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Technical Guiding Principle on Medical Devices Clinical Evaluation

Article 1 Objective

Medical devices clinical evaluation is the procedure for registration applicant to confirm whether the product can conform to operating requirement or application by clinical literatures, clinical experience data, clinical trial and other information. This guiding principle is aimed at providing technical guidance for registration applicant to conduct clinical evaluation, and provide technical reference for CFDA management department to examine the clinical evaluation data.

Article 2 Laws basis

1. The regulations for the Supervision and Administration of Medical Devices (State Council Regulation; Order No. 650)
2. Administrative Measures for Medical Device Registration (CFDA, Order No. 4)
3. Quality Management Rules for Medical Device Clinical Trial

Article 3 Application

This guiding principle applies to Class II and Class III medical device clinical evaluation work while register and declare. It does not apply to medical device clinical evaluation work of in vitro diagnostic reagents. The clinical evaluation for a specific product shall comply with the technical guiding principle which is published for the specific product.

Article 4 Basic principle

Clinical evaluation shall be comprehensive and objective, and collecting corresponding data by clinical trial and other means. The clinical performance, safety data, favorable and unfavorable data which are collected in the clinical evaluation process shall be involved in the analysis. The depth and breadth of clinical evaluation, needed data type and data size should match with the design of the product, the key technology, intended use and risk degree, should also be compatible with the level and degree of non clinical research.

Clinical evaluation shall confirm the scope of product (such as suitable crowd, applicable parts, human contact methods, indications, the extent and stage of the disease, usage requirements, usage the environment, etc.), usage, contraindications, precautions, warning information and so on.

Registration applicant should draw the following conclusion by clinical evaluation: under the condition of normal use, the product can achieve the expected performance; and compared with the

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expected benefit, risks of the product can be accepted; performance and safety of the product can get the appropriate evidence to support.

Article 5 Clinical evaluation requirements for products which list in "the catalogue of medical device which is free from clinical trial". (Hereinafter referred to as the catalogue)

For the products which are listed in the catalogue, the registration applicant shall submit the comparison information which is obtained by comparing the application relative information and detailed content in the catalogue, and the comparing explains obtained by comparing the application and the registered medical devices in the catalogue. The clinical information shall be submitted as following:

1. Submitting the comparison information which is obtained by comparing the application relative information and detailed content in the catalogue.
2. Submitting the comparing explains obtained by comparing the application and the registered medical devices in the catalogue. The comparing explains shall include《The table of comparison between application and registered medical devices》(see Attachment 1) and corresponding supporting data.
3. These data shall prove the application is equivalent to the registered medical devices in the catalogue. If these data cannot prove the equality, the relevant assessment shall be carried out in according with other requirements of this principle.

Article 6 Requirements for clinical evaluation by clinical trial and clinical data of the same variety

A. The same variety of medical devices

1. Definition:

Same variety of medical device refer to the products launched onto the market in China has equivalence property with application about basic principle, structure composition, manufacturing materials (for active products, it means the manufacturing materials which contact with human body), production process, performance requirements, safety evaluation, national or industrial standard, intend use, etc.

If the differences between the application and the same variety products have no adverse effects on

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the safety and effectiveness of the application, they are can be considered equivalent.

2. Determination of the same variety of medical devices

Registration applicant conducts the clinical evaluation on the application through the clinical trial and clinical data from the same variety of medical devices to prove its safety and effective. First, comparing the application to one or more the same varieties, to proving they are equivalent.

Compared items including but not limited to items listed in attachment 2. The compared content include the qualitative and quantitative data, verification and validation results, sameness and difference, whether the differences will cause adverse effects on the safety and effectiveness, verification and/or validation by its own data, such as non-clinical data, clinical literature data, clinical experience, and clinical data of a clinical trial which aim at the differences in China. The collection and evaluation of the corresponding data shall conform with the requirement of Part 6.3 and Part 6.4, and corresponding accessory specification.

Registration applicant shall provide the comparison information in form tabular (see attachment for format). if there are inapplicable items for one product,, shall explain the reason why they are inapplicable.

B. Evaluation pathway

The specific evaluation pathway is shown in attachment 4.

C. The collection of the corresponding data from the clinical trial and clinical usage data of the same variety of medical devices.

The clinical trial and clinical usage data (Hereinafter referred to as clinical data) can be obtained from the public scientific literature both in China and abroad, and the corresponding data legal, including clinical literature data, clinical experience. Registration applicant can choose appropriate data source and collection methods according with the product.

1 Collection of clinical literature data

Ensure the completeness and accuracy of the literatures while collecting the clinical literature data. Literature retrieval and screen elements, please refer attachment 5. Before literature retrieval, shall make literature retrieval and screening scheme (see attachment 6 for content and format). After literature retrieval and screening, shall make literature retrieval and screening report (see attachment 7 for content and format). Clinical literature retrieval and screening shall have

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repeatability. Literature searching and screening personnel shall have the corresponding professional knowledge and practical experience.

2 Collection of clinical experience data

The collection of clinical experience data shall include completed clinical research data, adverse events data and corrective action of clinical risk data and so on collection.

2.1 The collection of completed clinical research data

According to the type of clinical trial design, they can be divided into prospective study, retrospective study, randomized study, non randomized control study, single group study, case report and so on.

Registration applicant must provide the ethics committee's views (if applicable), clinical research protocols and clinical research report.

2.2 The collection of adverse events data

Registration applicant shall collect the data from databases which include database about complaints and adverse event built by registration applicant, database about adverse event reported by various country’s supervision organization, such as “Report of medical device adverse event information” and “The medical device vigilance alerts” issued by CFDA, FDA applicant and user institute device service data (MAUDE), MDA and so on.

Registration applicant shall provide the following information of the same varieties: quantity of complaints and adverse events, classified the cause of complaints and adverse events, quantity of all kinds of complaints and adverse events, whether complaints and adverse events related to the product information, etc. . For serious adverse events, should provide the specific information in form of list about event description, reason analysis, processing methods and processing results and so on.

2.3 The collection of corrective action of clinical risk data

Registration applicant shall collect and provide the specific information about corrective action relevant to clinical risk of the same varieties (such as recall, notice, warning and so on), and adopted risk control measures.

D. Conduct the clinical evaluation according to clinical data of similar kinds of medical device

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1 Quality evaluation of the data

Registration applicant shall classify clinical data in the analysis according to recognized clinical evidence level evaluation standard (such as “clinical evidence level evaluation criterion” made by Oxford Centre for Evidence Based Medicine). Some clinical data is not unfit for product effectiveness evaluation, but may still applicable to safety evaluation of the product.

2 Data set establishment

The collected clinical data can be concluded into several data sets according to data type and data quality. Registration applicant may also according to different evaluation purposes to establish data sets, such as the ethnic differences of some products’ clinical performance and/or the safety. In order to evaluate product safety and/or effectiveness in Chinese population, can establish data sets for Chinese population.

3 Statistical analysis

Choosing appropriate analysis methods to conduct the statistical analysis for different data set. Analysis methods for data sets consist of several study results include qualitative analysis and quantitative analysis.

4 Data evaluation

Synthesize the analysis results of different data sets to evaluate whether the product achieve the expected performance under the normal condition of use. The risks of the product are within acceptable levels by comparing with the benefited expectation whether or not.

E. Clinical evaluation report

Composing the clinical evaluation report after the evaluation is completion (see attachment 8 for format), as clinical evaluation data submitted while apply for registration.

Article 7 Requirements for clinical evaluation

Conducting clinical trial in China shall in clinical test institute which has qualification and according with medical device clinical trial quality management standard. Registration applicant shall submit clinical trial protocol and clinical trial report while apply for registration.

For the medical devices whose clinical trail are conducted outside China, if their clinical trial conform with relevant Chinese regulations, corresponding technical requirements of guiding

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principle of registration, such as number of samples, control group selection, evaluation index and principle, therapeutic effect evaluation index and so on. Registration applicant shall submit the clinical trial data which are submitted to the medical device department outside China when it is marketing oversea while apply for registration. The clinical trial data includes at least the views of ethics committee, clinical trial protocol and clinical trial report. Registration applicant also shall submit the relevant supporting data which can prove these is ethnical difference in the clinical performance and/or safety whether or not.

The medical devices shall be conducted clinical trial in China which list in the catalogue of 《The catalogue of Class III Medical Device Need Clinical Trial Approve》.

Attachments:

Attachment 1: Comparative table between application and registered product in China in catalogue.

Attachment 2: Compared items between application and same variety product.

Attachment 3: Format of Comparative table between application and same variety product.

Attachment 4: Clinical evaluation paths through clinical data and clinical usage data of same variety product.

Attachment 5: The requirement of literature retrieval and screen factors.

Attachment 6: The protocol of literature retrieval and screen factors.

Attachment 7: The report of literature retrieval and screen factors.

Attachment 8: Clinical evaluation report according to clinical data of same variety medical device.

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Atachment 1

Comparative table between application and registered product in China in catalogue

Item compared	Product in catalogue	Application	Difference	Supporting data overview
Rationale(Operating principle/Mechanism)				
Structural composition				
Manufacturing materials or the contacting manufacturing materials with human body				
Performance requirements				
Sterilization/ disinfection				
Range of application				
Usage				

Note: the item can be added according to the actual conditions.

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Attachment 2

Compared items between application and same variety product

（Passive medical device）

Passive medical device	对比项目 Compared items
	1. Basic principle
	2. Structure composition
	3. Manufacturing technique
	4. Manufacturing materials(such as material trademark, material of animal origin, allograft material, composition, ingredient, biological active substances, corresponding standard and so on)
	5. Performance requirement
	6. Safety evaluation(such as biocompatibility, bio-security and so on)
	7. National/Industry standard
	8. Range of application （1） Suitable The Crowd （2） Applicable parts （3） The way of Contacting with the human body （4） Indication （5） Applicable disease Stage and Degree （6）境 Environmental Conditions
	9. Usage
	10. Contraindication
	11. Precautionary measure and Warning
	12. Delivery State
	13. Sterilization method
	14. Packaging
	15. Labels
	16. Product specification

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Compared items between application and same variety product

（Active medical device）

Active medical	Compared items

	1. Basic principle （1） Working principle （2） Mechanism of action
	2. Structure composition （1） Product composition （2） Core components
	3. Manufacturing technique
	4. Manufacturing materials(such as material trademark, material of animal origin, allograft material, composition, ingredient, biological active substances, corresponding standard and so on)
	5. Performance requirement （1）Performance parameter （2）Functional parameter
	6. Safety evaluation(such as biocompatibility, biosecurity , electrical security, radiation security and so on)
	7. Software components (core algorithm)
	8. Applied national/industry standards
	9. Range of application: （1）Suitable The Crowd （2）Applicable parts （3）The way of Contacting with the human body （4）Indication （5）Applicable disease stage and degree （6）Environmental conditions
	10. Methods of application
	11. Contraindication
	12. Precautionary measure and warning
	13. Sterilization method
	14. Packaging
	15. Labels
	16. Product manual/specification

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Attachment 3

Format of Comparative table between application and same variety product

Compared items	Same variety product	Application	Differences	Supporting data overview
Basic orinciple				
Structural composition				
……				
……				
……				

Note: the compared items shall include all the items of attachment 2 at least.

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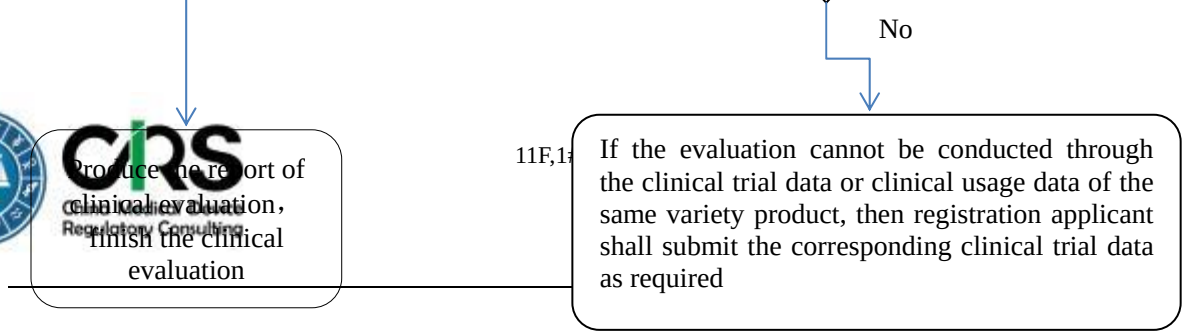
Attachment 4

Clinical evaluation paths through clinical data and clinical usage data of same variety product



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Attachment 5

The requirement of literature retrieval and screen factors

1. Retrieval database

Registration applicant shall select retrieval database according to specific circumstance(such as design characteristic, scope of application and so on) of the application/ the same variety product, and shall discuss the selection reason in the scheme. Selection of database shall be comprehensive, recommended databases as follow:

3.1 Science databases: such as America Medline, Netherlands EM, the China Journal Full-text Database and so on.

3.2 Clinical trial databases: such as Cochrane controlled trial registration center (CENTRAL), ClinicalTrials.gov and so on.

3.3 System assessment databases: such as Cochrane library and so on.

3.4 Special databases: such as MEDION, Bone joint registration database and so on.

2. Retrieval approach, Search words, logical relationship among the search words

In order to retrieve clinical literatures of application and same variety product fully and accurately, shall consider selection of retrieval approach, search words, the configuration of logical relationship among the search words comprehensively, make scientific search strategy. Common retrieval approaches include subject terms retrieval, keyword search, abstract retrieval, full text retrieval and so on. Search words should be adapt to the retrieval approaches, factors to consider include product's common name, trade name, manufacturer, basic principle, structural composition, manufacturing materials, designed feature, key technology, application and so on. Logic searching for retrieval words, should select logical operators properly to express the logical relationship among the retrieval words, such as logic OR expands the retrieval range, logic AND reduces the retrieval range. It is shall discuss reason to determine retrieval approach, search words, logical relationship among the search words.

3. Literature screening process and screening criteria

Suggest conduct "Screening of the detection literature" according to procedures set in figure 1. Registration applicant screen out may satisfactory literature according to title and abstract of the

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literature. Screen out incorporated literature according to full text of the literature. If cannot make sure whether bring into analysis or not according to full text, shall contact with the author to make judgment or direct elimination.

Screening criteria of literature is incorporate and exclusion criteria of literature, should be specific and have operability.

4. Output of literature retrieval and screening result

Output form of literature retrieval and screening result shall be consistent. The form includes author, title, journal name, publishing year, number of volumes (number of periods), page and so on. The full text shall be provided if the literature is selected as clinical evaluation.

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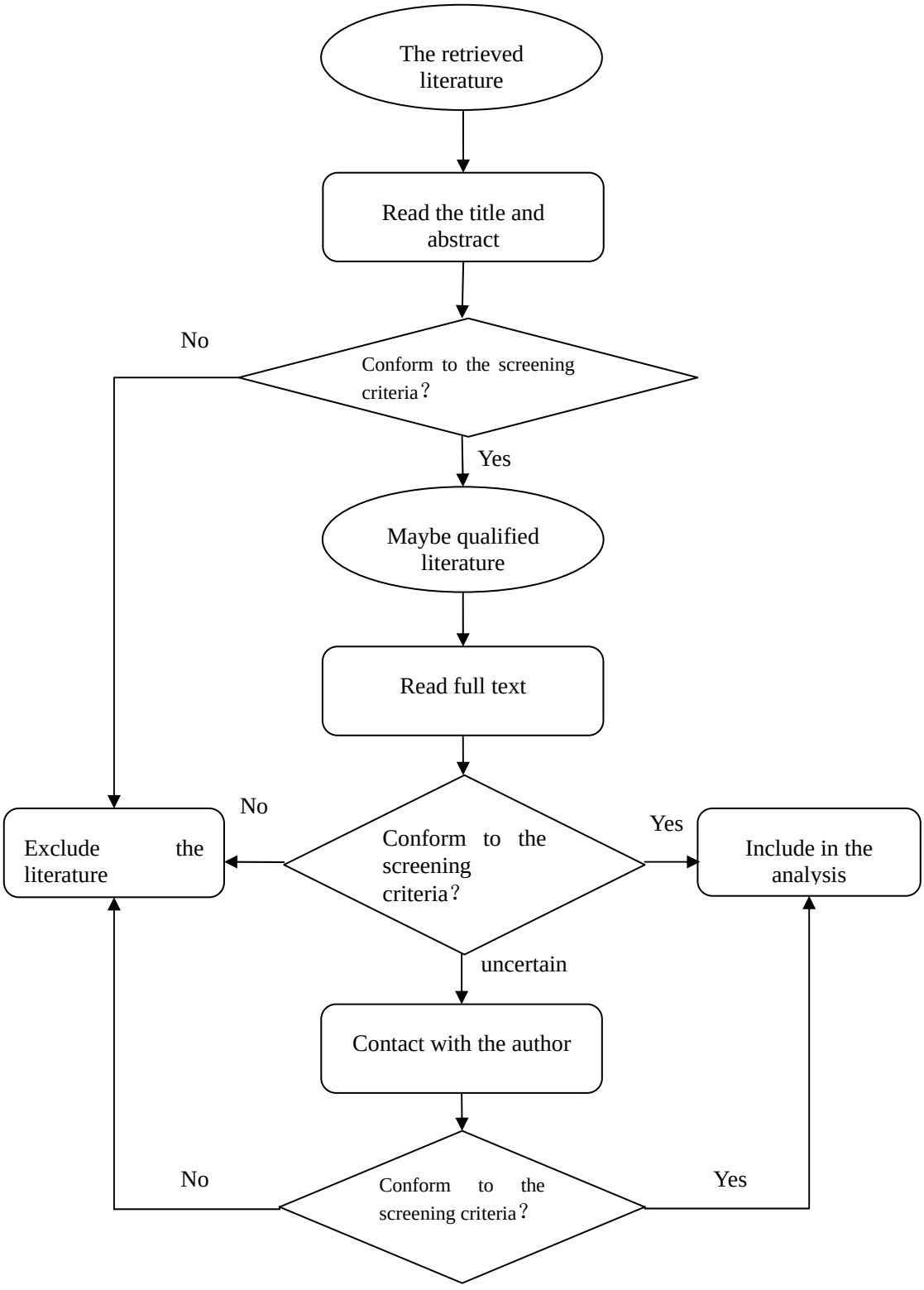
Figure 1 Literature screening procedure



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Attachment 6

The protocol of literature retrieval and screen factors

Name of medical device：

Model specification

Time range of retrieval

Retrieval database

Reason of selecting the retrieval database

Retrieval approach

Retrieval words

Logic assemble of retrieval words

Reasons for confirmation of retrieval approach, Search words, logical relationship among the search words

Output form of literature retrieval

Literature screening process

Screening criteria of literature

Purpose of making Screening criteria of literature

Output form of literature screening result

Literature retrieval and screening personnel name

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Attachment 7

The report of literature retrieval and screen factors

Name of the medical device

Model specification

Time range for retrieval

Retrieval databases

Retrieval approaches

Search words

Logical relationship among the search words

Output of retrieval result

Description, reason and influence to final result of deviated retrieval

Literature screening process

Literature screening criteria

Excluded literature

Exclude reason

Output of literature screening result

Description, reason and influence to final result of deviated retrieval

Note: retrieved and screened literature, suggest to make a list according to the form “author, title, journal name, publishing year, number of volume (number of period), page”.

Signature of the person who retrieve and screen the literature

Time:

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Attachment 8

Clinical evaluation report according to clinical data of same variety medical device

Product name：

Model specification：

Signature by the person who complete it

Completion time：

1. The judgement of the same variety medical device

The compared items and the format of the compared table of the application and the same variety medical device see attachment 2 and 3.

2. The pathway of evaluation

Describe the pathway of evaluation

3. Analysis and evaluation

Registration applicant shall choose the applicable provision according to the condition of application.

3.1 The same of the application and the same variety medical device

Discuss the sameness

3.2 The supporting data which confirms the difference between the application and the same variety medical device has no effect on the safety and effectiveness (non-clinical data, clinical literature data, clinical experience data and so on).

3.2.1 Non-clinical data

a. Overview of the trial

b. Provide the non-clinical report by attachment format.

3.2.2 The clinical literature and the file of collection and analysis of the application

Choose suitable data sources and collection method according to the condition of product. According to different data type, data quality and evaluation purpose, sum the collected data up in different data set to analysis and evaluate. Provide complete information of all kinds of data according to relevant requirements mentioned in this guiding principle, provide them in form of corresponding data set attachment. As following:

a. Clinical study data set

Overview of the data: such as data source, data type, data quality and so on

Analytical method: clear and definite specific analytical method and selection reason.

Data analysis: includes summary the data, analysis procedure and analysis result.

Attachment: such as full test of related literature, Ethics Committee approval letter (if applicable), clinical study protocol, clinical study report and so on.

b. Complaint and adverse event data set

Overview of the data

Analytical method: clear and definite specific analytical method and selection reason.

Data analysis: includes summary the data, analysis procedure and analysis result.

Explanation and evaluation of the analysis result

Attachment: time-to-market, cumulative sales number, number of complaints and adverse events, classification of reason for complaints and adverse events, number of each kind of reason for complaints and adverse events, whether complaints and adverse events related to product and other information in every country. For serious adverse events, shall a list about event description, analysis of the causes, handling and processing results and other specific information in the form of list

c. Data set of corrective actions related to clinical risk

Overview of the data

Data analysis and evaluation

Attachment: specific information of corrective actions related to clinical risk (e.g., recall, announcement, warning, etc.), risk control measures, etc.

d. Data set of Chinese population

Overview of the data: such as data source

Analytical method: clear and definite specific analytical method and selection reason.

Data analysis: includes summary the data, analysis procedure and analysis result.

Explanation and evaluation of the analysis result

Attachment: complete information of all kinds of data

Note: there is no limit of data set quantity, registration applicant shall compile them according to practical situation.

e. The comprehensive evaluation of multiple data sets

Overview of the data

The report and protocol of literature retrieval

The report and collection method of clinical experience data.

3.2.3 The clinical study data which is conducted in China amid at the difference

a. Overview of the clinical trial

b. The protocol and report of the clinical trial.

3.2.4 Other supporting data

a. Overview of the data

b. The full text of the data.

3.2.5 Conclusion

4. The analysis of the clinical trial and clinical usage data of the same variety medical device.

Choose suitable clinical literature data, data sources and collection method according to the condition of the same variety product. According to different data type, data quality and evaluation purpose, sum the collected data up in different data set to analysis and evaluate. Provide complete information of all kinds of data according to relevant requirements mentioned in this guiding principle, provide them in form of corresponding data set attachment. As following:

4.1 Clinical study data set

Overview of the data: such as data source, data type, data quality and so on

Analytical method: clear and definite specific analytical method and selection reason.

Data analysis: includes summary the data, analysis procedure and analysis result.

Attachment: such as full test of related literature, Ethics Committee approval letter (if applicable), clinical study protocol, clinical study report and so on.

4.2 Complaint and adverse event data set

Overview of the data

Analytical method: clear and definite specific analytical method and selection reason.

Data analysis: includes summary the data, analysis procedure and analysis result.

Explanation and evaluation of the analysis result

Attachment: time-to-market, cumulative sales number, number of complaints and adverse events, classification of reason for complaints and adverse events, number of each kind of reason for complaints and adverse events, whether complaints and adverse events related to product and other information in every country. For serious adverse events, shall a list about event description, analysis of the causes, handling and processing results and other specific information in the form of list

4.3 Data set of corrective actions related to clinical risk

Overview of the data

Data analysis and evaluation

Attachment: specific information of corrective actions related to clinical risk (e.g., recall, announcement, warning, etc.), risk control measures, etc.

4.4 Data set of Chinese population

Overview of the data: such as data source

Analytical method: clear and definite specific analytical method and selection reason.

Data analysis: includes summary the data, analysis procedure and analysis result.

Explanation and evaluation of the analysis result

Attachment: complete information of all kinds of data

Note: there is no limit of data set quantity, registration applicant shall compile them according to practical situation.

4.5 The comprehensive evaluation of multiple data sets

Overview of the data

The report and protocol of literature retrieval

The report and collection method of clinical experience data.

4.6 Conclusion

5. Conclusion

6. Other problem need explanations (where applicable)