How to improve participant compliance and retention in clinical trials？A Scoping Review

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Abstract

Background: The reliability of results can be compromised when subsets of participants who remain on a study differ from those who drop out. Although recent studies have investigated strategies for improving compliance and retention , there has been very little investigation of process factors, regardless of the type of literature and the publication date. factors that may influence how and why compliance and retention may be successful (or not).

Aim: To identify process factors that may influence participant compliance and retention in clinical trials, and potential strategies to improve the compliance and retention, from published studies, grey literature, and the reference lists of included articles to facilitate future design and implementation of trials.

Methods : Six databases and two clinical trial registries were searched on November 29, 2019. Surveys, interviews, retrospective data analyses, theoretical research, reviews and clinical studies aiming at investigating factors and potential strategies were included. Data synthesis followed an iterative process to develop a list of process factors and potential retention strategies.Results were presented mainly as texts, including visualization using word cloud, and descriptive data.

Results: 182 publications were included in this review, composed of 58 retrospective reflection of RCTs based on 1,132 clinical trials with 177804 participants, 27 implementation researches, 22 theoretical researches, 20 interviews, 18 surveys, 17 randomized controlled trials, 8 literature reviews, 5 systematic review and meta analysis, 3 mixed methods researches, 2 case report, 1 meta-ethnographic synthesis and 1 cohort study. We identified 70 process factors that may affect the compliance and retention . The most commonly addressed factors were age, education, economy, trust in clinical trials, supporting from surrounding people, safety concerns and effectiveness. We found 42 potential strategies to improve compliance and retention. Strategies reported most frequently were that researchers should pay attention to the changes on participants' psychological condition, try their best to build good relationships, provide some compensation and educate the participants about compliance and retention .

Conclusion: These factors that may affect the compliance and retention can help researchers predict participants who are less likely to adhere and develop screening tools to find efficiently their suitable participants. These potential strategies that may improve the compliance and retention.

Background

The compliance and retention of participants with clinical trial protocols is defined as the degree of participation according to the prescribed drug dose, medication, timeliness of response, retention, and careful treatment according to the doctor's request[1]. The reliability of results can be compromised when subsets of participants who enroll or remain on a study are differ from those who choose not to take part or subsequently drop out[2]. Difficulties in achieving the compliance and retention of participants in randomized controlled trials (RCTs) are well documented [3], and many clinical trials are stopped or extended due to issues about compliance and retention[4]. Directors of UK clinical trials units have identified “research into methods to boost recruitment in trials” and “methods to minimise attrition” as the top two priorities for trials methodology research[3,5].

Clinical trial researchers often focus more on the trial design, paying less attention to participant compliance and retention [6]. Although there is extensive information in the scientific literature on compliance and retention of participants in clinical trials, few researchers have summarized this systematically in China[6]. There are numerous factors that may affect compliance and retention and also a range of potential strategies for improving compliance and retention in clinical trials. Previous studies have suggested that a greater understanding of the factors that influence trial participation could help to provide solutions for improving compliance and retention [7]. Furthermore, findings from studies that successfully predict which participants are likely to comply with trial protocols could also be used to develop screening tools to enable researchers when planning trial recruitment to more efficiently identify participants who would be less likely to drop out [8].

The purpose of this comprehensive scoping reviewing is to investigate the process factors that influence participant compliance and retention in clinical trials, and potential strategies to improve compliance and retention, from published studies, to facilitate future improvements in the design and implementation of clinical trials.

Methods

Protocol

Although PROSPERO rejected the registration of the protocol, all research processes were carried out according to a pre-made protocol.

Search strategy

Literature searches were carried out in six databases (including Chinese databases) and two clinical trial registries before 2019-11-29: PubMed, Cochrane Library, Embase, CNKI, VIP and Wanfang Databases; clinical trials.gov and Chinese clinical trial registries. Search terms and strategies are provided in Appendix A. We also searched manually the grey literature that were not peer reviewed and investigated the reference lists of included articles and existing systematic reviews. No language or publication type restrictions were applied. The meeting abstracts were not included.

Eligibility criteria and selection process

Eligible articles were those which aimed to explore process factors that influence compliance and retention and/or reported potential strategies for improving compliance and retention, including theoretical research, descriptive epidemiological studies (cross-sectional surveys), systematic reviews and all types of

clinical studies, such as randomized controlled trials (RCTs), non-randomized clinical controlled trials (CCTs), cohort studies, case-control studies, case series and case reports.

Noteexpress was used for the management of articles. Firstly, titles and abstracts were retrieved and screened independently by two reviewers (MK and CH). Articles were included for full text screening as long as there was at least one reviewer who included them at this stage. Then duplicates were removed. Full-text articles of those that past title/abstract screening were retrieved and further screened by paired independent reviewers (MK and CH), too. Any disagreements were resolved through discussion or arbitrated by the senior author (Fei YT), if necessary. The reasons for exclusion were recorded and presented(As shown in Fig 1).

Data extraction and synthesis

Data were extracted from each study independently by three pairs of trained reviewers (two reviewers in each group) using a pre-designed pilot-tested topic collection form and performed two-person checks. The extracted data included: article and author information(publication date, funding, language, country); the information of study(disease, the purpose of article, study design, sample, number of study sites, topic source (for Secondary studies only)); process factors that may influence compliance; and potential strategies for improving compliance. Any disagreements were resolved through discussion or arbitrated by the senior author (Fei YT), if necessary. When new factors and strategies were identified, group discussion were conducted. When more than 2/3 of all members of the extraction team (MK Yu, ZY Lin, CH Liang, ZJ Zhang, KX Liu and CZ Li) agreed, the new factor or approach was added in the list. The process of topic extraction was used to iteratively develop a list of the process factors and potential strategies that may influence compliance and retention. The extracted topics were categorized and induced to investigate which are the key process factors and strategies. No test of statistical significance was performed.

Word cloud technique (https://www.weiciyun.com/) was used to identify the major concepts that were presented in the included papers that were relevant to compliance and retention. The font size of the concept (words or phrases) in the word cloud picture is positively correlated to the frequency of concept.

Definition of key information

We defined compliance and retention in RCTs as the ability to avoid loss of follow-up visits, including loss of contact with the research team (including subsequent loss of follow-up during the study and failure of the research team to re-establish contact), non-compliance with medication and attendance appointments.

Descriptive analysis was defined as: researchers use the statistics represented by various topic to conduct single-factor analysis (such as mean, percentage, etc.) to find the central tendency and dispersion trend of these topic.

Implementation research can be defined as scientific research that verifies that interventions can be applied to clinics and communities. The purpose is to improve the prognosis of patients and benefit the health of the population.In our study, it not only include retrospective research, theoretical research, interviews, surveys, randomized controlled trials, literature reviews, systematic review and meta analysis, mixed methods research, case report and cohort study.

Retrospective reflection of RCTs can be defined as the researchers reviewed the randomized controlled studies conducted in the past to obtain the process factors and improvement strategies that affect the subject compliance and retention.

Results

We identified a total of 46179 publications through the searches, and a total of 182 publications[6,9-189] met the inclusion criteria (Figure 1).

Study characteristics

The 182 publications included 58 retrospective reflection of RCTs(177804 participants) , 27 implementation researches, 22 theoretical researches, 20 interviews, 18 surveys, 17 randomized controlled trials, 8 literature reviews, 5 systematic review and meta analysis, 3 mixed methods researches, 2 case report, 1 meta-ethnographic synthesis and 1 cohort study (Appendix table 1).The compliance and retention of participants in trials for human immunodeficiency virus(HIV), cancer, diabetes, asthma, hypertension, parkinson, alcohol addiction, cocaine dependence, etc were identified and included. Researchers, pregnant women, minor, adolescents, seniors, and healthcare providers were investigated. 124 publications published in English, 56 published in Chinese, and 1 published in German.

Included studies were published between 1982 and 2019, with the number of publications increasing across time (Fig. 2). Studies were published across 21 countries, with the majority of first authors being located in the United States(n=77 studies), China (n=58 studies) or England (n=17 studies) .

Process factors that may influence compliance and retention

70 key factors affecting compliance and retention, which grouped into individual, environment, disease, protocol and investigator aspects (Table 1), were finally identified. The factors with highest frequencies were: age(55.4%), education(43.9%), economic(41.8%), investigators' skills on communication(41.2%), the adequacy of informed consent(39.5%), gender(39.0%), support from personal social relationship(39.0%), trust for the trials(36.2%), attitude(investigator's attitude towards research and patients)(34.0%) and safety concerns(32.9%).

Potential strategies to improve compliance and retention

42 key themes of potential strategies were eventually included. According the scenarios for actual clinical research, the included potential strategies were divided into three phases: protocol design, recruitment and informed consent, trial implementation period (Table 2).The potential strategies with highest frequencies were:(1)Researchers should pay attention to the changes on participants' psychological and building good relationships with participant(41.2%); (2)Money, gifts and other compensation can be provided(36.8%); (3)Researchers should carry out the education about compliance and retention during the study (including the knowledge of diseases, psychological and medication, trained in the broader context of medical ethics, cultural training)(35.7%); (4)Researchers should give full informed consent to the participant(safety concerns, effect, study protocol, the time they may take,etc)(29.6%);(5) Online reminder (phone, email, etc) should be provided(29.6%).

The analysis of process factors and improvement strategies based on diseases and population

According to the prognosis and course of the diseases, we divided the diseases into chronic non-fatal, chronic fetal, acute non-fetal, acute fetal ,and unclear. The population was divided into adults, women, juveniles, seniors, pregnant women, special population, minority, homosexuality, healthcare providers, or Ebola front-line workers and “not reported”. The division of the population is based on the original article. The process factors and improvement strategies were analyzed based on diseases and population(Shown in Figure 4-7). Data of different groups were not overlapped. We could find that process factors and improvement strategies varied in different populations. At the same time, Appendix figures 1-10 showed the process factors and improvement strategies under the combination of different diseases and populations.

In adults, the top five process factors were age(47), informed consent(40), education(35), gender(34), economic(33); the top five improvement strategies were expanding the channels of recruitment(28), carrying out education(20), recording 3-4 contact information of participants or their family(20), online data collection(20), paying attention to participants' psychological condition(19).

In women, the top five process factors were support from surrounding people(10), researchers’ attitude(10), age(9), economic(8), education(7), work commitment(7), time(7), safety concerns(7); the top five improvement strategies were paying attention to participants' psychological(11), full implementation of informed consent(7), carrying out education(7), flexible study time and location(7), money, gifts and other compensation(6).

In juveniles, the top five process factors were support from surrounding people(10), age(9), economic(6), race(6), culture(6), traffic(6), compensation(6), researchers’ skills on communication(6), researchers’ attitude(6); the top five improvement strategies were money, gifts and other compensation(10), providing online reminder(8), paying attention to participants' psychological condition(6), establishing the table of follow-up(6), flexible study time and location(6).

In seniors, the top five process factors were age(5), gender(5), special psychological characteristics(4), Informed consent(3), support from surrounding people(3); the top four improvement strategies were expanding the channels of recruitment(3), fixed researchers and healers(2), handle adverse reactions timely(2), flexible study time and location(2).

In pregnant women, the top two process factors were frequency of inspection(2), compensation(2); the top five improvement strategies were money, gifts and other compensation(3), flexible study time and location(3), recruiting full-time researchers(2), expanding the channels of recruitment(2), providing online reminder(2), carrying out education(2), recording 3-4 contact information of participants or their family(2), fixed researchers and healers(2).

In the special population with mental and physical disorders, the top five process factors were economic(3), gender(2), education(2), age(2), special psychological characteristics(2), race(2), language(2), mobility(2), traffic(2), support from private doctors(2); the top five improvement strategies were training researchers(1), improving the screening table based on factors(1), reducing the frequency of harmful inspection(1), full implementation of informed consent(1), expanding the channels of recruitment(1), paying attention to participants' psychological condition(1), money, gifts and other compensation(1), providing online reminder(1), recording 3-4 contact information of participants or their family(1), flexible study time and location(1).

In minority, the top five process factors were economic(1), gender(1), trust for the trial(1), special psychological characteristics(1), culture(1), language(1), researchers’ skills on communication(1), researchers’ attitude(1), researchers’ experience(1), the mastery of the study protocol(1), the education for participants(1); the top five improvement strategies were training researchers(1), pre-compliance and retention assessment(1), providing online reminder(1), researchers should adhere to the basic ethical principles(1).

In homosexuality population, the top five process factors were: education(1), economic(1), gender(1), work commitment(1), lost contact(1), race(1), culture(1), language(1), researchers’ skills on communication(1), researcher’ attitude(1), the relationship between researchers and participants(1); the top five improvement strategies were: paying attention to participants' psychological condition(1), money, gifts and other compensation(1), recording 3-4 contact information of participants or their family(1), establishing the table of follow-up(1), flexible study time and location(1).

In healthcare providers, or Ebola front-line workers, the top five process factors were age(1), economic(1), gender(1), work commitment(1), interest in the trial(1), lost contact(1), self-efficacy(1), religious(1), researchers’ experience(1), the mastery of the study protocol(1)the top five improvement strategies were develop simple and convenient design(1), training researchers(1), recruiting full-time researchers(1), paying attention to participants' psychological condition(1), money, gifts and other compensation(1), recording 3-4 contact information of participants or their family(1), flexible study time and location(1).

In some studies that did not report specific populations, the top four process factors were: the relationship between researchers and participants(35), researchers’ skills on communication(33), frequency of inspection(31), age(28), trust for the trial(28); the top five improvement strategies were: paying attention to participants' psychological condition(34), full implementation of informed consent(30), money, gifts and other compensation(28), carrying out education(25), pre-compliance and retention assessment(23).

In acute fatal diseases, the top four process factors were: age(4), education(3), gender(3), patient's condition(3); the top four improvement strategies were developing simple and convenient design(2), expanding the channels of recruitment(2), paying attention to participants' psychological condition(2), online data collection(2).

In acute non-fatal diseases, the top three process factors were gender(5), trust for the trial(4), age(4);the top five improvement strategies were money, gifts and other compensation(3), paying attention to participants' psychological condition(3), handle adverse reactions timely(3), the drug package should be accompanied by detailed information(3), online data collection(3).

In chronic fatal diseases, the top five process factors were age(31), education(21), gender(20), informed consent(18), researchers' skills on communication(18); the top five improvement strategies were paying attention to participants' psychological condition(18), expanding the channels of recruitment(17), carrying out education(15), providing online reminder(14), recording 3-4 contact information of participants or their family(13).

In chronic non-fatal diseases, the top five process factors were age(37), economic(30), education(27), gender(27), researchers' skills on communication(25), support from surrounding people(25); the top five improvement strategies were money, gifts and other compensation(26), paying attention to participants' psychological(23), providing online reminder(22), carrying out education(21), expanding the channels of recruitment(19).

In some studies with unclear diseases, the top five process factors were researchers' skills on communication(30), education(27), age(26), trust for the trial(26), support from surrounding people(26); the top five improvement strategies were paying attention to participants' psychological condition(29), carrying out education(26), money, gifts and other compensation(24), full implementation of informed consent(22), establishing the table of follow-up(20).

Discussion

Summary of results

182 publications were included in this review. We reviewed 58 retrospective researches from RCT based on 1,132 clinical trials with 177804 participants, and identified 70 factors, which were grouped into individual, disease, environment, protocol and investigators aspects, influencing participant compliance and retention; and 42 potential strategies, which could be adopted in three phases (protocol design, recruitment and informed consent, the trial implementation period) to improve compliance and retention. There were unique factors and strategies among different population and disease conditions. Most prevalent factors were participant age, gender, education, economic condition, researchers' communication skill, support from surrounding people and trust to the trial. Most proposed strategies were paying attention to participants' phycological condition, giving gifts or compensation, recording 3-4 contacts, expanding recruitment channels, carrying out participant education, flexible time and location and providing online reminder.

Strengths And Limitations

In past systematic map of digital tools for recruitment and retention we found that process factors were hardly studied[191], even though these may be important for understanding how and why strategies for improving retention work (or do not work). As far as we know, this is the first attempt to summarize the factors and the potential strategies of compliance and retention, regardless of the type of literature and the publication date. The results were from 177804 people (including pregnant women, minor, the elderly, college students, addicts, etc), 62 diseases (including cancer, HIV, cancer, diabetes, respiratory diseases, cardiovascular diseases, hypertension, parkinson, alcohol addiction, cocaine dependence, etc) and 22 countries (high income: the United States, Korea, Canada, Spain, etc; middle income: China, India, etc; lower income: Gambia)(Appendix table 1). The findings are more universal. The impact of different process factors and improvement strategies may be different in different diseases or populations. However, most previous studies have ignored them. Compared with previous literature[63,65], we analyzed the process factors and improvement strategies according to the characteristics of different diseases and populations to show their respective special factors and strategies. Scoping review methods and word cloud were used in our study. We used systematic and extensive approach to identify and analyze literature.However,the diverse factors and potential strategies reported in the included studies make it difficult to draw an overall and exact conclusion. The included studies were mainly reflections of conducting RCTs. At present, there was still a lack of risk bias evaluation tools for these types of research. So various types of study design limit our assessment of the risk of bias for included articles.[191]

Relationship with previous relevant works

The types of previous relevant works included systematic review(5) and traditional literature review(8). Most studies are only conducted on specific diseases(HIV, stroke, schizophrenia, smoke, Cataract, Amyotrophic lateral sclerosis, Arthritis, Alzheimer). The purpose of systematic review and meta analysis was to test the effect of potential strategies from some trials to improve the compliance and retention. The design of compliance and retention studies includes observational studies, cohort studies, and randomized controlled trials, etc. Variations in research design and lack of overlapping outcome variables often lead to failure to complete systematic reviews.[192]But the influencing factors of compliance and retention and theoretical perspectives were not provided in depth. The traditional literature review described the factors and potential strategies from other researches. But it is possible to miss some articles because the lack of systematic search. Compared with previous studies, the factors and potential strategies provided in our study are more comprehensive. We provide factors and methods for different diseases, populations and interventions. Their conclusions were summarized and analyzed in our study by scoping review. By scoping review, we systematically searched, selected, and integrated existing information to draw a picture of the status and association of compliance and retention studies. In addition, their conclusions were classified and displayed from these studies according to the different stages and characteristics of clinical trials.

Implications for practice and research

The factors identified in our study can help researchers predict participants who are less likely to adhere, and develop screening tools to find efficiently their suitable participants. The better researchers understand these factors, the better it will be to improve participant compliance and retention. The potential strategies for improving compliance and retention we found were generally targeting at the factors we identified. However, the factors were not sufficiently covered by the potential strategies we found. There is a need to develop more comprehensive potential strategies to address the factors we already know.

In addition, the disagreement between studies demonstrated that these factors may play different roles in different studies, sometimes positive, sometimes negative, and sometimes no effect. For example, age was a commonly reported factor influencing compliance and retention in the clinical trials, but it was reported that young people may increase or decrease participant compliance and retention. Therefore, most of the identified factors have been presented in a neutral form in our study. Researchers should well-thought-out according to their specific trial context.

The potential strategies mostly mentioned were that researchers should pay attention to the changes on participants' psychological condition, and try their best to build good relationships. Providing compensation (such as gifts, money, postcard) and educating the participants about compliance and retention during the study (including the knowledge of diseases, psychology and medication), full implementation of informed consent and reminding participants online (phone, email, etc) were also mentioned by many. Potential strategies still need to be comprehensively developed. Furthermore, adopting potential strategies are often resource demanding. Researchers need to realize this and try to prepare it when planning the trial. Cost-benefit analysis may be required.

In different population, women, juveniles, seniors, and people with physical or mental disorders may need more support from external conditions.In addition to objective conditions such as age and economics, they also need the support of people around them and researchers.Their psychology may be more sensitive and need to be paid more attention. They may also need more flexible research time and location in order to better complete the research. Culture, language and the efforts of researchers play an important role in influencing the compliance and retention of minorities. In different diseases, the severity of the diseases had an important effect in the compliance and retention of patient in acute fatal diseases. Patients who are overly ill may not tolerate the treatment so that they may withdraw or become less adherent. The trust for the trials was very important for acute non-fatal diseases. In chronic non-fatal and fetal diseases,the prolonged course of the diseases may cause them to need more support from people around them and researchers. In chronic fatal diseases, full informed consent is essential.

Qualitative methods could be used to make an in-depth exploration to the factors and potential strategies in the future research. More researches are also needed to find effective potential strategies to encourage the participants to return the sites for follow-up. Implementation research (including, but not limited to, randomized controlled trials) can be used to verify the effectiveness of these included potential strategies by evaluating specific outcomes, such as compliance and retention rate, compliance and retention improvement rate, retention rate, etc.

Conclusions

We identified 70 factors, which were grouped into individual, disease, environment, protocol and investigators aspects, influencing participant compliance and retention; and 42 potential strategies, which could be adopted in three phases (protocol design, recruitment and informed consent, the trial implementation period) to improve compliance and retention. The process factors and improvement strategies of different diseases and populations are specific. Women, adolescents, seniors, and patients with mental or physical disorders may need more support from relatives, friends and researchers than adults. The long process of treatment also requires them to give more support to patients with chronic diseases. These factors can help researchers predict participants who are less likely to adhere and develop screening tools to find efficiently their suitable participants. Before using these potential strategies, researchers should well-thought-out according to budget, the range of diseases, population, the design of their research and their usual follow-up procedures.

Abbreviations

UK:United Kingdom; CNKI:China national knowledge infrastructure; VIP:VIP for China Science and Technology Journal Database; RCT: Randomized controlled trial; HIV: Human immunodeficiency virus.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: All data and materials can be obtained from the corresponding author.

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Author contributions: YT F and MK Y conceived and designed the review. MK Y and YT Fei drafted the protocol. MK Y, ZY L CH L, CZ L, ZJ Z, KX L were responsible for the searching, screening and selecting studies. They all participated in data extraction and assessed study quality. MK Y and CZ L made forms and pictures and performed the statistical analysis. JP L, YT F and X L were all involved in critically revising the manuscript. All authors have read and approved the final manuscript to submit. All authors approved the final version of the article, including the authorship list.

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Tables

Table.1 The factors that affecting compliance and retention of clinical trials

Influencing factors	Explanation*	Frequency	Influencing factors	
		Individual		
Age	Older people may have poorer compliance and retention due to the bad mobility and memory. But they may also be more likely to accept researchers' advice than young people. Young people may also have poorer compliance and retention because they may prefer work or entertainment than participate in clinical trials[11-13,16,21,22,23,25,26,28-33,37,43,45,47,49,50,53,57-59,61-65,68,70,72,73,75,76,78,80-82,87,88,92,93,98,101,105,106,107,109,112,113,115-117,119,120,123-125,129-132,135,136,139,140,143-147,149-154,156-158,161-163,168-170,172,-174,176-178,182-189].	101/182	Education	P 3 1
Economic	People with high-income will have higher compliance and retention[9-11,15-18,28,29,31,36,37,40,45,48,49,58,59,61-63,65,71,72,80,81,85,87-93,97,98,100-103,105,112-114,117-120,123,125,129,130,131,133,139-144,146,147,149,150,152-156,161,162,168,172,178,182,186]	76/182	Gender	W 3 1
Trust for the trial	The more trust, the higher compliance and retention[9,11,12,14,16-19,27,29,31,32,36,38,41,45,47,48,53,55,58,61,63,64,69,71,73,79,81-83,87,92,93,96,97,100,102,103,105,107-109,112,114,116,119,120,124,127,137-139,140,142,146,147,149,152,153,157,161,165,166,172,178,181]	66/182	Work commitment	D 3 1
Special psychological characteristics	Special psychological characteristics(anxious, impatience, depression, etc) will reduce the compliance and retention[9,11-13,15-17,24,30,36-38,41,47,53,64,65,73,75,81,82,90,97,98,100,102,107,110-112,116,118,120,126,132,135,138,140,144,146,151,158,173,175,177-179,181-183,188,189].	52/182	Lost contact	L r 1
Race	Patients with different races have different compliance and retention. For example, minorities have lower or higher compliance and retention[10,11,13,18,19,25,28,30,31,37,57,71,72,76,81,82,88-90,92,102,109,116,118,120,123,130,136,137,142-144,150,151,153-156,162,168,169,171,185,186]	43/182	Habitat	C 7 1
Time	The more time the patient have, the higher the compliance and retention[10,16,18,19,28,29,30,31,36,43,45,48,56,57,66,69,71-74,82,88,97,100,103,104,108,110,130,131,135,137,142,144,160,169,170,178,188,189]	39/182	Culture	T r
Understanding for the trial	Patients who understand more about the trial may have higher compliance and retention. However, as their understanding deepens, they may also withdraw because the research does not meet their expectations. [11,17,22,31,35,38,41,45,47,48,52,57,61,64,66,71,73,82,87,97,107,119,121,127,138-141,147,153,158,159,165,181]	32/182	Expectations for the trial	I d 3
Character	The better the character, the higher the compliance and retention[32,36,61,63-65,70,72,77,79,93,97,109,113,114,124,125,132,140,147,149,152,153,156,170,172,173,189]	27/182	Interest in the trial	T r
Marriage	Married people may have higher compliance and retention[11,23,25,29,30,31,49,76,88,98,107,109,116,130,132,136,151,153,158,161,169,182,183]	23/182	Life experience	T a
Language	The degree of matching between researcher's language and patient's language influences compliance and retention[9,11,12,49,56,71,73,81,83,100,101,116,130,136,142,162,171].	17/182	Self-efficacy	T r
Dedication	People with dedication will be more compliant[18,48,74,79,80,83,104,121,132,136,138,141,173,177,186].	15/182	Previous clinical trial experience	P [
Religious	The degree of matching between research and religious influences compliance and retention. [26,34,54,63,65,125,131,146,147,152,189]	11/182	Insurance	P r
Memory	People who have good memory may have higher compliance and retention[32,62,66,78,92,107,115,119,144,189]	10/182	The level of pressure	T
Physique	The better the physique, the higher the compliance and retention[16,36,37,48,82,107,131,177,189]	9/182	Desire for pregnancy	I p t
Legal	Patients with legal concepts may have higher compliance and retention[12,66,80,90,117,141,171]	7/182	Mobility	P
Social position	People who have high social position may have higher compliance and retention[12,49,120,123,157,158].	6/182	Use of illicit drugs	P r
Lost or stolen drugs	Lost or stolen drugs may reduce the compliance and retention[44,119,185,186]	4/182	Morbidly obese	P
		Disease		
Patient's condition*	Patient with severe illness have higher compliance and retention than those with less severe illness. But they may also withdraw due to the worsening of their condition[17,24,31,33,36,47,48,56,57,59,64,70,72,78,81,93,97,102,105,109,119,123,134,135,136,140,146,150,151,156,157,161,170,172,173,178,179,182,185]	39/182	Types of diseases	D c d
Attitude towards disease	People who have positive attitude to disease may have higher compliance and retention[16,35,36,45,74,97,109,118,119,132,142,145,146,173,178,189].	17/182	Wanting more information about their illness	P r
		Environment		
Support from surrounding people	The more support from surrounding people (family, friends, patient groups), the higher the compliance and retention. [19,20,23,25,28,29,31,32,36,37,39,48,50,54,60,61,63-65,73,74,76,78,80-,82,85,87-90,93,97,100,102,105,107,108,112-114,116,117,123,124,127,131,136,140-145,147,149,150,153,157,159,160,161,165,166,170,171,174,178,183,186,189]	71/182	Traffic	T r 9
Distance	Patients who live closer to the study site have higher compliance and retention[12,16,18,29,33,36,37,44,47,48,50,58,61,64,67,69,78,81,85,87,88,92,93,97,103,105,107,108,109,112-114,117,119,127,133,137,146,147,153,157,160,161,164,165,177,186]	46/182	The environment of treatment	T a 1
Support from private doctors	The more support from private doctors, the higher the compliance and retention[36,52,54,63,64,78,79,92,93,96,97,100,113,114,125,134,146,147,149,157,159,165,172]	23/182	Media	P r
		Protocol		
Safety concerns	The higher the security, the higher the compliance and retention[11-13,14,17,22,30,31,35,40,41,48,50,53,55,60,61-63,66,67,73,74,78,80,81,83,87,94,96,102,105,107,112,119,120,124,126,135,138,139,141,147,152,153,160,165-167,170,171,174,175,178-180,185,187,189]	60/182	Effect	T 6 1

Compensation	Patient compliance and retention is higher in studies that have compensation[6,10,14,15,19,21,28,29,33,37,38,43,45,46,52,54,66,67,69,74,80,82,84,88,89,92,,97,99,104,109,114,120-123,127,135-137,141,148,153,158,159,161,170,180,183]	48/182	Frequency of inspection	T r 1
Intervention	Patients who are dissatisfied with intervention (medication, drip, surgery, etc) have worse compliance and retention[14,16,17,18,25,31,36,39,40,41,48,53,62,,78,79,80,83,85,92,101,105,116,119,121,124,125,134,138,144,166,168,176,178,181,183,184,185,186]	38/182	Frequency of treatment	T r
The complexity of the study protocol	The more complex the study protocol, the higher the compliance and retention[16,22,29,33,34,46,48,53,56-58,61-64,66,71,72,72,81,82,112,114,117,119,124,125,141,147,149,152,172,180,187,189]	36/182	Frequency of follow-up	T 1
Drug / Product	Patients who are dissatisfied with drug/product (taste, smell, etc) have worse compliance and retention[14,17,18,22,31,54,57,64,71,74,78,83,87,92,97,112,114,119,124,125,135,139,152,153,157,161,165,176,180,185,189]	31/182	Duration of treatment	T r
Randomly assigned	Patients who are dissatisfied with randomization have worse compliance and retention[16,24,38,40,70,72,74,80,98,101,104,108,119,120,132,138,146,173,175,178,181,182]	22/182	Different recruitment methods and locations	T h
Different study sites	Due to factors such as the treatment environment or the investigator, the compliance and retention of patients in different research sites also varies[14,20,38,40,56,101,115,118,121,144,161,166,169,177,182]	15/182	Feeling to be cured	F w
The way of inspection	Patients who are dissatisfied with the way of inspection have worse compliance and retention[29,46,79,80,92,93,125,134]	8/182	The level of study	F t
			Investigators	
Researchers' skills on communication	The better the investigator's communication skills, the higher the patient compliance and retention[6,9,12,17-20,22,27,29,31,38-40,44,47,50,52-54,58,61-64,69,76,78,79,83,85,87,92,93,95,96,101,103,104,107,111-114,120,124-126,136-141,144-146,147,151,153,155,157,161,165,168,171,172,175,177,180-182,184,186-188]	75/182	The adequacy of informed consent	T r 1
Researchers' attitude	The better the researcher's attitude, the higher the patient compliance and retention[6,9,14,19,22,24,25,27,29,31,35,38,42,44,46,50,53,57,58,61,62,65,66,71,74,77,79,80,85,87,88,95,104,105,107,112,114,117,120-122,124,126,134,138-142,149,153,155,157,158,161,162,167,171,177,180-182]	62/182	The relationship between researchers and participants	T c 1
Researchers' experience	The richer the researcher's experience, the higher the patient compliance and retention[9,19,20,26,27,31,38,53,54,63,66,74,80,85,90,92,105,108,109,113,120,125,126,130,131,134,147,153,157,160,161,164,165,171,177,178,181,183,186]	38/182	The mastery of the study protocol	T r
The education for participants	The more educated (such as standardized self-management, the normative education of taking medicine, etc) the patient, the higher the patient's compliance and retention[9,12,17,23,27,30,32,42,52,53,54,58,62,75,78,79,84,87,96,97,107,130,140,141,147,152,173,186,188]	29/182	Researchers' understanding of participants	T r
Researchers' race	Keeping the researcher's race consistent with the patient's race can improve patient compliance and retention[11,27,31,50,69,71,82,92,103,107,142,162,164]	13/182	The harmony of research team	T r

*Explanations derived from information rich studies

Space constraints inhibit the provision of all references. Some references are provided as examples.

Table.2 Potential strategies to improve compliance and retention

Potential Strategies	Frequency	Potential Strategies
The phase of protocol design		
Develop simple and convenient research or questionnaire design to make them conform to the patient's lifestyle[16,19,20,22-24,26,33-35,44,45,49,52,54,56,66,69,71,73,74,80,88,89,92,97,105,111,114,117,132,136,143,150,153,156,157,162,165,166,176,177,179,189]	45/182	Training researchers in advance (such [9,19,26,31,38,53,54,63,66,,74,80,90,113,120,130
Determining the frequency of follow-up reasonably[44,45,56,58,64,66,88,95,99,114,120,121,125,129,139,142,152,153,159,171]	21/182	Recruiting full-time researchers[13,26,2
Determining outcomes reasonably[12,29,31,53,58,97,132,153,174,177]	10/182	Improving the screening table based o
Conducting Nominal Group Meeting to explore measures to improve compliance[11,27,31,32,47,58,107–132,171,186]	10/182	Considering the compliance, determini
Reducing the frequency of harmful inspection (such as blood draws, etc)[14,16,31,44,52,73,79,92,121]	9/182	Considering the rate of dropout when
Providing multiple forms of research documents (online or on-site)[16,39,104,153]	4/182	Reducing the number of research files
Setting up a methodology team to explore measures to improve compliance[80,100,117]	3/182	Making full use of predictive factors[53
The phase of recruitment and informed consent		
Full implementation of informed consent(safety concerns, effect, study protocol, the time they may take,etc) [14,18,19,22,25,46,53,55,57,64,66,74,78-81,83,87,88,92,93,95-97,107,108,113,114,117,119,120,121,124-126,132,136,139,140,141,147,149,152,153,157,162,165,167,170,172,176,180,181,186]	54/182	Expanding the channels of recruitment[11,12,13,25,27,32,35,46,47,48,49 188,189]
Pre-compliance assessment[14,22,25,33-35,45,46,51,55,56,64,66,67,71,72,78-80,91-93,97,108,113,114,125,134,141,147,157,162,165,167,173,176,179]	37/182	Emphasizing participants' contributior
Conduct psychological consultation in advance to determine whether the patient is suitable for enrollment[18,61,62,120,133,140,173]	7/182	
The phase of the trial implementation period		
Paying attention to the changes on participants' psychological and building good relationships[6,9,17,19,20,22,25,26,29,32,35,36,38-40,45,46,50,52,53,55,57,61,63,64,69,74,78,79,83,85,87,88,90,92-97,101,103,104,107,112-114,120,121,125-129,133,134,139-142,146,147,152,153,155,157,158,160-162,167,170,172,180,185,189]	75/182	Money, gifts and other compensation[6 143,146,149,152,153,155,158-162,170,178,180]
Carrying out the education about compliance during the study (including the knowledge of disease, psychological and medication, trained in the broader context of medical ethics, cultural training))[9,11,12,14,23,27,29,31,34,35,50-58,61,63,67,71,73,78,79,83,86,87,91-94,97,98,100,107,108,112-114,118-120,123-125,129,130,132,134,139-141,143,147,152,153,157,158,160,164,167,171,174]	65/182	Providing online reminder (phone, ema 90,92,93,96,97,100,101,104,108,109,115,120,123
Recording 3-4 contact information of participants or their family[12,14,19,20,26,27,31-33,42,44,46,52-54,57,58,61,62,64,67,77,78,88,90,97,101,107,108,112,120,124,125,132,142,143,145,150,152,153,155,157,180,181,186]	45/182	Establishing the table of follow-up, foll 84,88,89,92,93,96,97,101,103,104,108,120,127,1
Flexible study time and location[16,19,20,25,26,31,39,44,45,46,54,56,66,69,82,84,85,86,88,89,90,101,103,104,108,118,119,121,123,127,142,146,155,157,160,162,169,170,180,181]	40/182	Handle adverse reactions timely during 42,53,55,63,64,74,78,86,87,92,93,95,107,109,113
Researchers should adhere to the basic ethical principles[9,19,20,29,38,53,59,66,78,80,83,85,88,95,99,107,112,114,120,124,125,129,140,141,146,147,152,153,157,160,172,181]	32/182	The drug package should be accompar reactions[12,31,42,44,52,67,71,75,77,78,80,92
Online data collection[12,13,30,31,48,75,104,106,107,111,112,124,130,132,144,145,151,164,177,183-189]	26/182	Fixed researchers and healers[16,25,27,
Emphasizing the importance of the participants' diary and checking in time[14,22,41,44,52,78,80,92,96,97,103,114,125,129,134,149,152,153,165,170,176]	21/182	Improving the environment of treatme
At each visit, checking compliance by counting the remaining medications with participants[14,35,51,66,67,78,80,92,97,114,125,157,167]	13/182	Intervention by pharmacists during th treatment plans, and improving the qu
Establishing a record system to dispense medicines and packing medicines according to the system[14,31,44,50,52,77,96,107,112,124,149,186,187]	13/182	Intervention by nurses during the stud
Reimbursement of traffic[6,12,54,85,103,126,130,159,160,171]	10/182	Conducting motivational interviews[17,
Paying in cash[19,69,84,104,127,160]	6/182	Reporting the effects at any time durin
Establishing a record system to remind doing inspection[67,107,186]	3/182	

Appendix

Appendix A

Search strategy

Pubmed

#1 ((adher* OR nonadher* OR complian* OR noncomplian* OR comply OR noncomply)

#2 (withdrawal OR drop outs OR drop out OR OR attrition OR retention)

#3 #1 OR #2

#4 patient OR participent OR subject

#5 trial

#6 #4 AND #5

#7 #3 AND #6

EMBASE & the Cochrane Library

#1 ((adher* OR nonadher* OR complian* OR noncomplian* OR comply OR noncomply)

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#10 #7 OR #8 OR #9

#11 Shiyan

#12 Suiji

#13 Duizhao

#14 #11 OR #12 OR #13

#15 #6 AND #10 AND #14

Appendix table 1 The characteristics of included studies[6, 11-188]

Study ID	Health conditions specified	Funding	The country of first author	Health condition	Sample population	Design	Sample size	Data source (for Secondary studies only)	Performance of poor compliance
Alter M1991[185]	Smoking	No	USA	Acute fatal disease	Adults	Retrospective reflection of RCT	73	1 RCT	1.2
Adubato S 2003[171]	Lead-exposure	No	USA	Chronic Non-fatal disease	minor	Retrospective reflection of RCT	780	1 RCT	1.2
Avins A L2005[163]	Cancer	Public	USA	Chronic fatal disease	Adults	Case report	1	Not applicable	1.2
Andrew Maurice2006[159]	Cancer	No	England	Chronic fatal disease	Women	Implementation research	100	Not applicable	3
Anne-Marie Shields2010[127]	End-stage renal disease	Public	USA	Chronic fatal disease	Adults	Implementation research	58	Not applicable	1.4
Atassi N2013[109]	Amyotrophic lateral sclerosis	Industrial	USA	Chronic non-fatal disease	NR	Literature Review	1815	55 Studies	2
Amy Corneli 2015[74]	HIV	No	USA	Chronic fatal disease	Women	Mixed methods approach	312	Not applicable	3
Anjanette A2015[82]	Major depressive disorder	No	USA	Chronic non-fatal disease	NR	Interview	9	Not applicable	1.2.4.5
Ashley Salazar2016[54]	Preterm birth, gestational diabetes, pregnancy-induced hypertension, etc	Public	USA	Chronic non-fatal disease	Pregnant women	Retrospective analysis based on RCTs	NR	9 RCTs	1.2
Atherton P J2016[57]	Cancer	public	USA	Chronic fatal disease	Adults	Retrospective reflection of RCT	1640	14 RCTs	5
Anna Kearney2017[43]	NR	No	England	Unclear	Researchers	Survey	75	Not applicable	1.2
Annette Grape2018[18]	Asthma	Public	USA	Chronic non-fatal disease	minor	Implementation research	373	Not applicable	1.2
Anne Daykin2018[19]	NR	Public	England	Unclear	NR	Interview	22	Not applicable	1.2
Arame Thiam-Diouf2018[20]	HIV	Public	USA	Chronic fatal disease	NR	Systematic review and meta-analysis	964	10 Studies	1.3.4
Boyd N F1992[184]	Cancer	Public	Canada	Chronic fatal disease	Adults	Retrospective reflection of RCT	280	1 RCT	1.2
Blumenthal D S1995[182]	Cancer	Public	USA	Chronic fatal disease	Women	Retrospective reflection of RCT	55	1 RCT	1.2
Bender B G1997[179]	Asthma	No	USA	Chronic Non-fatal disease	Adults and minor	Retrospective reflection of RCT	362	1 RCT	1.2
Bulpitt CJ2001[174]	Hypertension	Public	England	Chronic Non-fatal disease	Seniors	Retrospective reflection of RCT	4695	1 RCT	1.2
Bruce G2003[170]	Asthma	public	USA	Chronic Non-fatal disease	minor	Retrospective reflection of RCT	1041	1 RCT	1.2
Bradley N Collins2011[118]	Smoking	Public	USA	Chronic fatal disease	Pregnant women	Implementation research	279	Not applicable	1.2
Brubaker L 2011[121]	Pelvic floor disorder	No	USA	Chronic non-fatal disease	Women	Focus group interview	105	Not applicable	1.2
Busisiwe Magazi2014[88]	HIV	No	South Africa	Chronic fatal disease	Women	Focus Group Interview	102	Not applicable	4
Boden-Albala2015[71]	Stroke	No	USA	Chronic non-fatal disease	Adults	Mixed methods approach	93	Not applicable	NR
Blaha Robert Z2015[72]	Traumatic Brain Injury	No	USA	Chronic non-fatal disease	Adolescent	Implementation research	132	Not applicable	1.2
Barbro L 2015[73]	Diabetes	No	USA	Chronic non-fatal disease	minor	Retrospective reflection of RCT	8677	1 RCT	1.2
Babatunde O A2017[36]	Overweight	Public	USA	Chronic non-fatal	Seniors	RCT	412	Not applicable	3.4

				disease					
Beishuizen C R L2017[46]	Age-related diseases	Public	Netherland	Chronic non-fatal disease	Seniors	RCT	2994	Not applicable	3.4.5
Boada M2018[34]	Alzheimer	No	Spain	Chronic non-fatal disease	NR	Theoretical research	NR	Not applicable	1
Constance M 2005[162]	Sexually transmitted infections	No	USA	Chronic fatal disease	Women	Retrospective reflection of RCT	376	1 RCT	1.2
Claire S Leathem2009[143]	Coronary heart disease	No	Ireland	Chronic non-fatal disease	Doctors and patients	Survey	903	Not applicable	1.3.4
Chang MW2009[144]	Overweight	public	USA	Unclear	Women	Retrospective reflection of RCT	129	1 RCT	1.4
Cox LE2009[145]	HIV	Public	USA	Chronic fatal disease	Adults	Survey	238	Not applicable	3.4
CM Zhai2010[128]	Heart failure	No	China	Chronic fatal disease	NR	RCT	64	Not applicable	3.4
CC Xia2013[105]	Stroke	No	China	Acute fatal disease	Adults	Implementation research	68	Not applicable	1.2.3
CJ Feng2016[55]	Diseases of the endocrine system	No	China	Acute non-fatal disease	Adults	Retrospective reflection of RCT	410	15 RCTs	1.2
ComeliA 2016[60]	HIV	Public	China	Chronic fatal disease	Women	Interview	212	Not applicable	3.4
Chhatre S2018[24]	Cancer	public	USA	Chronic fatal disease	Adults	Implementation research	551	Not applicable	1.2
David C Mohr1999[175]	Multiple sclerosis	No	USA	Chronic Non-fatal disease	NR	Mixed methods approach	939	Not applicable	1.2.3.4
de Bruyn G2004[168]	HIV	Public	USA	Chronic fatal disease	Adults	Retrospective reflection of RCT	3033	48 RCTs	1.2
D. Lindström2010[132]	Smoking	Public	Sweden	Chronic fatal disease	Adults	Interview	30	Not applicable	4
DC Fan2010[134]	NR	No	China	Unclear	NR	Theoretical research	NR	Not applicable	3.4
DC Fan2010[135]	NR	No	China	Unclear	NR	Theoretical research	NR	Not applicable	3.4
Deborah A2011[119]	Tuberculosis prevention trial	No	USA	Chronic non-fatal disease	Adults	Interview	355	Not applicable	1.2.3.4
David olds2015[76]	NR	Industrial	USA	Unclear	Adults	Focus group interview	5969	Not applicable	1.2
David A. Rorie2017[39]	Hypertension	Public	England	Chronic non-fatal disease	NR	Implementation research	31695	Not applicable	1.3
Epstein E E1994[183]	Alcohol addiction	Public	USA	Chronic Non-fatal disease	Men	Retrospective reflection of RCT	105	1 RCT	1.2
Eivind Berge 2016[66]	Stroke	No	Norway	Chronic non-fatal disease	NR	Survey	46	Not applicable	1.2
Erica EM2016[68]	Schizophrenia	Public	Canada	Chronic non-fatal disease	NR	Literature Review	NR	48 Studies	1.2
Eleanor Ladd Schneider Leavens2019[10]	NR	No	USA	Chronic non-fatal disease	NR	Implementation research	42	Not applicable	1.2.3.4.5
Florence Clark2014[83]	NR	Public	USA	Unclear	Seniors	Retrospective reflection of RCT	460	1 RCT	1.2
Goldman AI1982[188]	Hypertension	No	USA	Chronic Non-fatal disease	Adults	Retrospective reflection of RCT	1012	1 RCT	1.2.3.4
Grilo C M1998[178]	Panic Disorders	No	USA	Chronic Non-fatal disease	Adults	Retrospective reflection of RCT	162	1 RCT	1.2
G Jónasson 1999[176]	Asthma	No	Norway	Chronic Non-fatal disease	minor	Retrospective reflection of RCT	163	1 RCT	3.4

GD Lu2008[153]	NR	No	China	Unclear	NR	Retrospective reflection of RCT	1181	Not applicable	1.2
GD Lu2008[154]	NR	No	China	Unclear	NR	Theoretical research	NR	Not applicable	3
GD Lu2009[136]	NR	No	China	Unclear	Adults	Survey	118	Not applicable	3.4
Guzmn Anglica2009[142]	Overweight	No	USA	Unclear	minor	RCT	123	Not applicable	1.4
Grill J D2010[129]	Alzheimer	Industrial	USA	Chronic fatal disease	NR	Literature Review	NR	Not applicable	4
Gul B R2010[131]	NR	No	USA	Unclear	Adults	Retrospective reflection of RCT	NR	Not applicable	1.2
Gatehouse C S2012[111]	Oral ulcer	Industrial	USA	Chronic non-fatal disease	Adults	Retrospective reflection of RCT	160	1 RCT	1.2.3
GX Chen2016[64]	NR	No	China	Unclear	NR	Theoretical research	NR	Not applicable	3.4.5.
Grace Cannard K2018[17]	Parkinson	Industrial	USA	Chronic non-fatal disease	Adults	Survey	29	Not applicable	1.2
Higginson Irene2008[151]	Multiple sclerosis palliative care service	No	England	Chronic fatal disease	Adults	Interview	52	Not applicable	1.2.3.4
Haleh Sangi-Haghpeykar2009[137]	Cancer/ Chronic obstructive pulmonary disease/Ashma	No	USA	Chronic fatal disease	NR	Retrospective reflection of RCT	541	1 RCT	4
HY Liu2009[139]	Digestive diseases	No	China	Chronic non-fatal disease	Adults	Survey	112	Not applicable	3
Hui D2012[116]	Cancer Palliative Treatment	Public	USA	Chronic fatal disease	NR	Retrospective reflection of RCT	1214	18 RCTs	1.2
HB Zhang2016[58]	Cancer	No	China	Unclear	Adults	Retrospective reflection of RCT	36	1 RCT	1.2
HY fan 2016[61]	Hypertension	Public	China	Chronic non-fatal disease	Adults	Retrospective reflection of RCT	614	18 RCTs	1.2
HY Li 2016[62]	Cancer	No	China	Chronic fatal disease	Adults	Implementation research	60	Not applicable	3.4
H Zhang2016[63]	NR	Public	China	Unclear	NR	Theoretical research	NR	Not applicable	3.4.5
HM Wang 2017[40]	Cancer	No	China	Chronic fatal disease	Adults	RCT	15	Not applicable	5
Henshall C 2018[15]	Diabetes	Public	England	Chronic non-fatal disease	Adults	Interview	20	Not applicable	1.2
H xiong2018[26]	NR	No	China	Unclear	Adults	retrospective reflection of RCTs	371	Not applicable	3.4
HL Duan 2018[35]	NR	NO	China	Unclear	NR	Literature Review	NA	Not applicable	1
Jordhøy M S 1999[177]	Cancer Palliative Treatment	Public	Norway	Chronic fatal disease	Adults	Survey	434	Not applicable	1.2.3.4
J Zeng 2003[172]	NR	NO	China	Unclear	NR	Theoretical research	NR	Not applicable	3
J Xiao2007[158]	NR	No	China	Unclear	NR	Theoretical research	NR	Not applicable	3
J Xiong 2011[125]	Asthma	No	China	Chronic fatal disease	NR	Retrospective reflection of RCT	NR	1 RCT	3.4
J Wei2014[96]	NR	No	China	Unclear	NR	Theoretical research	NA	Not applicable	1.2
Joseph A 2015[80]	Cancer	No	USA	Chronic fatal disease	NR	Theoretical research	NR	Not applicable	1.2.3.4
Julia Lawton 2017[37]	Diabetes	Public	England	Chronic non-fatal disease	Researchers	Interview	22	Not applicable	1.2.3.4
J. Lloyd 2017[38]	Overweight	Public	England	Chronic non-fatal disease	minor	Implementation research	1324	Not applicable	1.4

JJ Jin2017[50]	Blood disease	No	China	Unclear	NR	Retrospective analysis based on RCTs	200	19 RCTs	3.4.5
Joshua Wynne2018[22]	HIV	No	England	Chronic fatal disease	Women	Implementation research	322	Not applicable	1.3.4
JX Tao2018[30]	Hepatitis	Public	China	Acute non-fatal disease	Adults	Retrospective analysis based on RCTs	620	1 RCT	3.4
JH liu 2018[31]	NR	No	China	Unclear	Adults	RCT	90	Not applicable	3.4
J Yang2018[32]	NR	No	China	Unclear	NR	Retrospective analysis based on RCTs	56	4 RCTs	1.2
Joanna C Crocker2018[33]	NR	No	England	Unclear	NR	Systematic review and meta-analysis	2222	6 Studies	1.2
JS Liang2019[14]	NR	Public	China	Unclear	NR	retrospective reflection of RCTs	82	8 RCTs	3.4
Kvien TK1983[187]	Arthritis	Industrial	Norway	Chronic Non-fatal disease	Adolescent	Implementation research	80	Not applicable	3.4
Kalkhuis-Beam S2011[123]	Smoking	public	USA	Chronic fatal disease	Adolescent	RCT	710	Not applicable	1.2
Koog Y H2013[110]	Arthritis	NO	Korea	Chronic non-fatal disease	NR	Systematic review and meta-analysis	13593	266 Studies	2
Kadam R A2016[53]	NR	Industrial	India	Unclear	Researchers	Survey	73	Not applicable	1.2
Kati A K2017[42]	Serious mental health problems	No	Finland	Chronic non-fatal disease	Adults	RCT	1139	Not applicable	1.2
Lynette Dias2005[161]	Myopia	Public	USA	Chronic Non-fatal disease	minor	Survey	446	Not applicable	1.2
LJ Tian2009[140]	NR	Public	China	Unclear	NR	Survey	326	Not applicable	NR
Lesley J Burgess2010[126]	NR	No	South Africa	Unclear	NR	Retrospective reflection of RCT	1386	50 RCTs	1.2
L J Burgess 2011[122]	NR	No	South Africa	Unclear	Adults	Survey	302	Not applicable	1.2
Lewis AL2013[106]	Smoking	Public	USA	Chronic non-fatal disease	Adolescent	Retrospective reflection of RCT	98	1 RCT	7
LP Mai2014[91]	NR	No	China	Unclear	NR	Retrospective reflection of RCT	NR	10 RCTs	NR
Lopes R T 2014[98]	Major depressive disorder	public	Portugal	Chronic non-fatal disease	Adults	RCT	63	Not applicable	1.2.3.4.5
LangfordD P2015[75]	Fracture	Public	Canada	Acute non-fatal disease	Seniors	RCT	30	Not applicable	1.2
L Zhang2015[78]	NR	No	China	Unclear	NR	Retrospective reflection of RCT	1351	40 RCTs	1.2
L Mood2015[81]	Disability	Public	Portland	Chronic non-fatal disease	Persons with physical disabilities	Literature Review	NR	Not applicable	1.2
Louise Robinson2016[65]	NR	No	England	Unclear	minor	Systematic review and meta analysis	154	28 RCTs	1.2
Laura A. Novak 2019[11]	Post-traumatic stress disorder(PTSD)	No	USA	Acute non-fatal disease	Adults	Survey	666	Not applicable	1.2
Morse EV1991[186]	HIV	Public	USA	Chronic fatal disease	Adults	Retrospective reflection of RCT	40	1 RCT	3.4
Marion Good1997[181]	NR	Public	USA	Unclear	NR	Case report	8	Not applicable	1.2
Mazzuca S A2004[167]	Arthritis	public	USA	Chronic Non-fatal disease	Women	Retrospective reflection of RCT	432	1 RCT	1.2.3.4
Mor M2006[160]	Intestinal polyps	No	USA	Chronic Non-fatal disease	Adults	Survey	31	Not applicable	1.2

Merran Toerien2009[138]	NR	Public	England	Unclear	NR	Literature Review	NR	Not applicable	1.4
Magner R2010[130]	Diabetes	Public	USA	Chronic fatal disease	Adults	Implementation research	276	Not applicable	1.4
Murphy E J2013[102]	Major depressive disorder	Public	USA	Chronic non-fatal disease	NR	Retrospective reflection of RCT	3222	1 RCT	1.2.3.4.5
Margaret Pribulick2013[103]	Cardiovascular disease	Public	USA	Chronic fatal disease	Rural women	Retrospective reflection of RCT	167	1 RCT	1.2.3
Marjorie C2014[84]	Hearing loss	Public	USA	Chronic non-fatal disease	Farm operators	RCT	709	Not applicable	1.2.4.5
Mary Fischer2014[85]	Osteoporosis	Public	USA	Chronic non-fatal disease	Women	Interview	43	Not applicable	3.4
M Yang2015[79]	NR	No	China	Unclear	NR	Theoretical research	NR	Not applicable	2
Miguel AQ2016[59]	Cocaine dependence	Public	Brazil	Chronic non-fatal disease	Adults	RCT	65	Not applicable	1.2.3.4
Megan Comerford2017[47]	Hepatitis	Industrial	India	Chronic non-fatal disease	Adults	Retrospective analysis based on RCTs	387	1 RCT	1.2
MK Yu2019[6]	NR	Public	China	Unclear	NR	Literature Review	NR	Not applicable	1.2.3.4
Natalie A. Johnson2015[70]	Alcohol addiction	No	USA	Chronic non-fatal disease	Adults	Retrospective reflection of RCT	837	1 RCT	1.2
HS Zhang2013[108]	Asthma	No	China	Chronic Non-fatal disease	Adults	Retrospective reflection of RCT	68	1 RCT	1、2、3、4、5
Olubukola T Idoko 2014[89]	NR	No	Gambia	Unclear	minor	Retrospective reflection of RCT	300	1 RCT	1.2.4.5
Okhomina V2018[27]	Cardiovascular disease	Public	USA	Chronic non-fatal disease	Adults	Cohort study	375	Not applicable	1
Peter M. Milgrom1997[180]	Periodontal disease	No	USA	Chronic Non-fatal disease	NR	Implementation research	70	Not applicable	1.2.3.4
P Huang 2014[94]	NR	Public	China	Unclear	NR	Theoretical research	NA	Not applicable	1.2
Plummer M L2014[100]	HIV	Public	England	Chronic fatal disease	Women	Retrospective reflection of RCT	1305	1 RCT	2.3.5
Pfammatter A F2017[41]	NR	No	USA	Unclear	Adults	Implementation research	150	Not applicable	1.2
Paul A. Leighton2017[44]	Fracture	No	England	Acute non-fatal disease	Adults	Focus Group Interview	26	Not applicable	1.2
QW Rao2012[113]	NR	No	China	Unclear	NR	Theoretical research	NR	Not applicable	3
Q Zhang2014[92]	NR	No	China	Unclear	NR	Theoretical research	NA	Not applicable	3.4
Raymond E G2004[166]	Pregnancy	Public	USA	Unclear	Women	Retrospective reflection of RCT	1514	1 RCT	1.2
Russell E Glasgow2007[157]	Overweight	No	USA	Chronic Non-fatal disease	Adults	Retrospective reflection of RCT	2311	1 RCT	1.2
Romina Kim 2014[90]	Smoking	public	USA	Chronic non-fatal disease	Patients with mental illness	Retrospective reflection of RCT	100	1 RCT	1.2.3.4
Robert S. Ware2017[48]	Intellectual disability	Public	USA	Chronic non-fatal disease	Adolescent with mental retardation	RCT	556	Not applicable	1.2
Rachel Schoor2018[16]	Multiple sclerosis	Public	USA	Chronic non-fatal disease	Adults	Motivational interview	75	Not applicable	1.2.3.4
Rosalind J 2018[25]	Ebola	public	USA	Acute fatal disease	Healthcare providers, or Ebola front-line workers	RCT	7979	Not applicable	3
Rios-Romenets S2018[28]	Alzheimer	Public	Colombia	Chronic non-fatal disease	Adults	Implementation research	252	Not applicable	1.2
Sonawalla Shamsah B2002[173]	Major depressive disorder	No	USA	Chronic Non-fatal	Adults	Retrospective reflection of	119	1 RCT	1.2

				disease		RCT			
Sears S R2003[169]	Cancer	Public	USA	Chronic fatal disease	Women	Retrospective reflection of RCT	558	1 RCT	1.2
Steven K2005[164]	Major depressive disorder	Public	Portland	Chronic Non-fatal disease	Adults	Interview	31	Not applicable	1.2.3.4
Siddiqi A A2008[152]	Cancer	NO	USA	Acute fatal disease	Adults	Implementation research	713	Not applicable	1.2
SS Bull2008[155]	HIV	industrial	USA	Chronic fatal disease	NR	Implementation research	2623	Not applicable	1.2
SX Wang2009[141]	NR	Public	China	Unclear	Adults	Survey	632	Not applicable	1.2
SM Xue 2009[149]	Orthopaedics	NO	China	Chronic non-fatal disease	NR	Theoretical research	NR	Not applicable	3
Sharika Gappoo 2009[150]	HIV	No	South Africa	Chronic fatal disease	Women	Implementation research	5045	Not applicable	1.2
Sue Penckofer2011[120]	Diabetes	No	USA	Chronic non-fatal disease	Women	Theoretical research	NR	Not applicable	1.2.3.4
S Knippschild2013[99]	Cataract	No	Germany	Chronic non-fatal disease	NR	Literature Review	2834	18 Studies	1.2.4.5
SY Liu2013[107]	Cancer	No	China	Chronic fatal disease	Women	Implementation research	20	Not applicable	3.4
Sophie G 2018[23]	HIV	public	USA	Chronic fatal disease	Adults	Interview	25	Not applicable	1
Soumya J. Niranjan2019[9]	Cancer	No	USA	Chronic fatal disease	Researchers	Interview	91	Not applicable	1.2
Ulrich C M2018[29]	Cancer	Public	USA	Chronic fatal disease	Adults	Retrospective analysis based on RCTs	27443	134 RCTs	1.2
Thayabaranathan T2016[56]	Stroke	No	USA	Chronic non-fatal disease	Nurse	Interview	2	Not applicable	1.2
Thomas M 2016[67]	NR	No	USA	Unclear	NR	Retrospective reflection of RCT	NR	Not applicable	3
Theresa A2017[45]	Preeclampsia	public	South Africa	Chronic non-fatal disease	Pregnant women	Implementation research	1354	Not applicable	3.4.5
Victoria Villacorta2007[156]	HIV	Public	Peru	Chronic fatal disease	Esquineros/Men who have sex only with men /Movidas	Implementation research	1263	Not applicable	1.2
Vellas B2012[115]	Alzheimer	Public	France	Chronic fatal disease	NR	Theoretical articles	NR	Not applicable	1.2
V C Brueton2013[104]	NR	No	England	Unclear	Researchers	Interview	29	Not applicable	1.2
V C Brueton2015[69]	Smoking/Headache/Asthma, etc	Public	England	Chronic non-fatal disease	NR	Systematic review and meta-analysis	4751	38 Studies	1.2
Warner E T2013[101]	Overweight/Hypertension	Public	USA	Chronic non-fatal disease	Adults	Implementation research	474	Not applicable	1.2.4.5
W Wang2014[86]	Chronic obstructive pulmonary disease	No	China	Unclear	Seniors	RCT	150	Not applicable	3
Wenke Zheng2014[97]	NR	No	China	Unclear	NR	Retrospective reflection of RCT	NR	Not applicable	3.4
Wisk LE2019[13]	Diabetes	Industrial	USA	Chronic non-fatal disease	College students	Survey	227	Not applicable	1.2
X Zhang2009[146]	NR	No	China	Unclear	NR	Theoretical research	NA	Not applicable	3
XX Wang2009[147]	NR	Public	China	Unclear	NR	Theoretical research	NA	Not applicable	3
XN wang 2011[124]	Stroke	No	China	Acute non-fatal disease	Adults	RCT	92	Not applicable	1.3
XW Qiao2014[87]	Respiratory diseases	No	China	Chronic non-fatal	Adults	Interview	52	Not applicable	1.2.4.5

				disease					
XX wang 2015[77]	Cancer	No	China	Chronic fatal disease	Adults	Single-arm clinical research	80	Not applicable	NR
YP Bao2009[148]	NR	Public	China	Unclear	NR	Literature Review	2831	18 RCTs	1.4
YJ Huang 2010[133]	Cancer	No	China	Chronic fatal disease	Adults	Interview	20	Not applicable	3.4
YY Kou 2012[112]	Cancer	No	China	Chronic fatal disease	Adults	Implementation research	68	Not applicable	2.3.4
YM Hu2012[114]	NR	No	China	Unclear	NR	Retrospective reflection of RCT	954	48 RCTs	1.3.4.5
Y zhang2012[117]	NR	NO	China	Unclear	NR	Theoretical research	NR	Not applicable	3
YG Li2014[93]	Diabetes	No	China	Chronic non-fatal disease	NR	Retrospective reflection of RCT	51	14 RCTs	1
YG Li2014[95]	NR	No	China	Unclear	NR	Theoretical research	NA	Not applicable	1.2
YW Zhang2017[51]	NR	No	China	Unclear	NR	Retrospective analysis based on RCTs	828	38 RCTs	1.2
Y Jin2017[52]	Cancer	No	China	Chronic fatal disease	NR	Retrospective analysis based on RCTs	405	24 RCTs	1.2
YS Xu2018[21]	NR	No	China	Unclear	NR	Survey	22	Not applicable	3.4
J Zhang2005[165]	NR	No	China	Unclear	NR	Theoretical research	NR	Not applicable	3
ZC Cai2017[49]	Cancer	No	China	Chronic fatal disease	Adults	Implementation research	70	Not applicable	3.4.5
Zhou Q2019[12]	Cancer	Public	USA	Chronic fatal disease	Adults	Survey	110	Not applicable	1.2
Zoë C Skea2019[189]	NR	Public&Industrial	United Kingdom	Unclear	NR	Meta-ethnographic synthesis	177804	13 RCTs	1.2.3.4

Note:

USA: the United States of America

RCT: Randomized controlled trial

Not Reported: NR

Performance of poor compliance：1.Loss of follow-up during the study; 2.Failure to treatment ;3.Non-compliance with medication;4.Non-compliance with attendance appointments;5.Non-compliance with filling out the form; 6. Not reported

Figures

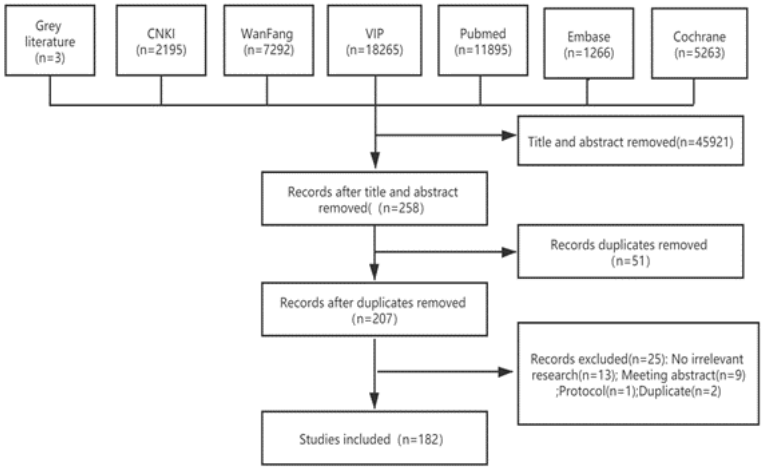

Figure 1

Study flow diagram

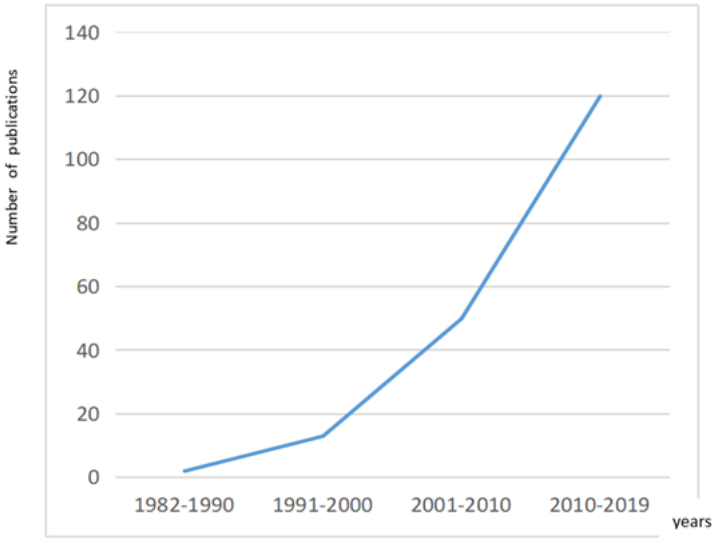

Figure 2

Annual outputs of publications regarding participants compliance and retention in clinical trials from 1982 to 2019.

Figure 3

The word cloud about factors affecting the compliance and retention The font size of a word or phrase reflects the frequency of factors in at least two studies.

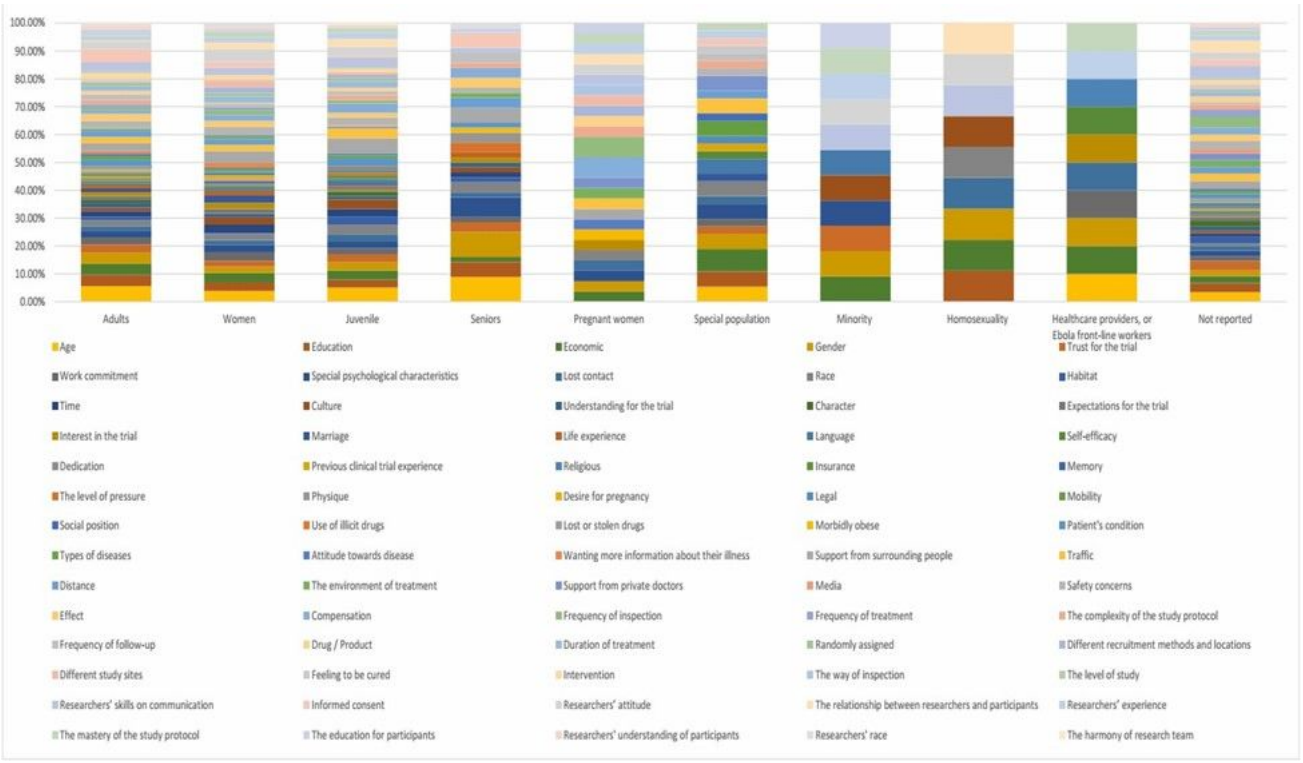

Figure 4

The process factors in different populations

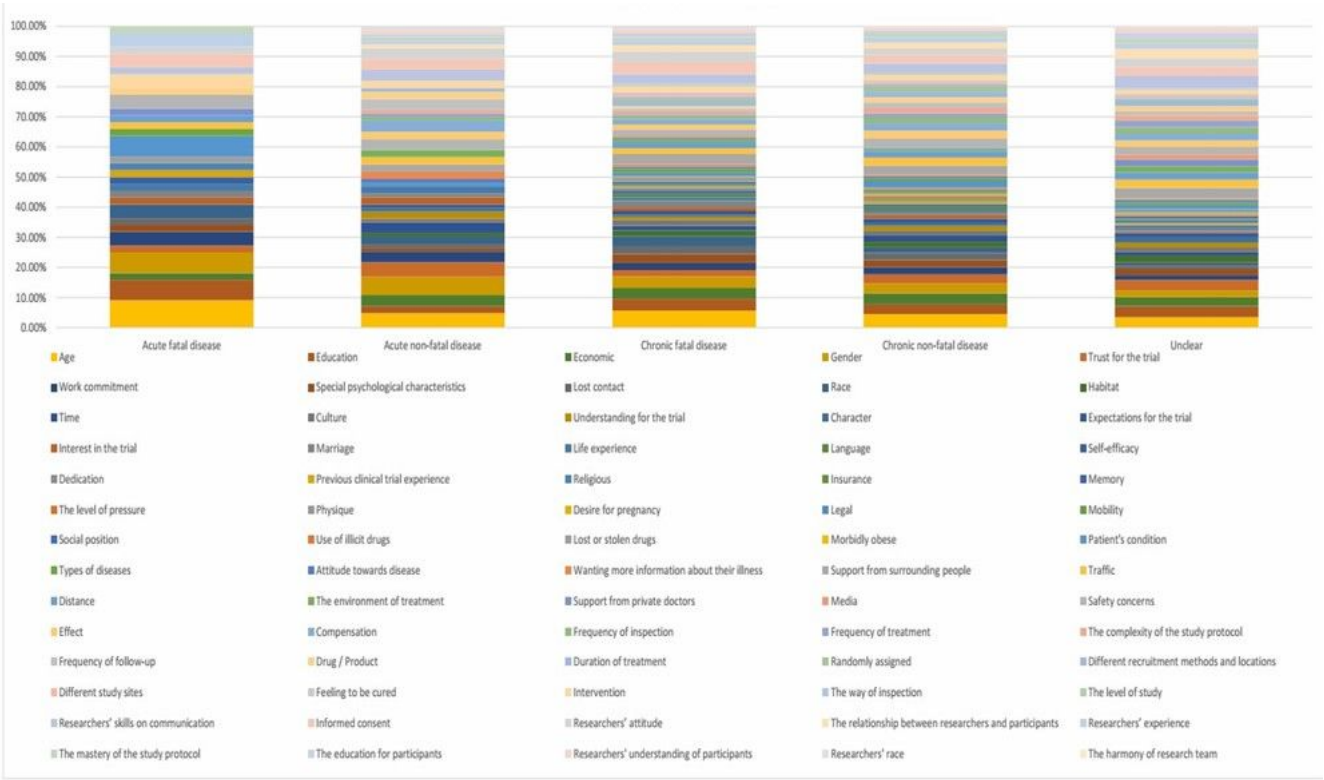

Figure 5

The process factors in different diseases

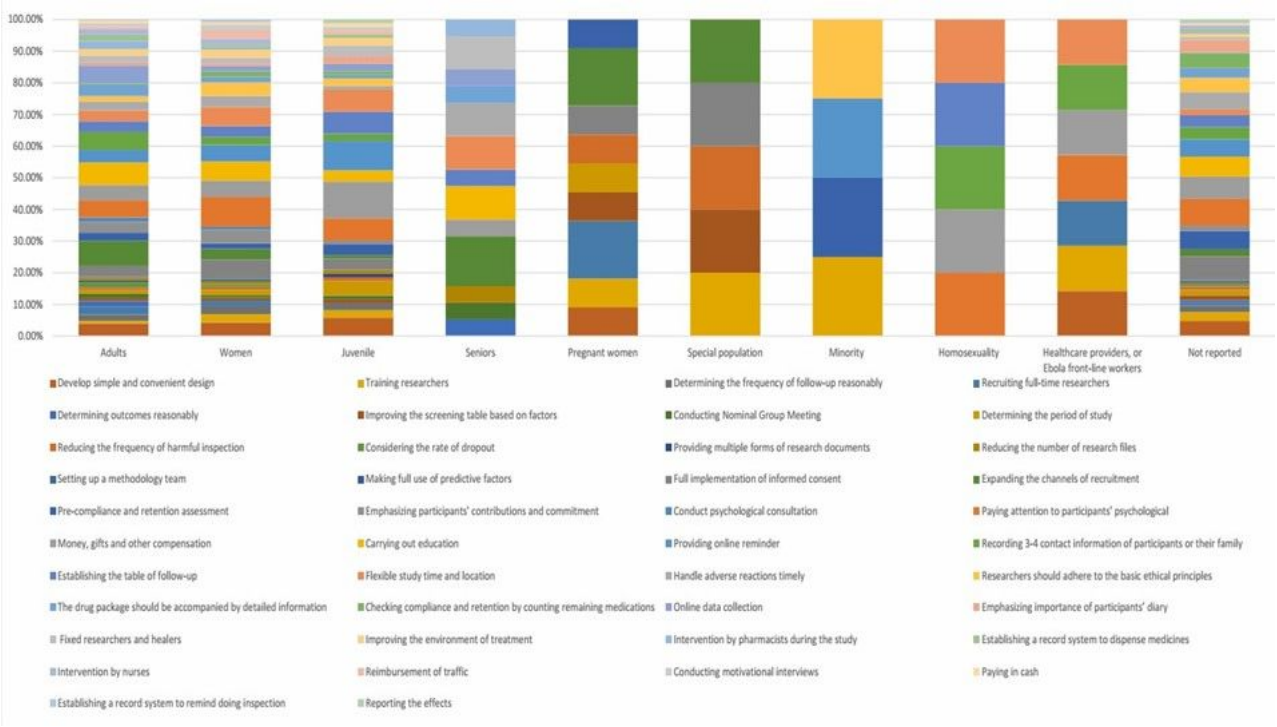

Figure 6

The improvement strategies in different populations

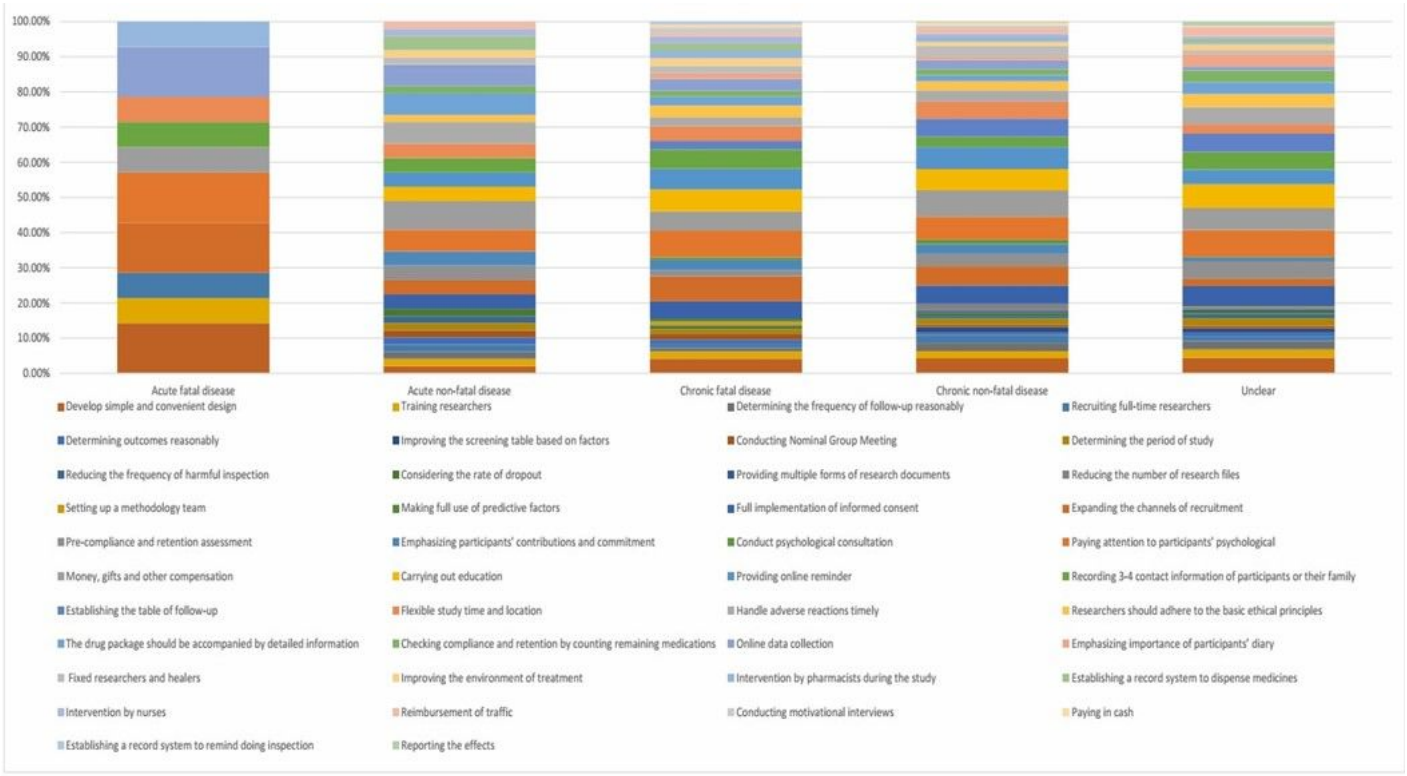

Figure 7

The improvement strategies in different diseases

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendixfigure1.pdf

- Appendixfigure2.pdf
- Appendixfigure3.pdf
- Appendixfigure4.pdf
- Appendixfigure5.pdf
- Appendixfigure6.pdf
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