Appendix

Guiding Principles of Clinical Evaluation Technology of Medical Devices

I. Compilation Purpose

The clinical evaluation of medical devices is the process that the registration applicant confirms whether products meet the operating requirements or scope of application through the clinical literature data, clinical experience data, clinical trials and other information. The guiding principles aim at providing clinical evaluation for the registration applicant and also providing the technical guidance for the examination and evaluation of the China Food and Drug Administration on the clinical evaluation data.

II. Legal Basis

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

(II) *Medical Device Registration Administration Method* (Decree No. 4 of the China Food and Drug Administration)

(III) Relevant provisions of medical device clinical trial quality management

III. Scope of Application

The guiding principles are applicable to the clinical evaluation work of Class II and Class III medical devices during registration and declaration and not applicable to the clinical evaluation work of IVD reagents according to the medical device management. If there is release of guiding principles of clinical evaluation technology on a particular product, the clinical evaluation work of the corresponding product should follow the relevant requirements.

IV. Basic Principles

The clinical evaluation shall be comprehensive and objective, the data should be collected through a variety means including clinical trial, and the collected clinical performance and safety data and the favorable and unfavorable data collected in the course of clinical evaluation shall be included in analysis. The depth and breadth of clinical evaluation and the data type and quantity needed for clinical evaluation shall be adapted to the design characteristics, key technology, scope of application and risk degree of products and also the level and degree of non-clinical research.

The clinical evaluation shall confirm the scope of application (such as applicable people, applicable parts, mode of contact with human body, indication, disease stage and degree, operating requirements, operating environment, etc.), operating method, contraindication, precautions, warnings and other clinical use information.

The registration applicant shall draw the following conclusions through the clinical evaluation: under the conditions of normal use, the products can reach the expected performance; compared with the expected benefits, the risk of products can be accepted; the product clinical performance and safety are supported by appropriate evidence.

V. Clinical Evaluation Requirements of Products Listed into the *List of Medical Devices Free from Clinical Trials*

For the products listed into the *List of Medical Devices Free from Clinical Trials (Hereinafter*

referred to as List), the registration applicant shall submit comparison data between relevant information of declared products and described contents of the *List* as well as the comparison between declared products and the medical device in the *List* that has obtained permission to be registered domestically. Detailed clinical evaluation materials to be submitted are as the following:

(I) Comparison data between relevant information of declared products and described contents of the *List;*

(II) Comparison between declared products and the medical device in the *List* that has obtained permission to be registered domestically. The comparison should include Comparison Table of Declared Product and The Medical Device in the List That Has Obtained Permission to be Registered Domestically (see Appendix 1) and relevant supporting materials.

The above mentioned materials should be able to verify the equality between declared products and the products described in the *List*. If the equality between declared products and the products described in the *List* cannot be verified, corresponding work should be carried out according to other requirements in the guiding principles.

VI. Analysis Evaluation Requirement on Data Obtained from Clinical Trial and Clinical Application of medical devices in the same variety

(I) medical devices in the same variety

1. Definition of medical devices in the same variety

Medical devices in the same variety are the products which have obtained permission to be registered domestically and basically equivalent with the basic principles, structure composition, manufacturing materials (the active products are made of manufacturing materials for the parts of contact with the human body), production technology, performance requirements, safety evaluation, applicable national/industrial standards, intended use and other aspects of declared products.

If the difference between the declared product and same variety of medical devices does not adversely affect safety and effectiveness of the product, they can be regarded as basically equivalent.

2. Determination of medical devices in the same variety

When the registration applicant carries out the analytical evaluation through the clinical trial or clinically obtained data of medical devices in the same variety to prove the safety and effectiveness of medical devices, the equivalence of the declared products and one or several medical devices of the same variety should be compared to prove that the two devices are basically equivalent.

The comparison with medical devices of the same variety shall include but not be limited to the items listed in Appendix 2, and the comparison contents include qualitative and quantitative data, verification and confirmation results. The similarity and differences between the two devices should be elaborated. Whether the differences can adversely affect safety and effectiveness of the product should be verified and/or confirmed through the product data, if the non-clinical study data, clinical literature data, clinical experience data, and data of clinical trials conducted in the territory of China on the differences of declared product. Relevant data collection, and analysis and evaluation should comply with requirements of part (III) and part (IV) of this section and relevant appendix. Clinical trial should comply with relevant requirements of GCP.

The comparison information shall be provided by registration applicant in the form of a list (see Appendix 3 for the format). The reasons for inapplicability shall be explained if the inapplicable items exist.

(II) Evaluation path

For detailed evaluation path, please see Appendix 4.

(III) Collection of clinical trials or clinically obtained data of medical devices in the same variety

Clinical trials or clinically obtained data (hereinafter referred to as "clinical data") can come from the publicly published scientific literature and clinical experience data obtained at home and abroad and legally obtained data, including clinical literature data and clinical experience data. The registration applicant can select the appropriate data sources and collection methods according to the specific situations of products.

1. Collection of clinical literature data

The recall and precision of literature should be guaranteed in the collection of clinical literature data. The literature retrieval and screening elements recommended for consideration are shown in Appendix 5. Before the literature retrieval is carried out, the literature retrieval and screening scheme shall be formulated (see Appendix 6 for the content and format). After the completion of the literature retrieval and screening, the literature retrieval and screening report shall be prepared (see Appendix 7 for the content and format). The clinical literature retrieval and screening shall have repeatability. The literature retrieval and screening personnel shall have the corresponding professional knowledge and practical experience.

2. Collection of clinical experience data

Clinical experience data collection should include the collection of completed clinical study, adverse events, corrective measures related to clinical risks and other data.

(1) Completed clinical research data collection

According to the design type of clinical research, it can be divided into perspective study, retrospective study, randomized controlled trial, non-randomized controlled trial, single group study, case report, etc.

The registration applicant shall collect and provide ethics committee opinions (if applicable), clinical research scheme and clinical research report.

(2) Data collection of adverse events

Registration applicant should collect including the complaint and adverse event databases established by registration applicant and relevant data of adverse events in the adverse event databases issued by the regulatory authorities in various countries, such as the *Information Notification of Medical Device Adverse Events* and *Medical Device Alert Newsletter* issued by the China Food and Drug Administration, the database (MAUDE) used by the applicant and user equipment of the American Food and Drug Administration, the British medical device alerts, etc.

The registration applicant shall provide the number of complaints and adverse events of medical devices in the same variety , classification of reasons for complaints and adverse events, number of complaints and adverse events of various reasons, complaints and adverse events whether related to products and other information. For the serious adverse events, the event description, reason analysis, processing mode and other specific information shall be provided in the form of a list.

Detailed information such as marketing date of declared products in various countries, cumulative sales volume, and treatment results of SAE should be provided for declared products.

(3) Corrective measures data collection related to clinical risk

Registration applicant should collect and provide the specific information of corrective measures (such as recall, announcement, warning, etc.) of medical devices in the same variety related to clinical risk, risk control measures adopted, etc. shall be provided.

(IV) Clinical data analysis evaluation obtained f of medical devices in the same variety.

1. Data quality evaluation

The data included in analysis shall be classified by registration applicant according to the recognized clinical evidence level evaluation standards (such as the clinical evidence level evaluation standards formulated by the Oxford Centre for Evidence-based Medicine). The clinical data unsuitable for the product effectiveness evaluation may still be applicable to the safety evaluation of products.

2. Establishment of data set

According to the difference of data types and data quality, the collected clinical data can be grouped into multiple data sets. The registration applicant can also respectively establish data sets according to different evaluation purposes; for instance, the different of human species exists in the clinical performance and/or safety of some products. In order to evaluate the safety and/or effectiveness of the produces used by the Chinese population, the Chinese population data set can be established.

3. Statistical analysis of data

The appropriate data analysis methods shall be selected to carry out the statistical analysis on different data sets. The data set analysis methods formed by multiple research results include qualitative analysis and quantitative analysis. The qualitative analysis is to analyze and summarize multiple research results without the quantitative statistics and mergence.

4. Data evaluation

According to the analysis results of different data sets, evaluate whether the declared product is under normal service condition and whether the product can achieve expected performance; compared with expected benefits, whether the risk of products can be accepted.

(V) Clinical evaluation report

After the completion of clinical evaluation, the clinical evaluation report shall be composed (see Appendix 8 for the format) and submitted as the clinical evaluation data during application for registration.

VII. Relevant Requirements of Clinical Trials

For the medical devices to be carried out for clinical trials in the territory of China, their clinical trials shall be carried out in the qualified clinical trial institution according to the requirements of the quality management standards of medical device clinical trials. When registration applicant is registering for declaration, the submitted clinical evaluation data shall include clinical trial scheme and clinical trial report.

For clinical trials of imported medical devices to be carried out in abroad, if the clinical trial complies with relevant technical requirements of Chinese laws and regulations and registration technical guidelines, such as sample size, selection of control group, evaluation

indicator and principles, efficacy evaluation indicator and other requirements, registration applicant can submit clinical trial materials submitted to foreign medical device competent departments. The submitted materials should at least include EC Comments, Clinical Trial Protocol and Clinical Trial Report. Applicant should also submit relevant supporting data that evaluate whether racial differences exist in product clinical performance and/or safeness.

For the medical devices listed into the List of Class III Medical Devices In Need of Clinical Trials, clinical trial should be conducted within the territory of China.

Appendix

1. Comparison Table of Declared Products and Medical Device That Has Been Approved to be Registered in the Territory in the List

2. Comparison Items of Declared Products and Medical Devices in the Same Variety

3. Format of Comparison Table of Declared Products and Medical Devices in the Same Variety

4. Path of Clinical Evaluation Made through Data Obtained from Clinical Trial or Clinical Application of Medical Device in the Same Variety

5. Literature Retrieval and Screening Elements Requirements

6. Literature Retrieval and Screening Scheme

7. Literature Retrieval and Screening Report

8. Report of Analysis and Evaluation Based on Clinical Trial or Clinical Application Data of the Same Variety of Medical Devices

Appendix 1

Comparison Table of Declared Products and Medical Device That Has Been Approved to be Registered in the Territory in the *List*

Comparison items	Medical devices in the *List*	Declared products	Difference	Overview of supporting data
Fundamental principle (working principle/working mechanism)				
Structural composition				
Product manufacturing materials or manufacturing materials that contact with human parts				
Performance requirement				
Sterilization/disinfection method				
Scope of application				
Method of application				
……				

Note: Comparison items can be added according to actual needs.

Appendix 2

Comparison Items of Declared Products and Medical Devices in the Same Variety

(Passive Medical Devices)

Passive medical devices	Comparison items
	1. Basic principles
	2. Structure composition
	3. Production technology
	4. Manufacturing materials (such as material trademark, animal source materials, allogeneic materials, ingredients, pharmaceutical ingredients, bioactivators, applicable standards, and other information)
	5. Performance requirements
	6. Safety evaluation (such as biocompatibility, biosafety, etc.)
	7. National/industry standards which products meet
	8. Scope of application: (1) Applicable people (2) Applicable parts (3) Mode of contact with human body (4) Indication (5) Applicable disease stage and degree (6) Operating environment
	9. Operating method
	10. Contraindication
	11. Precautions and warnings
	12. Delivery state
	13. Sterilization/disinfection method
	14. Packaging
	15. Label
	16. Product specifications

Comparison Items of Declared Products and Medical Devices in the Same Variety

(Active Medical Devices)

	Comparison items
Active medical devices	1. Basic principles (1) Operating principle (2) Action mechanism
	2. Structure composition: (1) Product composition (2) Core components
	3. Production technology
	4. Manufacturing materials for the parts of contact with the human body (such as material trademark, animal source materials, allogeneic materials, ingredients, pharmaceutical ingredients, bioactivators, applicable standards, and other information)
	5. Performance requirements (1) Performance parameters (2) Functional parameters
	6. Safety evaluation (such as biocompatibility, biosafety, electrical safety, radiological safety, etc.)
	7. Software core function
	8. National/industry standards which products meet
	9. Scope of application: (1) Applicable people (2) Applicable parts (3) Mode of contact with human body (4) Indication (5) Applicable disease stage and degree (6) Operating environment
	10. Operating method
	11. Contraindication
	12. Precautions and warnings
	13. Sterilization/disinfection method
	14. Packaging
	15. Label
	16. Product specifications

Appendix 3

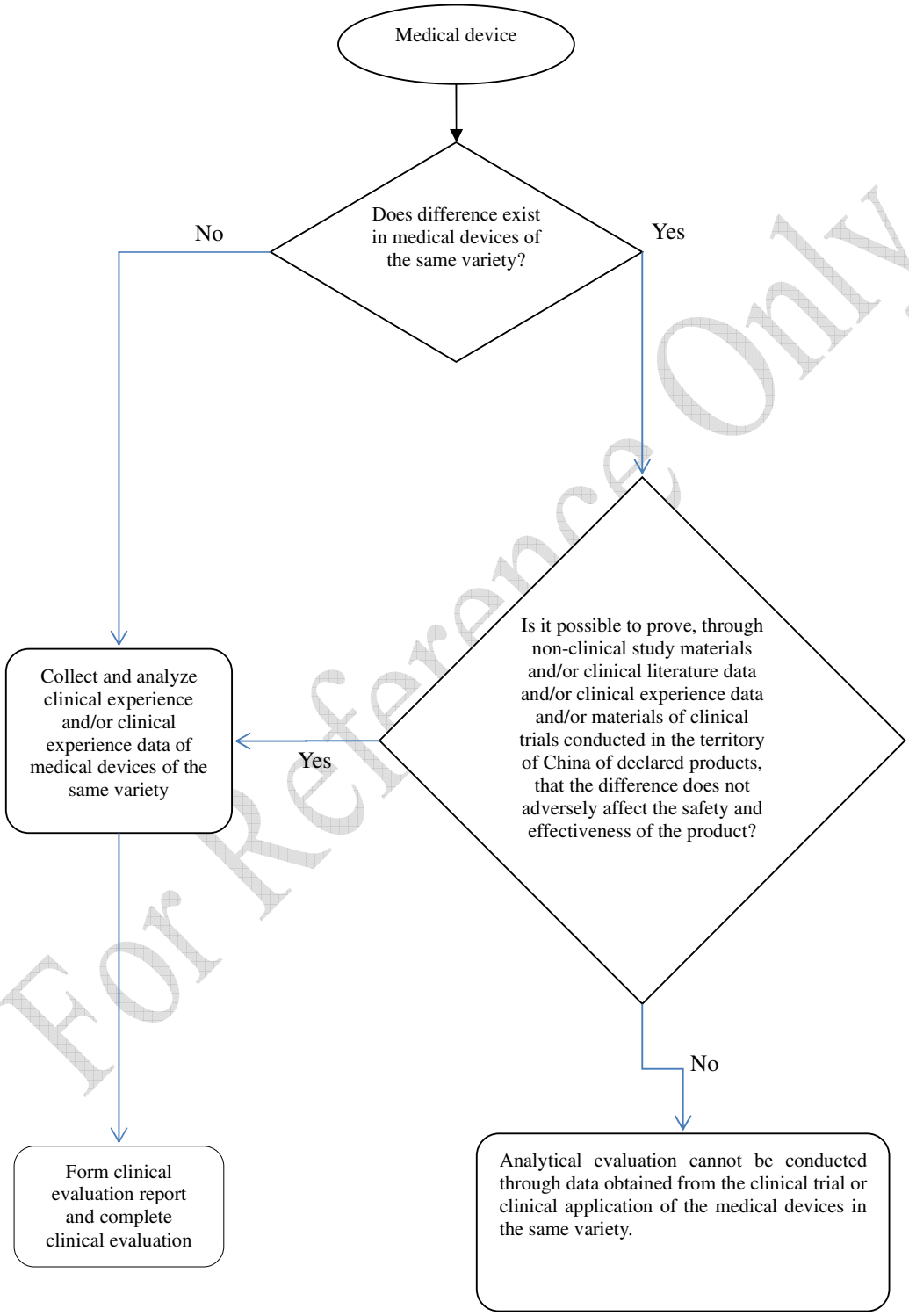
Format of Comparison Table of Declared Products and Medical Devices in the Same Variety

Comparison items	Same variety of products	Declared products	Difference	Overview of Supporting data
Basic principles				
Structural composition				
…				
…				
…				

Note: Comparison items should at least include all items of Appendix 2.

Appendix 4

Path of Clinical Evaluation Made through Data Obtained from Clinical Trial or Clinical Application of Medical Device in the Same Variety



Appendix 5

Literature Retrieval and Screening Elements Requirements

I. Retrieval Database

According to the specific situations (such as sign characteristics, scope of application, etc.) of declared products/medical devices in the same variety, the registration applicant shall select the retrieval database and discuss the reasons for selection in the scheme. The selection of database shall be comprehensive, and the examples of the considerable database types are as follows.

1. Scientific databases: Chinese journal full-text database, American *Medical Index* (Medline), Dutch *Excerpta Medica* (EM), etc.

2. Clinical trial databases: Cochrane controlled trial registration center (CENTRAL), clinical trial registration database (ClinicalTrials.gov), etc.

3. System evaluation databases: Cochrane library, etc.

4. Professional databases: diagnostic test index database (MEDION), bone joint registration database, etc.

II. Retrieval Ways, Retrieval Words, Logical Relationship of Retrieval Words

In order to comprehensively and accurately retrieve the clinical literature of declared products/medical devices in the same variety, the selection of retrieval ways and retrieval words and the configuration of the logical relationship between all retrieval words shall be considered comprehensively to formulate the scientific retrieval strategies. Common retrieval ways include subject word retrieval, keyword retrieval, abstract retrieval, full-text retrieval, etc. The retrieval words shall be adapted to the selected retrieval ways, and the common name, trade name, manufacturing enterprise, basic principle, structural composition, manufacturing materials, design characteristics, key technology, scope of application and other factors of products shall be considered. During the logical combination of retrieval words, the logical operators shall be correctly select to express the logical relationship between retrieval words, such as logical or expanded retrieval scope, logical and narrowed retrieval scope. The reasons for the determination of retrieval ways, retrieval words and logical relationship of retrieval words shall be discussed in the retrieval scheme.

III. Literature Screening Process and Criteria

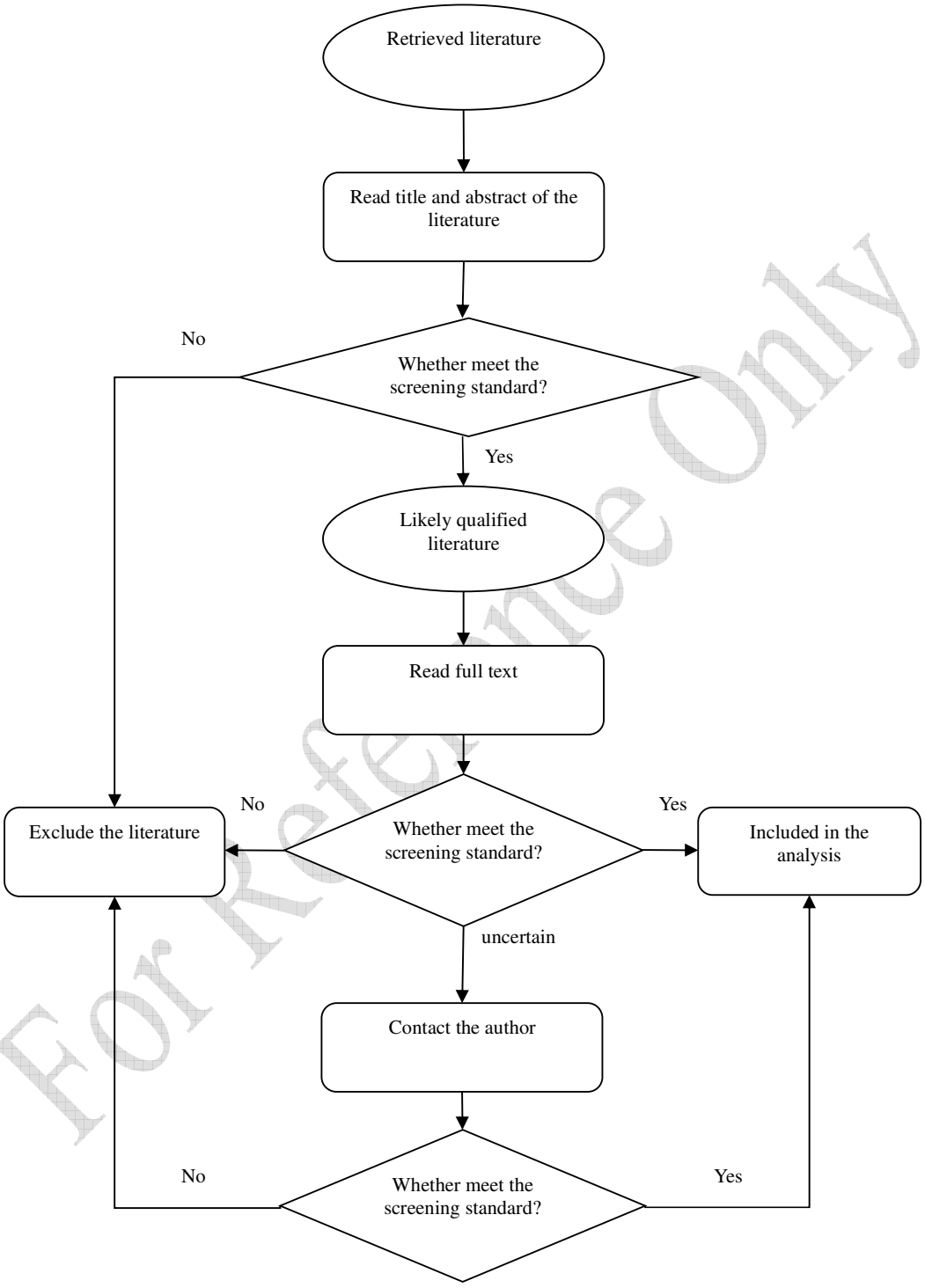
The screening of retrieved literatures shall be carried out according to the steps set in Figure 1. According to the title and abstract of the literature, the registration applicant shall be able to screen the literature which may meet the requirements; according to the full text of the literature, the registration applicant shall screen the literature included in analysis; if it still can not be determined whether the literature is included in analysis according to the full text, the registration applicant may contact the author to make decisions or directly exclude.

The literature screening criteria (namely the literature inclusion and exclusion criteria) shall be explicit and operable.

IV. Output of Literature Retrieval and Screening Results

The output form of literature retrieval and screening results adopt citation form of literature and the uniformity of format need to be maintained. Citation form of literature includes author, title, name of journal, publication year, number of volume (issue), page number, etc. The full text of the literature included in the clinical evaluation through screening shall be provided.

Figure 1 Literature Screening Process



Appendix 6

Literature Retrieval and Screening Scheme

Product name:

Model and specifications:

Retrieval time range:

Retrieval database:

Reasons for the selection of retrieval database:

Retrieval ways:

Retrieval words:

Logical combination of retrieval words:

Reasons for the determination of retrieval ways, retrieval words and logical combination of retrieval words:

Output form of retrieval results:

Literature screening process:

Literature screening criteria:

Reasons for the formulation of literature screening criteria:

Output form of literature screening results:

Name of literature retrieval and screening personnel:

Appendix 7

Literature Retrieval and Screening Report

Product name:

Model and specifications:

Retrieval time range:

Retrieval database:

Retrieval ways:

Retrieval words:

Logical combination of retrieval words:

Output of retrieval results:

Description and reasons of retrieval deviation and its influence on results:

Literature screening process:

Literature screening criteria:

Excluded literatures:

Reasons for exclusion:

Output of literature screening results:

Description and reasons of screening deviation and its influence on results:

Note: The retrieved and screened literatures should be listed in the consistent format. It is recommended that the format should include information such as “author, title, journal title, publishing year, number of volumes (number of periods), and page number”.

Signature of literature retrieval and screening personnel:

Time:

Appendix 8

Report of Analysis and Evaluation Based on Clinical Trial or Clinical Application Data of the Same Variety of Medical Devices

Product name:

Model and specifications:

Signature of completion personnel:

Completion time:

I. Determination of the Same Variety of Medical Devices

See Appendix 2 and 3 for the compared items and the comparison table format of declared products and the same variety of products.

II. Evaluation Path

Describe the selected evaluation path.

III. Analysis and Evaluation

The registration applicant shall choose the applicable provisions based on the specific situations of declared products.

(I) Declared products are the same as the same variety of products

Describe their similarities.

(II) Supporting materials proving that the difference between the declared product and same variety of medical devices does not adversely affect safety and effectiveness of the product (self non-clinical study, clinical references, data, clinical empirical data, etc.)

1. Non-clinical study data:

(1) Study overview;

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

2. Clinical literatures and data collection and analysis materials of declared products:

The suitable data sources and collection methods will be selected according to the specific situations of products. According to the difference of data types, data quality and evaluation purposes, the collected data will be grouped into different data sets for analysis and evaluation. According to the relevant requirements of the main body of the guiding principles, the complete information of various data will be provided as appendix. The examples of various data sets are as follows:

(1) Clinical study data set

Data overview: data source, data type, data quality and other information;

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

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

Interpretation and evaluation of analysis results:

Appendixes: such as full-text literature involved, ethics committee comments (if applicable), clinical study protocol, clinical study report, etc.

(2) Data sets of complaints and adverse events

Data overview:

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

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

Interpretation and evaluation of analysis results:

Appendixes: marketing date in various countries, number of complaints and adverse events, classification of reasons for complaints and adverse events, number of complaints and adverse events of various reasons, whether complaints and adverse events are related to products and other information. For the serious adverse events, the event description, reason

analysis, processing mode, processing results and other specific information shall be provided in the form of a list.

(3) Data set of corrective measures related to clinical risk

Data overview:

Data analysis and evaluation:

Appendixes: specific information of corrective measures (such as recall, announcement, warning, etc.) related to clinical risk, risk control measures adopted, etc.

(4) Chinese population data set

Data overview: data source and other information;

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

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

Interpretation and evaluation of analysis results:

Appendixes: complete information of various data.

Note: The number of data sets is unlimited, which will be formulated by the registration applicant according to the actual situation.

(5) Comprehensive evaluation of multiple data sets and conclusions

Study overview;

Literature retrieval and screening plan and report;

Empirical data collection and analysis report.

2. Materials of clinical trials conducted in China according to the differences:

(1) Trial overview;

(2) Clinical trial protocol and clinical trial report.

3. Other supporting materials:

(1) Materials overview;

(2) Full-text materials;

4. Conclusions

IV. Clinical Trials or Clinically-used Data Analysis of the Same Variety of Medical Devices

The suitable clinical literature data and clinical empirical data sources and collection methods will be selected according to the specific situations of the same variety of medical devices. According to the difference of data types, data quality and evaluation purposes, the collected data will be grouped into different data sets for analysis and evaluation. According to the relevant requirements of the main body of the guiding principles, the complete information of various data will be provided as appendix. The examples of various data sets are as follows:

(1). Clinical study data set

Data overview: such as data source, data type, data quality etc.

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

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

Interpretation and evaluation of analysis results:

Appendixes: such as full-text literature involved, ethics committee comments (if applicable), clinical study protocol, clinical study report, etc.

(2). Data sets of complaints and adverse events

Data overview:

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

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

Interpretation and evaluation of analysis results:

Appendixes: number of complaints and adverse events, classification of reasons for complaints and adverse events, number of complaints and adverse events of various reasons, whether the complaints and adverse events are related to products and other information. For the serious adverse events, the event description, reason analysis, processing mode and other specific information shall be provided in the form of a list.

(3). Data set of corrective measures related to clinical risk

Data overview:

Data analysis and evaluation:

Appendixes: specific information of corrective measures (such as recall, announcement, warning, etc.) related to clinical risk, risk control measures adopted, etc.

(4). Chinese population data set

Data overview: data source and other information;

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

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

Interpretation and evaluation of analysis results:

Appendixes: complete information of various data.

Note: The number of data sets is unlimited, which will be formulated by the registration applicant according to the actual situation.

(5). Comprehensive evaluation of multiple data sets and conclusions

Study overview;

Literature retrieval and collection plan and report;

Empirical data collection and analysis report.

(6). Conclusions

V. Conclusions

VI. Other issues to be declared (if applicable)