Chapter 19
Epidemiology Design in Clinical Research

Yi Wang

Key Points

- The process of clinical research include forming research questions, selecting proper epidemiology design, collecting clinical data and doing statistical analysis, preparing reports to publish. The PICO process could help investigators to form research question. For different types of questions, there are different appropriate epidemiological designs could be selected.
- Some checklist items should be included in clinical research reports. The checklists composed reporting guidelines. The reporting guidelines for clinical research include STROBE for observational studies, STARD for diagnostic/prognostic studies, CONSORT for clinical trials, PRISMA for systematic reviews/Meta-analysis, et al.
- Real-world studies are used widely in clinical research now. Real-world studies are different from randomized control trials in many aspects.RCT provides evidence for clinical practice guideline recommendation and real-world study tests if guideline recommendation is practicable.

In previous chapters, we introduced different types of epidemiological study designs and discussed their strengths and weaknesses. The overall strategy of clinical research is the same as that utilized in other areas of epidemiology: observation of incidences between groups and then extrapolation based on any differences. In clinical research studies, the defining characteristics of groups can be symptoms, signs, diseases, diagnostic procedures, or disease treatment. The discussion that follows in this chapter will consequently summarize and integrate the core epidemiological topics involved in the previous chapters. We will concentrate mainly on observational studies, diagnostic/prognostic studies, clinical trials, and systematic reviews looking for the general principles frequently applied in clinical research.

Y. Wang (✉)
School of Public Health and Management, Wenzhou Medical University, Wenzhou, China
e-mail: wang.yi@wmu.edu.cn

C. Wang, F. Liu (eds.), *Textbook of Clinical Epidemiology*,
https://doi.org/10.1007/978-981-99-3622-9_19

Clinical epidemiological studies prefer randomized groups to epidemiological studies. Firstly, the "exposure" in clinical research is usually a treatment approach that tends to be more randomized than the exposures considered in most epidemiological studies (e.g., tobacco or alcohol consumption, diet, or personal or environmental characteristics). Secondly, the results uncovered in clinical epidemiological studies, such as disease progression, complications, or mortality, are comparatively frequently found in the patient groups being compared, making randomized studies more feasible. Thirdly, the potential for confounding is particularly high in clinical epidemiological studies where there is no randomized grouping. In a large number of nonrandomized treatment studies in which a correlation has been detected, it is unclear whether changes in patients' risk of disease progression, complications, or death are related to the type of treatment they receive.

19.1 Design and Implementation of Clinical Research

Good epidemiological studies are complicated to design and conduct, and the interpretation of their consequences and findings is not as straightforward as researchers would like it to be. So, what can we do to make the best research design? How can we make the most of the clinical practice information available to us? When we read or write clinical research papers, the central question we need to answer is "Are the findings valid?". If a relationship between predicted values and results is reported by researchers, is this true? If they come up empty, can we trust them? Or could there be another interpretation of the findings, namely, chance, bias, and/or confusion? When investigators perform the clinical study, they almost certainly must read individual articles and reports, especially the guidelines for clinical research published in professional journals. They may produce some of their scientific papers when they are engaged in clinical research.

The first stage in establishing clinical research is to design the study issue that you aim to answer. Then, you would utilize several epidemiological designs to try to uncover the explanation. Therefore, first of all, investigators need to focus on what clinical questions should be answered. Secondly, researchers should also consider whether the research design was suitable for replying to the questions raised. A highly practical approach is very necessary, which we will outline in the parts that follow.

19.1.1 Forming Research Questions

Usually, clinical problems could be divided into two categories: background question and foreground question. The background question is about the general knowledge of disease such as "what is tuberculous pericarditis?" and "what are the antituberculosis drugs?" The foreground question is the actual problems that

physicians or surgeons encounter in the process of diagnosis and treatment of patients. For instance, physicians want to know "how the utility of the ascites adenosine deaminase (ADA) in the diagnosis of the tuberculous peritonitis?" and "does tuberculous pericarditis require glucocorticoid treatment?". The foreground question is the main problem in clinical practice. According to different process of clinical practice, there are four types of foreground questions: treatment question, diagnosis question, etiology question, and prognosis question. When physicians are confronted with clinical foreground questions, they want to design a study to solve these problems, they could use "PICO" process to decompose the research problems into specific research content.

In "PICO" process, "P" is an abbreviation for patients or population. It refers to the clinical features of research patients or population. "I" is an abbreviation for intervention or exposure. It means treatment measures or exposure issues that are concerned. "C" is an abbreviation for comparison. It means the control measure and usually means the "gold standard" if it is a diagnostic study. "O" is an abbreviation for outcome. It is the outcome indicators that the research focused on. In Table 19.1, it listed some examples of how to use "PICO" framework to form research question in four different question types.

19.1.2 Commonly Used Epidemiological Design in Clinical Research

The most important point in clinical research is to identify the research question. If clinicians have proposed a research question, there are different epidemiological designs that could be selected to help answer these questions. Commonly used epidemiological design in clinical research includes cross-sectional study, case-control study, cohort study, nonrandomized controlled trials, and randomized controlled clinical trials. In general, prospective study design has the most content, the most complex methods, and the most representative of epidemiological data analysis. Figure 19.1 illustrates how to decide which epidemiological design to select.

Previously, we have introduced four types of foreground questions. For different types of questions, different epidemiological designs could be selected. For the evaluation of treatment efficacy, the most appropriate study design is a randomized control trial (RCT). However, it is very difficult to carry out an RCT in real clinical practice, especially conducted it in a multicenter study. Besides RCT, a cohort study, case-control study, case report could be selected for the treatment questions. For prognosis question, the most appropriate study design is a cohort study. In Table 19.2, it listed best design could select for each type of foreground questions.

Table 19.1 Examples of application of the PICO process in clinical research

Question type	Clinical question	PICO	Research content
Treatment question	Do patients with tuberculous pericarditis need to be treated with glucocorticoids?	P: adult patients with tuberculous pericarditis I: antituberculosis + glucocorticoid C: antituberculosis O: death	Can glucocorticoids reduce the risk of death in adult patients with tuberculous pericarditis?
Diagnosis question	What is the utility of the ascites adenosine deaminase (ADA) in the diagnosis of the tuberculous peritonitis?	P: patients with celiac effusion I: ascites adenosine deaminase examination C: gold standard diagnostic method for tuberculous peritonitis O: validity of diagnosis for tuberculous peritonitis	How about the sensitivity and specificity of the ascites adenosine deaminase examination for the diagnosis of tuberculous peritonitis?
Etiology question	How about the risk of a vegetarian suffering from tuberculosis?	P: adults I: vegetarian diet C: common diet O: tuberculosis	Are vegetarians at more risk to develop tuberculosis than nonvegetarians?
Prognosis question	Do patients with tuberculous pericarditis could develop into constrictive pericarditis?	P: tuberculous pericarditis patients O: constrictive pericarditis (there usually have no "I" and "C" in the prognosis question)	What is the probability of patients with tuberculous pericarditis to develop constrictive in the future? What are the prognostic factors to predict patients with coarctation?

19.1.3 Collection and Analysis of Clinical Research Data

Routine clinical epidemiological data are primarily those with health, illness, and clinical services that are routinely collected in the population for other uses, such as patient data routinely collected in hospitals. In addition, some are disposable, irregularly collected data, but others are data from specific epidemiological studies (such as prospective studies), such as the purpose of the analysis is not to answer the original questions of the study, but to use the data to explore new non-primary research questions. They are collectively referred to as routine clinical epidemiological data. Routine clinical epidemiological data analysis steps: (1) Analyze the time frame of the data and the characteristics of the variables; (2) Ask questions that can be explored to determine the final research question; (3) Compare with the best

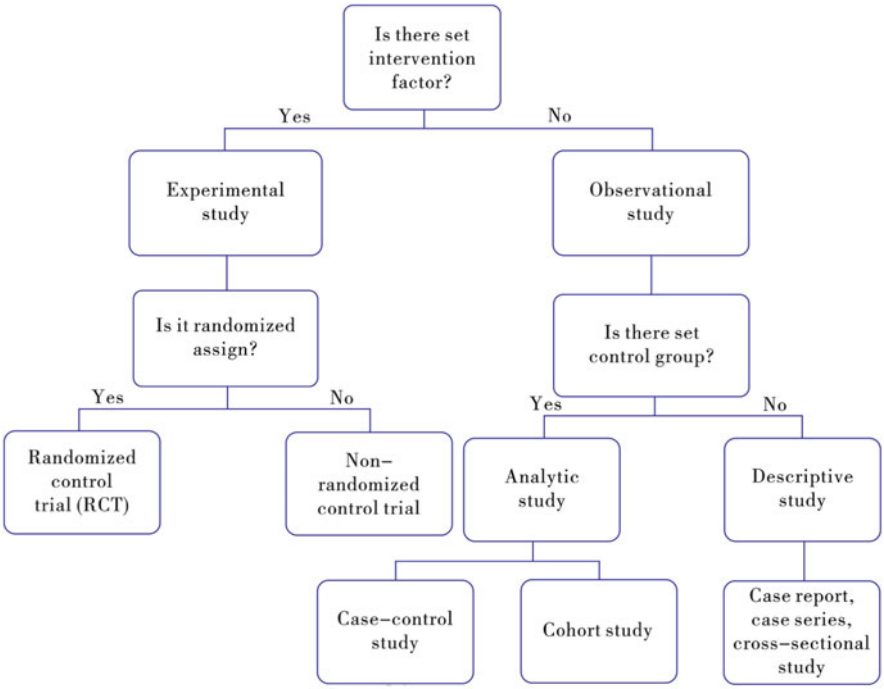

Fig. 19.1 The flow chart of selection of epidemiological design in clinical research

Table 19.2 Best study design to select for different clinical questions

Question type	Best study design
Treatment question	RCT
Adverse effect of treatment question	RCT
Diagnosis question	Cross-sectional study
Prognosis question	Cohort study
Etiology question	Cohort study, case-control study

research design, check data for "research design" defects; (4) Estimate the necessary indicators and their confidence intervals; (5) Analyze other possible biases in the data (selection bias, information bias, and confounding bias); (6) Integrated design flaws, biases, and results, and draw conclusions on research issues.

19.1.3.1 Data Collection

The collection and management of clinical research data is the main content in the design and implementation phase of clinical research. It involves management techniques and skills and requires researchers to invest a great deal of time and effort. The collection and management of clinical data is a process. Understanding

Fig. 19.2 Process of clinical research data collection

the content of each link in the process and the relationship between the various links can be a good job in clinical research design and implementation. The process of collecting and organizing clinical data is characterized by a linear process, multi-stage, and multi-link. Figure 19.2 shows this process.

Clinical research is the process of collecting, sorting, storage, analysis, and evaluation of clinical data. It is a linear process and can only be carried out in a sequential manner. The starting point of clinical research is the research object. The researchers have to use various technical methods to obtain clinical data from the research object, then transfer the clinical data to the case report form (CRF), and then transfer the clinical data from the CRF to the database, and prepare for the later statistical analysis and evaluation work. In the process of clinical data collection, the completion of CRF filling and the establishment of the database are treated as a two-phased landmark in the collection of clinical research data. The completion of the CRF design marks important progress in the design of the clinical research implementation plan. The establishment of a database is a key link between the collation and storage of clinical data. There are sophisticated methods and techniques, and the workload is large. The quantity and quality of the input data are guaranteed, and it is organized for later data analysis. The data completed by the CRF, the quality, and the completion of the database are the main evaluation indicators for evaluating the implementation phase of the clinical research organization.

Besides collecting clinical data from practice clinics or hospitals, clinicians could collect clinical data from some open access databases, like SEER (surveillance, epidemiology, and end results). Here, we will introduce an open access database commonly used in clinical oncology research – TCGA. The Cancer Genome Atlas (TCGA) program was launched in 2005 to apply the latest genomic analysis technology. In particular, the whole genome sequencing technology, in-depth understanding of cancer gene changes, and promoting the discovery of new cancer treatment programs, diagnostic methods and prevention strategies, plans to draw a wide range of tumor types and tumor subtypes, multidimensional map of the key genome changes. Moreover, all the data can be shared for free in scientific practice. The TCGA plans to collect sample data for 11,000 patients and 33 cancers (Table 19.3). In 2015, the amount of data collected and generated by the TCGA program had reached 20PB, including 10 million mutations. Investigators could choose interested cancers to download the gene and clinical information and analyze them for particular purpose.

Table 19.3 TCGA plan cancer sample distribution (33 cancers, 11,000 patients)

Cancer symbol	Type of cancer	Number of samples	Cancer symbol	Type of cancer	Number of samples
BRCA	Breast invasive carcinoma	1097	THYM	Thymoma	124
KIRC	Kidney renal clear cell carcinoma	536	SKCM	Skin cutaneous melanoma	470
LUAD	Lung adenocarcinoma	521	ACC	Adrenocortical carcinoma	80
THCA	Thyroid carcinoma	507	DLBC	Lymphoid neoplasm diffuse Large B-cell lymphoma	48
PRAD	Prostate adenocarcinoma	498	LGG	Brain lower-grade glioma	516
LIHC	Liver hepatocellular carcinoma	377	LAML	Acute myeloid leukemia	200
LUSC	Lung squamous cell carcinoma	504	MESO	Mesothelioma	87
HNSC	Head and neck squamous cell carcinoma	528	OV	Ovarian serous Cystadenocarcinoma	586
COAD	Colon adenocarcinoma	461	TGCT	Testicular germ cell tumors	150
UCEC	Uterine corpus endometrial carcinoma	548	UCS	Uterine carcinosarcoma	57
KIRP	Kidney renal papillary cell carcinoma	291	UVM	Uveal melanoma	80
STAD	Stomach adenocarcinoma	443	CESC	Cervical squamous cell Carcinoma and endocervical adenocarcinoma	307
KICH	Kidney chromophobe	66	PCPG	Pheochromocytoma and paraganglioma	179
BLCA	Bladder urothelial carcinoma	373	SARC	Sarcoma	261
ESCA	Esophageal multiforme	185	CHOL	Cholangiocarcinoma	36
READ	Rectum adenocarcinoma	171	GBM	Glioblastoma multiforme	528
PAAD	Pancreatic adenocarcinoma	185			

The TCGA research team has collected and generated various types of histological and genetic data for these cancers, including gene expression, exon expression, small RNA expression, copy number changes (CNV), single nucleotide polymorphism (SNP), loss of heterozygosity (LOH), gene mutations, DNA methylation, and

protein expression. The clinical information includes patient's basic geographic information, treatment method, historical or clinical stage, survival status, and so on.

By analyzing the cancer genome information to understand the mechanism of cancer development and discover cancer markers and drug effect on gene targets, it can provide support for the accurate diagnosis and treatment of cancer. The TCGA plans to collect data on a large number of cancer genomes and clinical phenotypes. There are potential molecular markers and drug targets for cancer that need to be tapped. Scientific data management programs provide protection for cancer genome research. The practical exploration of cancer genomic map planned in data management can provide a reference to the development and implementation of large-scale scientific programs such as precision medicine and data-driven collaborative research models.

19.1.3.2 Data Analysis

Unlike basic medical research, clinical epidemiological research is an applied research conducted in the population to quantitatively explore the general rule of disease, health, and clinical practice, and the results can be directly applied to clinical practice. Clinical epidemiological studies need to be based on specific research questions, selecting designs, controlling bias, collecting data, and then analyzing the data to quantitatively answer research questions. Therefore, data analysis is an important and indispensable part of clinical epidemiology research. Clinical questions generally include etiology questions, diagnosis questions, treatment questions, and prognosis questions. The purpose of data analysis is to scientifically and quantitatively answer these practical questions. Data analysis must have a clear purpose for analysis. The common purpose of clinical epidemiology is shown in Table 19.4. Clearly studied issues are the premise of data analysis. After the question is clarified, it is necessary to put forward a specific and clear analysis purpose. Its content generally includes the following: (1) describe the change in the number of subjects, (2) variable classification and data sorting, (3) describe and compare baseline data between groups, (4) estimate the frequency of outcome events, (5) estimate the magnitude of the effect, (6) the confidence interval of the estimated effect, (7) identify and control the confounding, (8) identify and measure effect modification effects, (9) identify and measure dose-response relationships, (10) other

Table 19.4 The purpose of clinical epidemiological data analysis

	Research purpose
1.	Estimating relevant statistical indicators such as relative risk and sensitivity
2.	Estimating the confidence interval for the statistical indicator
3.	Controlling for possible confounders
4.	Analysis of dose-response relationships
5.	Analysis of possible effect modification factors
6.	Analysis of other possible biases

analysis. Although the design principles of different studies could variate and the clinical problems, the purpose, contents, and methods of analysis are also different, the analysis of other research data can be regarded as one or more components of the data analysis of prospective research.

In addition, the estimation of this indicator must simultaneously control possible confounding factors. In a randomized control trial, investigators could thoroughly control confounding factors through randomized assign research objects to different groups. However, in observational studies (such as nonrandomized allocation trial studies, cohort studies, and case-control studies), the most effective and feasible method for controlling confounding factors is multivariate regression analysis. The premise of controlling confounding is to recognize possible confounding factors, and the baseline data with confounding factors were collected at the beginning of the study. Other analytical purposes may include identifying and measuring effect modifiers, identifying and describing dose-response relationships, and analyzing and controlling other possible biases.

19.1.4 Preparing Papers for Publication

The following recommendations provide a guide for investigators to prepare clinical research reports:

19.1.4.1 Choose Target Journal(s)

Selecting the intended journal category for publication is always the first step for the researchers while drafting the report. When selecting target journals, investigators should take the following issues into account.

How High to Aim

A question that researchers will face is what height your paper may reach. Many investigators believe that five top general medical journals are particularly attractive carriers for their article: *The Lancet*, *The New England Journal of Medicine* (*NEJM*), *The Journal of the American Medical Association* (*JAMA*), *Annals of Internal Medicine*, and *British Medicine Journal* (*BMJ*). Investigators often have the question of whether their research is suitable for these or other famous journals. It is also challenging to predict success (or lack of success) for experienced researchers, which makes it very difficult to select the most appropriate target journals. In general, if it is adequate for you to seriously consider contributing to a famous journal, it means that your research has been well designed and implemented, and beyond that, you are so courageous. More commonly, the internal debate (within you or your survey team) may be whether you first submitted to a secondary journal (e.g.,

possibly a top journal in your subspecialty field) or are more likely to accept a journal with a lower reputation for your manuscript. One advantage of foresight is that sharp comments may help you improve your article. It is unusual to make substantial improvements to your manuscript based on the opinions of reviewers, but it can happen in some cases. Therefore, if multiple submissions do not make you tired, and receiving too many rejection letters from magazines does not hurt your self-esteem, set a higher goal. If your mental state is irritable and fragile, then choosing a journal with a less high impact factor is more likely to accept your manuscript at the first submission.

Selecting a Journal with a Fondness for Researcher Topic

Some certain topics or fields are often favored by certain journals. If research in an area that is closely related to your study has previously been published by a journal, it is eligible to be one of your chosen targets. In the meantime, the lack of articles in your field or using your methodology provides the information you should search for elsewhere.

Tailoring Content to the Target Journal

The majority of the manuscripts you write will be reporting on the clinical investigations you conduct. However, in some cases, investigators may write a paper that focuses more on research methods. These papers explored some issues, such as the best research design, measurement methods, or results interpretation. Researchers can consider publishing their manuscripts in these three types of journals: general medical journals, subspecialty journals, and methodologically oriented journals. Many articles on clinical research are likely to be published in multiple target journals.

Tailoring Format to the Target Journal

Almost every journal has its own format requirements. Most of these requirements are relatively trivial (e.g., section titles or reference citation styles), and when you are ready to submit your manuscript, you must modify it as required. Of course, there are other more important issues that researchers should address them early on.

19.1.4.2 Choose a Clear Message

The work may be exceedingly complicated, and a definite result might not be obvious. Until a clear message is determined, investigators must continue to evaluate the essence of the results. Just considering what the reader is going to take away from

a single point, what is that point? After determining the information, the investigator needs to craft the introduction so that readers will be convinced of the significance of the research. Your research should be presented to readers as a narrative. The reader's curiosity should be piqued by the introduction, satisfied by the outcome, and reinforced by the discussion, which should highlight how significant the finding is.

19.1.4.3 Achieve High Quality in Writing

Here are some tips for creating a high-quality manuscript. (1) Use the active voice: Passive writing is a well-established medical practice. Although the passive voice makes writing more awkward and difficult to understand, adds extra words, and makes the work lose some power, this tradition still exists. The use of active voice is advised in all current publications on writing quality from a variety of nonmedical professions as well as writing suggestions offered by the top medical magazines. (2) Delete unnecessary words: Unnecessary words are utilized by medical writers. Eliminating these terms makes the writing more direct and clearer to read. Journal articles must adhere to strict space restrictions as well. Use as few adverbs and adjectival phrases as you possibly can. (3) Avoid using the verb "to be": The verb "to be" and the passive voice frequently has the same impact. It robs the writing of vigor and energy. (4) Keep paragraphs short: Each paragraph in the article should not exceed five sentences. Clarity will be considered a priority.

19.1.5 Common Problems in Clinical Research Design

According to the analysis of clinical papers published, there are six major problems in the design of clinical research programs.

1. Researchers are unclear about the design scheme adopted by their institute
   After investigating the research questions that are of interest to the researcher, the researchers must determine the research design plan based on the results they expect, the strength of the causal connection, and the feasibility.
2. Unclear definitions of primary and secondary study end points
   A study generally has only one primary end point, but there can be several secondary end points. In some studies, it is not correct to write only what the study end point is, but not to distinguish between the primary and secondary end points. In the design plan, the primary and secondary end points of the study need to be clearly written out, which is conducive to the establishment of hypotheses and the calculation of sample size. It is not possible to write all the indicators in parallel and regardless of primary and secondary levels.
3. Have no scientific hypothesis

The entire research process is the process of testing the hypothesis. The hypothesis is based on scientific research problems. Based on the hypothesis, the researcher can determine the sample size, follow-up time, and determine the type of quantitative collection, and statistical methods. Researchers need to establish reasonable assumptions based on the primary end point after the design of the study.

4. Have no controls or unreasonable controls

   The four principles of clinical trial design are "random," "control," "blinding method," and "repetition." The establishment and selection of appropriate controls for the control group is an important part of the research design. Researchers can design blanks, placebo controls, positive standard controls, and other controls based on the purpose of the study. Parallel control is best for the same period.

5. Nominally a randomized control study but not an actual randomized grouping

   The stochastic method includes two layers of meanings: One is the generation of random distribution sequences and the other is the concealment of random distribution sequence schemes. If the scheme is not hidden, randomization may be disrupted, resulting in selection bias and measurement bias. The purpose of blinding is to make the research executor not know the specific stochastic method and do not know whether the research object in accordance with the random sequence belongs to the experimental group or belongs to the control group so that complete randomization can be achieved. Researchers should be trained in systematic clinical epidemiology or clinical research methodologies. The significance of clinical research method training is similar to that of standardized training for clinicians. It is an important foundational work and requires the support and efforts of all parties.

6. No sample size was calculated

   In addition to exploratory research, because no basic data cannot calculate the sample size, a general clinical study needs to estimate the sample size in advance. A too small sample size will result in large sampling errors, resulting in poor representativeness and poor reproducibility. Researchers should pay attention to the significance of sample size and know the concept of power. As long as there is a consciousness of calculating sample size, the calculation process is not a problem. Now there are many statistical software applications for calculating sample size.

19.2 Reporting Guidelines for Clinical Research Reports

19.2.1 Observational Studies Reporting Guidelines

In September 2004, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) working group was founded and convened in the United Kingdom to draft the normative meeting of the observational research report. After many revisions, a list containing 22 items (STROBE statement) was released in

2007, which is divided into 6 major aspects including the title, abstract, introduction, method, result, and discussion. Eighteen of these items are applicable to all three major observational research designs (cross-sectional, case-control, and cohort design), and the remaining four are specially used for cohort, case-control, or cross-sectional design, respectively. A new STROBE statement extension was released in 2014 by the Lancet Infectious Diseases. Enhance Molecular Epidemiology Reporting for Infectious Diseases (STROME-ID). The goal is to provide guidelines for effective scientific reporting of molecular epidemiology research to urge authors to take particular hazards to reliable inference into account. The official website (http://www.strobe-statement.org) offers free downloads of the STROBE statement and STROME-ID statement.

19.2.2 Diagnostic/Prognostic Studies Reporting Guidelines

In 2003, Bossuyt PM, an authoritative expert in the field of diagnostic tests, convened a group of experts to establish the STARD group to develop a report on the diagnostic accuracy study – Standards for Reporting of Diagnostic Accuracy (STARD), which was used to standardize diagnostic test studies. In order to solve new problems in diagnostic tests, streamline the reporting process, increase its applicability, and align STARD with CONSORT-2010, Bossuyt PM again convened a group of experts in 2015, including epidemiologists, statisticians, evidence-based medicine experts, doctors, editors, and journalists, and 85 people, based on the STARD 2003, developed a STARD 2015 guide using document research, drafting entries, expert surveys, and group discussions. The STARD statement could be downloaded from http://www.stard-statement.org.

19.2.3 Clinical Trials Reporting Guidelines

The CONSORT (Consolidated Standards of Reporting Trials) declaration was created by a team of scientists and editors to enhance the caliber of RCT reporting. It was revised in 2001 after being initially published in 1996. The statement includes a flow diagram and checklist that researchers can employ to report an RCT. The CONSORT declaration has received support from several top medical publications and influential international editorial organizations. The claim makes it easier to evaluate and understand RCTs critically. The ideas underpinning the CONSORT statement were clarified and expanded upon during the 2001 CONSORT revision to assist researchers and others in writing or evaluating trial reports. In 2001, the CONSORT declaration and an essay explaining and expanding upon it were both published. The CONSORT statement was further amended following an expert meeting in January 2007 and is now available as the CONSORT 2010 Statement. This revision clarifies and updates the prior checklist's language and includes

suggestions for subjects like selective outcome reporting bias which have just recently gained attention. This explanation and elaboration paper, which has also undergone substantial revision, aims to improve the use, comprehension, and diffusion of the CONSORT declaration. Each newly added and revised checklist item is explained along with its purpose, with illustrations of effective reporting and, if available, references to pertinent empirical research. There are several flow diagram examples provided. Resources to aid with randomized trial reporting include the CONSORT 2010 Statement, the updated explanatory and elaboration paper, and the related website (CONSORT, http://www.consort-statement.org).

19.2.4 Systematic Reviews Reporting Guidelines

In 1996, the Quality of Reporting of Meta-Analyses (QUROM) guide was published, which focused on the quality of reporting of randomized controlled trial meta-analysis, which was the earliest reporting specification for systematic review/meta-analysis quality. In the classic monograph "Systematic reviews in health care: meta-analysis in context," QUROM was recommended as the "gold standard" for evaluating the quality of systematic reviews/meta-analysis reports. The items involved in the QUROM report specification are divided into 6 parts and 18 items, including the title, abstract, introduction, method, result, and discussion. The results section includes the search process and gives the reasons for identifying, including, and excluding randomized controlled trials and exclusions. In 2009, QUROM updated Systematic Reviews and Meta-Analyses for Protocols (PRISMA) in order to improve the quality of systematic review, and meta-analysis article reports. PRISMA is more comprehensive and complete than the QUROM developed in the past. It has a wide range of applications, not only for meta-analysis, but also for systemic evaluation; not only for systematic evaluation of randomized controlled trials but also as a basic specification for evaluation reports of other types of research systems. The PRISMA Reporting Guide consists of a list of 27 items, a four-phase flow chart, and detailed explanations and explanations of relevant items. All these materials could be downloaded from http://www.prisma-statement.org.

19.3 Real-World Study

The collection and storage of enormous volumes of health-related data via computers, mobile devices, wearables, and other biosensors have been expanding quickly. This information has the potential to help us design and carry out clinical research in the health-care sector more effectively to provide answers to previously

unanswerable problems. Additionally, we are better equipped to examine these data and apply the findings to the development and approval of medical products as a consequence of the development of sophisticated, new analytical skills. As a result, a growing number of clinical trial designs are being designed which have been derived from real-world data and evidence.

19.3.1 Definition of Real-World Study

Real-world studies (RWS) originate from effective clinical trials and refer to the nonrandom choice of interventions based on the patient's actual condition and willingness to perform long-term evaluations based on the larger sample size (covering a representatively larger number of subjects). Focus on meaningful outcome indicators to further evaluate the external effectiveness and safety of interventions. The RWS covers a wide range of areas and can be used for diagnosis, prognosis, etiology, in addition to curative studies. The RWS focuses on the effectiveness of research, namely, the size of the evaluation interventions in the real clinical environment. RWS can also be used to evaluate the cost-effectiveness of different health interventions.

19.3.2 The Difference Between RWS and RCT

Although RWS is very different from RCT (Table 19.5), RCT and RWS are not contradictory or alternative relations of opposition but are complementary and forming a connecting link between the preceding and the following. RCT is the highest level of evidence-based medicine; is the "gold standard" of clinical trial design. It is a recommendation to formulate corresponding treatments guidelines based on RCT, which tells doctors that they can do and should do, rather than have to do it. Therefore, the guideline cannot replace clinical practice. It needs RWS as an effective supplement, and RWS can be used to determine the true benefits, risks, and therapeutic value in clinical practice, so that clinical research conclusions will return to the real world after RCT. Therefore, RWS and RCT are not antagonistic, but complementary to each other.

Overall, RCT provides evidence for clinical practice guideline recommendation. RWS tests if guideline recommendation is practicable, whether answers clinical questions and summarizes treatment recommendations, then returns to clinical practice. Among them, RWS plays a more and more important role nowadays.

Table 19.5 Differences between RCT and RWS

	RCT	RWS
Research purposes	The outcome of an ideal situation	The outcome of the real situation
Research environment	Strictly controlled conditions	Actual clinical conditions
Research design	Randomized controlled trials	Nonrandomized Control/Effective Randomized Control/Observational Study
Research scheme	Cannot be changed after the program is fixed	Can be adjusted according to clinical practice
Research object	Strict inclusion/exclusion criteria and good homogeneity	Inclusion/exclusion criteria are loose, and diversity is good
Sample size	Minimum sample size	As much as possible
Control group	Standard treatment/placebo	Effective treatment/no placebo
Research data	Designed before the start of the trial, prospectively collecting data	Forward-looking/retrospectively collecting data according to need
Study outcomes	Most recent indicators	Mostly long-term indicators
Follow-up time	Short	Long
Follow-up completion	Better	Uncertain
Ethical review	Need	Need
Clinical registration	Need	Need
Internal effectiveness and safety	Good	Poor
External effectiveness and safety	Poor	Good
Difficulty of work	Relatively small difficulty	Very difficult
Evaluation angle	Evaluating effectiveness from a medical perspective (efficacy)	Evaluate the effect from the patient (effectiveness)