appendix

药物临床试验不良事件相关性评价技术指导原则

（试行）

2024 年 6 月

Table of contents

1. Overview

2 In drug clinical trials, any

3 Unfavorable medical events are called adverse events (AEs).

4 can manifest as diseases, symptoms, signs or laboratory abnormalities,

5 The event does not necessarily have a causal relationship with the investigational drug.

6. In clinical trials of drugs, the test drugs may cause harmful or non-

7 The expected reaction is called an adverse drug reaction (ADR).

8. Evaluating and judging the relevance of adverse events to the trial drug is a

9A very important link in clinical safety research, evaluation and risk control.

10 Researchers and sponsors need to carefully collect relevant information and analyze possible

11 Influencing factors, scientifically, accurately and objectively evaluate adverse events and

12Whether there is a correlation between the experimental drugs and the strength of the correlation.

13 The purpose of developing these guidelines is to conduct

14 One step to standardize the correlation between adverse events and test drugs in drug clinical trials in China

15 Evaluation methods and standards for drug clinical trial sponsors, researchers, and regulatory agencies

16 Institutions and other relevant personnel conduct monitoring and identification of adverse reactions in drug clinical trials

17. Provide reference for the work related to identification, evaluation and control to better implement clinical trials

18Minimize risks and protect the safety of subjects.

19. The evaluation of the relevance of adverse events in drug clinical trials includes individual case evaluation and group evaluation.

20 Individual evaluation. Individual evaluation is the premise of group evaluation and the basis of group evaluation and drug

21 The basis for safety analysis and evaluation.

22 Evaluation of the relevance of individual adverse events during the trial to the trial drugs.

23 This guideline applies to drug clinical trials conducted for the purpose of drug registration.

24- bed trial. Other clinical studies can also be used for reference.

25. Considerations

26 Accurately evaluate the correlation between adverse events in clinical trials and trial drugs, which may

27Affected and restricted by many factors, including incomplete case information

28 or there are biases, limitations in the professional background knowledge of the evaluators, etc.

29 incidents, an accurate and reliable evaluation of their relevance requires not only a deep understanding of the relevant

30 Epidemiological characteristics, pathological mechanisms, clinical manifestations, and metabolism of experimental drugs

31 Kinetic characteristics, mechanism of action, pharmacological effects, toxicological study results, known

32 , and also need to fully and carefully understand the adverse reactions of the patients.

33. Subjects' current medical history, past medical history, personal and family history, history of drug and food allergies, etc.

34 Relevant details, especially any concomitant diseases, concomitant medications or other treatments

35 Detailed information. Only after comprehensive and complete collection of relevant information about the subjects

36 or above, and then we can conduct a comprehensive analysis based on medical and pharmaceutical knowledge and sort out

37 In addition to possible confounding factors and other potential causes, the adverse events and the

38 Make scientific, reasonable and accurate judgments on the relevance of drugs.

39 Common considerations mainly include the following aspects.

40 1. Experimental drugs

41 1. Drug exposure (including exposure time and exposure dose)

42 Based on the time of medication and the time of adverse events,

Analyze from 43 perspectives whether there is a reasonable time relationship between the two.

44 Consider the different doses and adverse events or adverse events according to the dosage.

Is there any correlation between the 45 weights?

46 Evaluate and determine whether there is a dose-exposure-effect relationship, i.e., dose or exposure

47 The higher the exposure level and the longer the exposure time, the greater the probability or severity of adverse events.

48 degrees is more serious.

49

2. Pharmacokinetic characteristics

50 Consider whether the occurrence of adverse events is related to the metabolic kinetics of the investigational drug.

51 characteristics (such as absorption, distribution, metabolism, excretion, etc.).

52 Is the onset or disappearance time related to the change in drug concentration?

53 Based on the metabolic characteristics (e.g., the drug is basically cleared from the body after 5 half-lives),

54 Pay attention to whether adverse events continue to exist after drug discontinuation and when the adverse events end.

55 Stop or improve, combined with the administration time, half-life, expansion status (such as cell therapy

56 products), a comprehensive analysis of the time of onset and disappearance of adverse events is helpful to judge

57 The adverse events were not related to the trial drug; however, some adverse events were

58 In addition, delayed allergic reactions, such as delayed hypersensitivity reactions, occur with a time lag and are related to the blood drug concentration in the body.

59The relationship does not conform to the general rule.

60

3. Pharmacological action

61 Based on the pharmacological mechanism and pharmacodynamic characteristics of the experimental drug, adverse events should be judged.

62 cases were suspected to be related to the trial drug.

63

4. Results of nonclinical safety studies

64 Reference to nonclinical safety studies, such as safety pharmacology and toxicology studies.

65 Study results to determine whether there is a possible correlation between adverse events and trial drugs.

66

5. Previous relevant clinical research safety results

67 Review relevant information to confirm the test drug and its ingredients, similar drugs

68. Have similar adverse reactions or adverse events been reported?

69 In summary, based on the nonclinical studies of the trial drug and the clinical studies provided by the sponsor,

70 research data and other relevant safety information, and also refer to drug epidemiology studies,

71 Known safety characteristics of similar drugs can help determine whether adverse events occur.

72 with a possibility of being related to the trial drug.

73 (II) Disease factors

74 Understand the subject's current and past medical history in detail, and on this basis, make a judgment

75 Is the adverse event related to the subject’s original/specific disease (including clinical trial related

76 specific diseases, other basic diseases or concomitant diseases, potential diseases)

77Clinical manifestations or progression.

78 Consideration should be given to the fact that subjects may have other diseases that may affect the investigational drug.

79 The metabolism of the drug may be affected differently, thus leading to the occurrence of adverse events.

80 In general clinical trials, the age range of subjects is relatively large, with elderly subjects

81 The subjects may have more comorbidities (such as the same subject also has coronary heart disease

82 disease, diabetes, renal insufficiency, etc.), the evaluation of the relevance of adverse events should be

83Don't pay attention.

84 (III) Combined medication or other treatments

85 Understand whether there are any concurrent medications in the recent period (not limited to when the adverse event occurred)

86 (including chemical drugs, traditional Chinese medicines, biological products, etc.), as well as the types of combined medications,

87Specific drugs, dosage, start time, stop time, etc.

88 On this basis, determine whether the combined medication or other medications before the adverse event occurred

may cause adverse events, and whether there may be

90% of the drugs used may interact with each other, leading to adverse events.

Understand whether the patient has received other treatments recently (not limited to when the adverse event occurred).

Therapy (such as surgery, radiation therapy and other physical therapy, special diets, dietary supplements,

herbal medicines, etc.) or preventive measures (such as vaccinations, etc.), as well as the start and stop times.

Stop time, etc. On this basis, determine whether other treatment or preventive measures can be used.

adverse events occurred.

(IV) Personal characteristics and related information of the subjects

The personal characteristics and other relevant circumstances of the subjects should be understood in detail, such as:

1. Age, gender, height, weight, region/country, race/ethnicity;

2. Occupational characteristics, work environment, family and living environment, mental/psychological status

states;

3. Personal living habits (such as diet, exercise, work and rest, whether to absorb

smoking, drinking, and even drug exposure, etc.);

4. History of drug and food allergies;

5. Vaccination and previous adverse reactions;

6. Family history (such as whether there are infectious diseases, genetic diseases,

Sexual diseases and diseases/symptoms/signs/laboratory abnormalities similar to those of the patient

, etc.);

All of the above factors may affect the occurrence and frequency of adverse events in subjects.

The severity and duration of the test will be affected.

symptoms, living and working environment, etc., help to scientifically and accurately

Determination of the relevance of the 111 event to the trial drug.

112 (V) De-stimulation and Re-stimulation

113 1. To stimulate

114 Dechallenge refers to the discontinuation of drug administration during clinical administration.

115 During the clinical trial, adverse events naturally disappeared after the subjects stopped taking the drug.

116 or alleviated, is called the drug de-excitation positive; conversely, it is de-excitation

117 negative.

118 If the adverse event is relieved after drug discontinuation and targeted treatment,

The results of 119 rounds should be considered unknown, as no accurate judgment can be made in this case.

120 2. Re-stimulation

121 Rechallenge refers to the resumption of medication after previous discontinuation.

122 Subjects had adverse events that had disappeared or alleviated after re-administration.

If 123 appears or worsens, it is called a positive re-stimulation of the drug; otherwise, it is called a re-stimulation of the drug.

124 challenge negative. It should be noted that rechallenge should be carried out in drug clinical trials.

125 should be carried out with extreme caution and under the premise of ensuring the safety of the subjects and complying with ethics.

126 Do not subject subjects to the risk of (serious) disease after re-administration of the drug just to verify the correlation.

127Risk of adverse events.

128 3. Special instructions

129 It should be noted that in some cases, de-excitation and re-excitation are not applicable, such as

130 Single-dose therapy and for irreversible adverse events or after discontinuation of treatment

131 adverse events, etc.

132 The implementation of de-stimulation and re-stimulation should be determined according to the specific situation and strictly follow

133 Follow medical and ethical requirements; when judging the results, relevant interfering factors should be excluded.

134 draw scientific and reliable conclusions.

135 Both dechallenge and rechallenge positivity are helpful in determining the relationship between adverse events and the test results.

136 The relevance of the tested drugs, especially the positive re-challenge, indicates the occurrence of adverse events and

137 The possibility of correlation between the experimental drugs is very high.

138 (VI) Special adverse reactions

139 Special adverse reactions refer to those that are unrelated to conventional pharmacological effects and are not dose-dependent.

140 is rare in the general population, with a low incidence but high severity, and is usually difficult to

141 is predicted, but is known to be an abnormal reaction closely related to drug exposure.

142 Single cases also highly suggest the possibility that the drug caused the event.

143Vince Johnson syndrome, toxic epidermal necrolysis, etc.

144 III. Basic principles and key points of evaluation

145 In clinical drug safety studies, individual adverse events are related to the test drug.

146 Relevant judgment is the foundation and important basis for the overall evaluation of adverse drug reactions.

147 Every adverse event needs to be evaluated scientifically, objectively and accurately.

148 On this basis, necessary risk control measures should be taken according to the circumstances to protect the

149Testers are safe.

150 1. Basic principles

151 For the evaluation of the relevance of individual adverse events to the test drug, the

152 Follow the following basic principles:

153 1. Timing

154 Timing means that there should be a reasonable time between the test drug and the occurrence of adverse events.

155 relationship, and in accordance with the time law of drug metabolism.

156 The first condition is to judge the relationship between the administration of the test drug and the occurrence of adverse events.

157 The time interval should be consistent with its pharmacokinetics/pharmacodynamics and adverse events.

158 pathophysiological characteristics, otherwise the correlation cannot be determined.

159 Allergic shock usually occurs within a few minutes of medication. Phenothiazines cause liver damage.

160 usually appears 3-4 weeks after taking the medicine.

161 2. Reasonableness

162 Reasonableness means that the adverse events observed in clinical trials are consistent with the

163 The drug has a known pharmacological mechanism and may cause adverse events in medicine

164. Such as hypoglycemia caused by hypoglycemic drugs, gastrointestinal

165 bleeding. However, the judgment of rationality also depends on the current level of medical cognition.

166 When the mechanism of action is unclear or cannot be explained by existing medical knowledge, it may be

167 This is further confirmed by the fact that plausibility is intended to encourage the exploration and identification of mechanisms of action to support

168 sexual inference.

169 3. Dose-exposure-effect relationship

170Dose -exposure-effect relationship, which can reflect the dose and exposure of the test drug

171 and adverse events. That is, the higher the dose or exposure level, the greater the

The longer the interval, the greater the probability of adverse events or the more serious the degree of adverse events .

173 Strong evidence of an association between adverse events.

174 4. Experimental/trial evidence support

175 Experimental/trial evidence support refers to evidence based on laboratory, clinical, or epidemiological

176 Research that can replicate, eliminate or prevent drug-related adverse events under controlled conditions

177 occurrences support the correlation within the experimental/test setting and can be used as

178 Evidence of high correlation strength. For example, positive dechallenge test, positive rechallenge test

179 , etc.

180 5. Repeatability

181Repeatability means that the same thing can be observed to happen under the same factors.

182 Unexpected adverse reactions in the same subject after initial and subsequent exposure to the same test drug

183 Adverse events are consistent; adverse events occur in different subjects after exposure to the same test drug.

184 cases of similar types and occurrence.

185 6. Analogy

186 Analogy means that two similar factors can cause similar results. Chemical structure

187 Drugs that are similar or have similar mechanisms of action may have similar adverse reactions.

188 Most of the statins on the market have adverse reactions that cause liver damage.

189 Liver injury occurred in clinical trials of statins, which increased the relationship between liver injury and neoadjuvant therapy.

190 The possibility of association between statins. Safety information of clinical trial drugs

191 Pairs: Less, analogous evidence for judging the relevance of adverse events to the trial drug

192 is of reference value, but not strong evidence for relevance evaluation.

193 7. Consistency

194Consistency refers to the relationship between the adverse event and the test drug and the existing

195 theory, knowledge, etc., especially to obtain support from other test results.

196 The explanation of the existence of correlation should not conflict with general medical and biological facts.

197 Consistency ensures the credibility of the inference of relevance and keeps it consistent with the current state of knowledge.

198 are consistent.

8. Specificity

Specificity means that there are no other possible causes of adverse events observed in clinical trials.

If the cause and explanation are not available, then the possibility of the trial drug being related to the adverse event is compared

The adverse event description should include details on whether there are concurrent medications, underlying diseases, and

Other treatments, these factors will affect the judgment of the relationship between the trial drug and the adverse event

Therefore, alternative explanations should be considered.

When other possible explanations exist, the likelihood of a relationship to the trial drug is greater.

In summary, in specific clinical trial cases, adverse events and experimental drugs

In the relevance evaluation of , it is not necessary to meet all the above principles or conditions.

However, the more conditions that are met, the greater the likelihood that the correlation will hold.

Among them, timing is the primary and necessary condition.

2. Evaluation points

Generally speaking, in clinical trials, individual adverse events are related to the test drug.

In the evaluation, the following five core aspects should be focused on for comprehensive analysis:

and consider:

1. Whether there is a reasonable time relationship between the trial drug and the occurrence of adverse events;

2. Whether the adverse event is consistent with the known mechanism of action, characteristics or

known adverse reactions;

3. De-stimulation results (if applicable);

4. Rechallenge results (if applicable);

5. Whether adverse events can be evaluated by the subject's disease progression (including concomitant diseases)

disease), the effects of combined medication, other treatment measures or interfering factors, etc.

221 to explain.

222 IV. Evaluation classification method and judgment basis

223 Evaluation of the correlation between adverse events in clinical trials and drugs.

224 unified and recognized classification methods and standards. In practical work, various classification methods are often used.

There are 225 methods and standards, and the classification names used to describe the correlation results are also varied.

226 It is not conducive to the scientific, standardized and efficient clinical trial of all parties involved in the clinical trial.

227 Safety research, evaluation and risk management. Therefore, further unification and standardization of our

Classification methods and standards for adverse event relevance evaluation results of drug clinical trials in 228 countries

229 is of great significance.

230 In clinical trials of drugs, it is required to make a

231 Comprehensive and in-depth research, analysis and evaluation, which will ultimately serve as the basis for registration and listing

232 and guidance on safe use of drugs after marketing.

233 The relevance of adverse events to the trial drug was rigorously and carefully evaluated.

234 In the early stages of clinical trials, little is known about the adverse reactions of drugs.

235During clinical trials, it is often difficult to assess the relevance of individual adverse events.

236 To determine the situation. Therefore, according to the strength of the correlation evidence, the

237 Establish reasonable correlation classification methods and standards to facilitate research doctors to classify some difficult

238 clearly distinguished the cases, and further paid attention to, collected and improved the relevant

239 levels of evidence information, and then make a clearer and more reasonable relevance judgment.

240 At present, relevant academic research at home and abroad and domestic actual work situation, this guideline

241 Suggestions: In general, the relevance of adverse events in individual drug clinical trials should be determined

242 The results can be divided into five categories: definitely related, very likely related, possibly related,

243 is irrelevant and irrelevant.

244 In addition, the international community also adopts a binary approach, which can more conveniently

245 International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

246 Harmonisation of Technical Requirements for Pharmaceuticals

247 for Human Use (ICH) guidelines to relevant national/regional drug regulatory authorities

248 lines of rapid reporting of individual safety information during clinical trials.

249 Clinical trials related to drug registration, such as international multi-center clinical trials or their supplements

250 trials and clinical trials intended for overseas registration and marketing, or the sponsor's

251 Considering the global development plan of the product, it is also possible to follow a unified clinical trial approach.

Case 252 requires a dichotomy: relevant and irrelevant.

253 ### 1. Five-point method

254 Based on the five evaluation points (whether there is a reasonable time relationship, whether it is consistent with

255 Combined with the known mechanism of action, characteristics or known adverse reactions of the drug, to stimulate

256 results, and then stimulate the results to see if they can be explained by other reasonable reasons).

257 Evaluation of the correlation between individual adverse events in clinical trials and the test drugs, according to different situations

258 , the judgment results are divided into five categories: definitely related, very likely related, possibly related

Level 259 , probably irrelevant, irrelevant.

260 The classification of the judgment results and the basis for judgment can be found in Table 1.

261 ### 2. Dichotomy

262 According to the judgment criteria in Table 1, the following conditions are met: definitely related, very likely related,

263 can be related, according to the dichotomy, can be classified as "related";

264 levels can be classified as “irrelevant” according to the dichotomy.

265 The classification of judgment results and judgment basis can be found in Table 1.

266 (III) Others

267 If other classification methods and criteria are used, they should be included in the clinical trial protocol.

268 explains its scientific rationality.

269 Table 1 Classification and basis for the determination of the relevance of adverse events in drug clinical trials

Five-point method	Judgment basis	dichotomy
Definitely related	ÿ Have a reasonable time relationship ÿ Comply with known mechanisms of action, properties or known adverse reactions ÿ To stimulate positive ÿ Re-stimulation positive ÿ No other reasonable explanation	Related
Probably related	ÿ Have a reasonable time relationship ÿ Comply with known mechanisms of action, properties or known adverse reactions ÿ To stimulate positive ÿ Lack of positive evidence for rechallenge ÿ No other reasonable explanation	
May be related	ÿ Have a reasonable time relationship ÿ Lack of positive evidence for rechallenge ÿ Manifested as any of the following: ÿConsistent with known mechanisms of action, characteristics or known adverse reactions, ÿ The test result is positive, but it can also be explained by other reasonable reasons; ÿ It is consistent with the known mechanism of action, characteristics or known adverse reactions, Lack of positive evidence for de-challenge and no other reasonable explanation; ÿ Does not conform to the known mechanism of action, characteristics or known adverse reactions ÿDoes not conform to the known mechanism of action, characteristics or known adverse reactions. There is no other plausible explanation for the lack of positive evidence for de-challenge. release;	
Probably not relevant	ÿ Time relationship cannot be ruled out ÿ Lack of positive evidence for de-challenge ÿ Lack of positive evidence for rechallenge ÿ Manifested as any of the following: ÿAlthough consistent with known mechanisms of action, characteristics or known adverse reactions ÿ The drug does not conform to the known mechanism of action, characteristics or known adverse reactions. Should, and can be explained by other reasonable reasons;	Not relevant
No reasonable time relationship		

	ÿ Does not conform to known mechanism of action, properties or known adverse reactions ÿ Lack of positive evidence for de-challenge ÿ Lack of positive evidence for rechallenge ÿ Other reasonable reasons can be used to explain	

270 Special Notes:

271 1. The adverse events and drugs should be analyzed by relevant personnel with medical expertise.

272 Relevance evaluation.

273 2. Table 1 may not cover all situations in actual work.

274 If the judgment basis in 1 cannot be completely matched, you can refer to the table for

275 Professional judgment logic on the correlation between adverse events and drugs, making the most reasonable

276 The result of the reasonable judgment.

277 3. More information about adverse events and drugs is collected during the progress of clinical trials.

278 When determining the relevance of information and evidence, you can modify the previous

279 However, sufficient reasons should be provided for the relevance judgment made.

280 4. Lack of positive evidence for de-challenge includes the following situations:

281 Negative; de-challenge has not been performed; de-challenge is not applicable;

282 Lack of positive evidence for rechallenge includes the following situations:

283 Negative; no rechallenge has been performed; rechallenge is not applicable.

284 5. In order to facilitate the work, the main contents of Table 1 can be simplified into Table 2.

285 Table 2 Special instructions for use are the same as Table 1.

286

287

288

289

290 Table 2. Brief table for determining the relevance of adverse events in drug clinical trials

Judgment result / Judgment basis	Related						Not relevant			
	affim related	Very likely related	possible related				possible Unrelated		none close	
Is there a reasonable time? Does	+	+	+				±		-	
the relationship match known Use mechanism, characteristics or Known adverse reactions	+	+	+		-		+ -		-	
To stimulate the results	+	+	+ -/?	+ -/?			-/?		-/?	
Re-stimulation results	+	-/?	-/?				-/?		-/?	
Are other reasonable Explanation of the reasons	-	-	+ -		-	- ++	+ +			

291 Note: + indicates affirmative, or positive result;

292 - Indicates a negative result, or a situation where the result has not yet been obtained;

293 ± indicates that a temporal relationship cannot be excluded;

294 ++ means that it can be explained by other "more" reasonable reasons;

295 -/? indicates that the dechallenge/rechallenge result is negative or has not been performed yet

296 De-energize/re-energize, or do not apply de-energize/re-energize.

297 V. Requirements for individual reports of suspected and unexpected serious adverse reactions

298 Suspected and unexpected serious adverse reactions during drug clinical trials

299 ÿSuspected unexpected serious adverse reaction, SUSARÿÿÿ

300 In the reporting process, the five-point judgment basis in this guideline is used to make judgments.

301 SUSAR with a determination of “definitely relevant”, “probably relevant” or “possibly relevant”

All 302 cases require rapid reporting;

SUSAR cases that are determined to be “relevant” based on the 303 determination need to be quickly reviewed.

304 Speed Report.

305 If other classification methods and criteria are used, attention should be paid to their scientific rationality.

306 , and follow the ICH E2A guidelines for SUSAR cases that meet the requirements

307 Quick Report.

308VI . References

309 1. National Drug Administration, National Health Commission.

310 Announcement on Good Clinical Practice (No. 57, 2020).

April 311

312 2. CIOMS Working Group VI on the Management of Safety

313 Information from Clinical Trials ÿCouncil for International

314 Organizations of Medical Sciences. Management of Safety

315 Information from Clinical Trials: Report of CIOMS Working

316 Group VI .New York :Renouf Pub Co Ltd,2005 .

317 https://cioms.ch/publications/product/management-of-safety-

318 information-from-clinical-trials-report-of-cioms-working-

319 group-vi/.

320 3. WHO-UMC.The use of the WHO-UMC system for

321 standardised case causality assessment[EB/OL].Uppsalaÿ

322 WHO-UMCÿ2018-04-06[2023-02-01]. https://who-

323 umc.org/media/164200/who-umc-causality-assessment_new-

324 logo.pdf

325 4. Danan G , Teschke R . RUCAM in drug and herb induced
326 liver injury: The update[J].International Journal of Molecular
327 Sciences, 2015, 17(1):14.
328 5. ICH Guideline.E2A:Clinical Safety Data Management:
329 Definitions and Standards for Expedited
330 Reporting.[EB/OL].ICH,2018-04-06.[2023-02-01].
331 https:// database. ich. org/ sites/
332 default/files/E2A_Guideline.pdf.
333 6. Austin Bradford Hill.The environment and disease:
334 association or causation?[J].J R Soc Med. 2015 Jan; 108(1):
335 32– 37.DOI:10.1177/0141076814562718.
336 7. Wang Dayou. Evaluation of adverse drug reaction report evaluation: causal evaluation in drug
337 The role and status of drug vigilance. Journal of Adverse Drug Reactions. 1999(01): 41-
338 44.
339 8. Zhu Yonggong. On the adverse reactions and causal relationship analysis and evaluation of new drugs.
340 Chinese Journal of Medical Guide. 1999(01): 51-52.
341 9. Wei Shuiyi, Wang Shimin, Shu Lixin. Evaluation methods for drug safety (III) - Drug
Causal evaluation of adverse drug events. Journal of Adverse Drug Reactions. 2001(04): 244-
343 248.
344 10. Saad AW Shakir , Deborah Layton.Causal association in
345 pharmacovigilance and pharmacoepidemiology: thoughts on
346 the application of the Austin Bradford-Hill criteria[J].Drug

347 Saf. 2002;25(6):467-71. doi: 10.2165/ 00002018-

348 200225060- 00012.

349 11. Sun Dingren, Qi Ping, Jin Yinghua. Adverse drug reactions (3rd edition). People's Daily Online

350 Health Publishing House, 2007. 4-38.

351 12. Zhou Wen. Drug epidemiology. People's Medical Publishing House, 2007. 110-112.

352 13. Zeng Fandian, Zheng Rongyuan, Zhan Siyan, Du Xiaoxi. Pharmacoepidemiology (2nd edition).

353 China Medical Science and Technology Press, 2016. 341-343.

354 14. Lv Xiongwen. Pharmacoepidemiology. China Medical Science and Technology Press, 2021.

355 15. Manel De Silva Wijayasinghe, Inna Pendrak, Nicholas Rees.

356 Rapid Reporting Standard II: Severity and Causality Evaluation. China Drug Police

357 Jie.2009(05): 317-320.

358 16. Wei Jing, Wang Yuxin. Overview of causal relationship evaluation methods for adverse drug reaction reports.

359Chinese Journal of Pharmacovigilance. 2011.8(10): 600-603.

360 17. Wei Xu, Xie Yanming. Interpretation of the principles and evaluation methods for causal judgment of adverse reactions at home and abroad

361 Read. Chinese Journal of Traditional Chinese Medicine. 2012.37(18): 2744-2747.

362 18. Zhong Ying. Comparison of causal relationship evaluation methods for adverse drug reactions. Guangzhou Journal of Traditional Chinese Medicine

363 ÿ.2015. DOI: CNKI:CDMD:2.1015.363404.

364 19. Wang Chunhua, Hu Xiao, Yang Cuicui, et al. Causality of adverse events in phase I clinical trials

365 relationship evaluation. Journal of Adverse Drug Reactions. 2019(01): 30-35.

366 20. Huang Qian, Wen Zehuai. Propose to establish a coordinated and unified causal relationship of adverse drug reactions

367 evaluation criteria. Chinese Journal of New Drugs. 2021(12): 1132-1136.

368 21. State Food and Drug Administration. General principles for clinical research of new Chinese medicines

369 (November 2015)

370 22. Drug Evaluation Center of State Drug Administration. Clinical Trial of Traditional Chinese Medicine-Induced Liver Injury

371 Bed Evaluation Guidelines. (June 2018).

372 23. State Drug Administration. Notice on the release of individual adverse drug reaction collection and

Notice on the guidelines for 373 reporting (National Medical Products Administration No. 131, 2018).

374 (December 2018).

375 24. Drug Evaluation Center of the State Drug Administration. Application for marketing approval of innovative anti-tumor drugs

376 Technical guidelines for the preparation of safety summary materials. (December 2020).

377 25. Center for Drug Evaluation of the State Drug Administration. Immunological aspects of anti-tumor therapy

378 Technical guidelines for adverse event evaluation. (May 2022).

379 26. Center for Drug Evaluation, State Drug Administration. Drugs in clinical trials

380 Guidelines for the identification, management and evaluation of liver injury. (July 2023)