II. Supporting Data (e.g. Non-clinical Studies, Clinical Literature Data, and Clinical Experience Data, etc. of the Device under Application) Showing that Differences Between the Device under Application and the Equivalent Medical Device will not Result in any Negative Impact on Safety and Effectiveness of the Product.

1. Non-clinical Study Data:
    1) Study overview;
    2) Non-clinical study report, which should be provided as annexes.
2. Clinical Literature and Analysis of Data Collection for the Product under Application:
    Select the appropriate data sources and collection methods in accordance with the specific circumstances 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 as an annex. The examples of data sets are as follows:
    1) Data Sets of Clinical Studies
        Summary of Data: data source, data type, data quality, etc.
        Analysis Methods: clarify the specific analysis methods and reasons for selection;
        Data Analysis: including data summarization, analysis process and analysis results;
        Explanation and Evaluation of Analysis Results:
        Annex: such as related full text of literature, opinions of ethics committee (if applicable), clinical study protocol, and clinical study report, etc.

2) Data Sets of Complaints and Adverse Events

Summary of Data:

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

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

Explanation and Evaluation of Analysis Results:

Annexes: time on market in different countries, number of complaints and adverse events, reasons classification of complaints and adverse events, number of complaints and adverse events classified by different reasons, relationship of complaints and adverse events with the products, etc. For serious adverse events, the specific information of event description, cause analysis, corrective action and results should be provided in the form of a table.

3) Data Sets of Corrective Measures Associated with Clinical Risks

Summary of Data:

Analysis and Evaluation of Data:

Annexes: specific information of corrective measures associated with clinical risks (e.g. recall, announcements, warnings, etc.) and risk control measures adopted.

4) Data Sets of Chinese Population

Summary of Data: such as data source;

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

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

Explanation and Evaluation of Analysis Results:

Annex: the complete information about all types of data

Note: the number of data sets is unlimited and can be prepared by the registration applicant based on the actual situation.

5) Comprehensive Evaluation and Conclusion of Multiple Data Sets

Study overview;

Protocol and report of literature search and screening;

Experience data collection and analysis report.

3. Data of Clinical Trials Conducted in China to Address Differences:
    1) Trials overview;
    2) Protocol and report of clinical trials
4. Other Supporting Documents:
    1) Documents overview;
    2) Full text of the documents
5. Conclusions

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

Select the appropriate clinical literature and experience data sources, and collection methods in accordance with 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 as an annex. The examples of data sets are as follows:

I. Data Sets of Clinical Studies

Summary of Data: data source, data type, data quality, etc.;

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

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

Explanation and Evaluation of Analysis Results:

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

II. Data Sets of Complaints and Adverse Events

Summary of Data:

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

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

Explanation and Evaluation of Analysis Results:

Annexes: number of complaints and adverse events, reasons classification of complaints and adverse events, number of complaints and adverse events classified by different reasons, relationship of complaints and adverse events with the products, etc. For serious adverse events, the specific information of event description, cause analysis, and corrective action should be provided in the form of a table.

III. Data Sets of Corrective Measures Associated with Clinical Risks

Summary of Data:

Analysis and Evaluation of Data:

Annexes: specific information of corrective measures associated with clinical risks (e.g. recall,

announcements, warnings, etc.) and risk control measures adopted.

IV. Data Sets of Chinese Population

Summary of Data: such as data source;

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

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

Explanation and Evaluation of Analysis Results:

Annex: the complete information about all types of data

Note: the number of data sets is unlimited and can be prepared by the registration applicant based on the actual situation.

V. Comprehensive Evaluation and Conclusion of Multiple Data Sets

Study overview;

Protocol and report of literature search and screening;

Experience data collection and analysis report.

VI. Conclusions

V. Conclusions

VI. Other Issues Need to be Addressed (if Applicable)