How to improve participant compliance in clinical trials: A Scoping Review of process factors

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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 approaches for improving compliance, 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 may be successful (or not).

Aim

To identify process factors that may influence participant compliance retention in clinical trials, and potential approaches to improve the compliance, from published studies, 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 influencing participant compliance and potential approaches for improving compliance retention were included. Data synthesis followed an iterative process to develop a list of process factors and potential retention approaches. Results were analysed descriptively, including visualization using word cloud.

Results

181 publications were included in this review, composed of 58 retrospective analysis 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 and 1 cohort study. We identified 70 process factors that may affect the compliance. The most commonly addressed factors were age, education, economy, trust in clinical trials, supporting from surrounding people, safety concerns and effectiveness. We found 44 potential approaches to improve compliance. Approaches 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.

Conclusion

These factors that may affect the compliance can help researchers predict participants who are less likely to adhere and develop screening tools to find efficiently their suitable participants. These potential approaches that may improve the compliance provide suggestions for improving compliance.

Background

The compliance 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. 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. Difficulties in achieving the compliance of participants in randomized controlled trials (RCTs) are well documented, and many clinical trials are stopped or extended due to issues about compliance. 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.

Clinical trial researchers often focus more on the trial design, paying less attention to participant compliance. Although there is extensive information in the scientific literature on compliance of participants in clinical trials, few researchers have summarized this systematically in China. There are numerous factors that may affect compliance and also a range of potential approaches for improving compliance 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. 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.

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

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/or reported potential approaches for improving compliance, 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. We defined compliance 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.

Titles and abstracts and full text articles were retrieved and screened independently by two reviewers (for full-text screening these were MK and CH) against the eligibility criteria. Any disagreements were resolved through discussion or arbitrated by the senior author (Fei YT), if necessary. Articles that reported the same study were screened together to avoid studies being double counted. The reasons for exclusion were recorded.

Data extraction and synthesis

To ensure consistency and reduce subjectivity in data extraction, the data were extracted from each study independently by two reviewers using a pre-designed pilot-tested data collection form that included: article and author information; the information of study; process factors that may influence compliance; and potential approaches for improving compliance. Any disagreements were resolved through discussion or arbitrated by the senior author (Fei YT), if necessary. The process of data extraction was used to iteratively develop a list of the process factors and potential approaches that may influence compliance. The list was updated after group discussion when new factors and approaches were identified in studies and the final list was used as a template for recording which factors and approaches were reported in each of the 181 included studies.

The extracted data were analysed descriptively to investigate which are the key process factors and approaches that may influence compliance in RCTs according to the literature. No tests of statistical significance were 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 trial compliance. 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

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 doesn't include retrospective researches, theoretical researches, interviews, surveys, randomized controlled trials, literature reviews, systematic review and meta analysis, mixed methods researches, case report and cohort study. Retrospective researches. Retrospective analysis of RCTs can be defined as a study in which process factors are obtained by summarizing the experience of randomized controlled trials.

Results

We identified a total of 46178 publications through the searches, and a total of 181 publications met the inclusion criteria (Figure 1).

Study characteristics

The 181 publications included 58 retrospective analysis 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 and 1 cohort study (Appendix table 1). The compliance 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, children, 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).
Process factors that may influence compliance

70 key factors affecting compliance, grouped into individual, environment, disease, protocol and investigator aspects (Table 1), were finally identified. The factors with highest frequencies were: age (54.3%), education (43.4%), economic (41.3%), investigators’ skills on communication (40.7%), the adequacy of informed consent (38.5%), gender (38.0%), support from personal social relationship (38.0%), trust for the trials (35.8%), attitude (investigator’s attitude towards research and patients) (33.7%) and safety concerns (32.1%).

Discussion
Summary of results

181 publications were included in this review. We reviewed 58 retrospective researches from RCT based on 1,132 clinical trials with 177,804 participants, and identified 70 factors, which were grouped into individual, disease, environment, protocol and investigators aspects, influencing participant compliance; and 44 potential approaches, which could be adopted in three phases (protocol design, recruitment and informed consent, the trial implementation period) to improve compliance.

Strengths And Limitations

In past systematic map of digital tools for recruitment and retention we found that process factors were hardly studied\[190\], even though these may be important for understanding how and why approaches 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 approaches of compliance, regardless of the type of literature and the publication date. The results were from 177,804 people (including pregnant women, children, 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. Scoping review methods and word cloud were used in our study. We used systematic and extensive approach to identify and analyze literature with the following objectives: 1. Examining the scope of the compliance study; 2. Addressing a wide range of the compliance issues; 3. Including all available research, regardless of study design; 4. Providing a description of the available evidence on compliance issues \[190\]. But the diverse factors and potential approaches reported in the included studies make it difficult to draw an overall and exact conclusion. In addition, due to the inherent limitations of scoping review and the narrative nature of our topic, our research may focus more on the breadth of information than the depth, so we did not evaluate the quality of the included articles.

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 approaches from some trials to improve the compliance. The design of compliance 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 \[191\]. But the influencing factors of compliance and theoretical perspectives were not provided in depth. The traditional literature review described the factors and potential approaches 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 approaches 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 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. The potential approaches for improving compliance we found were generally targeting at the factors we identified. However, the factors were not sufficiently covered by the potential approaches we found. There is a need to develop more comprehensive potential approaches 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 in the clinical trials, but it was reported that young people may increase or decrease participant compliance. 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 approaches 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 during the study (including the knowledge of disease, psychology and medication), full implementation of informed consent and reminding participants online (phone, email, etc) were also mentioned by many. Potential approaches still need to be comprehensively developed. Furthermore, adopting potential approaches are often resource demanding. Researchers need to realize this and try to prepare it when planning the trial. Cost-benefit analysis may be required.

Qualitative methods could be used to make an in-depth exploration to the factors and potential approaches in the future research. More researches are also needed to find effective potential approaches 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 approaches by evaluating specific outcomes, such as compliance rate, compliance 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 44 potential approaches, which could be adopted in three phases (protocol design, recruitment and informed consent, the trial implementation period) to improve compliance. 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 approaches, researchers should well-thought-out according to budget, the range of disease, 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.

Competing interests: There are no conflicts of interest in this study.

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Author contributions: YT Fei and MK Yu conceived and designed the review. MK Yu and YT Fei drafted the protocol. MK Yu, ZY Lin, CH Liang, CZ Li, ZJ Zhang, KX Liu were responsible for the searching, screening and selecting studies. They all participated in data extraction and assessed study quality. MK Yu and CZ Li made forms and pictures and performed the statistical analysis. JP Liu, YT Fei and X Li 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 of clinical trials
| Influencing factors      | Explanation*                                                                 | Frequency | Influencing factors      | Explanation*                                                                 | Frequency |
|-------------------------|------------------------------------------------------------------------------|-----------|-------------------------|------------------------------------------------------------------------------|-----------|
| Individual              |                                                                              |           | Age                     | Older people may have poorer compliance 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 because they may prefer work or entertainment than participate in clinical trials[21,49,53]. | 100/181   |
|                         |                                                                              |           | Education               | People with higher education will have higher compliance[62,58,64].           | 80/181    |
| Economic                | People with high-income will have higher compliance[91,100,112]              | 76/181    | Gender                  | Women may have higher compliance[91,100,112]                                   | 70/181    |
| Trust for the trial     | The more trust, the higher compliance[9,14,16]                                | 66/181    | Work commitment         | Different work may affect compliance[25,35,36].                               | 51/181    |
| Special psychological characteristics | Special psychological characteristics(anxious, impatience, depression, etc) will reduce the compliance[9,16,140] | 51/181    | Lost contact            | Lost contact (moving, jailing, death, etc) will reduce the compliance[38,54,65]. | 44/181    |
| Race                    | Patients with different races have different compliance. For example, minorities have lower or higher compliance[13,18,30] | 43/181    | Habitat                 | Good habits will improve compliance[42,58,63].                                | 42/181    |
| Time                    | The more time the patient have, the higher the compliance.[28,30,131]        | 38/181    | Culture                 | The degree of matching between research and culture influences compliance.[28,82,145] | 33/181    |
| Understanding for the trial | Patients who understand more about the trial may have higher compliance. However, as their understanding deepens, they may also withdraw because the research does not meet their expectations.[47,61,71] | 32/181    | Expectations for the trial | If the patient's expectations for the study are too high, their compliance may decrease when the treatment effect does not meet expectations.[30,132,184] | 31/181    |
| Character               | The better the character, the higher the compliance[77,79,132]               | 26/181    | Interest in the trial   | The more interested in the experiment, the higher the compliance[28,71,131]    | 25/181    |
| Marriage                | Married people may have higher compliance[28,30,130]                          | 22/181    | Life experience         | The greater the impact of clinical trials on the life of the subject, the higher the non-compliance rate[31,61,145]. | 18/181    |
| Language                | The degree of matching between researcher's language and patient's language influences compliance[49,58,188] | 17/181    | Self-efficacy           | The higher the self-efficacy, the higher the compliance[12,130,145].           | 15/181    |
| Dedication              | People with dedication will be more compliant[17,82,104,etc].                | 15/181    | Previous clinical trial experience | People who have previous clinical trial experience may have higher compliance.[32,67,105,etc] | 12/181    |
| Religious               | The degree of matching between research and religious influences compliance.[25,33,92,etc] | 10/181    | Insurance               | People who have insurance may have higher compliance[72,96,131,etc]           | 10/181    |
| Memory                  | People who have good memory may have higher compliance[31,58,82,etc]         | 9/181     | The level of pressure   | The greater the pressure, the worse the compliance[15,83,178,etc]             | 9/181     |
| Physique                | The better the physique, the higher the compliance[35,83,182,etc]            | 8/181     | Desire for pregnancy    | If a person wants to become pregnant, she is more compliant in studies that increase the probability of pregnancy. But she may be more likely to withdraw from other clinical studies due to the exclusion criteria[100,144,166,etc] | 8/181     |
| Legal | Patients with legal concepts may have higher compliance[^119,141,171,etc] | 7/181 | Mobility | People who have good mobility may have higher compliance[^48,82,94,etc] | 7/181 |
| Social position | People who have high social position may have higher compliance[^20,158,159,etc] | 6/181 | Use of illicit drugs | People who are using the illicit drugs may have worse compliance[^168,171,183,etc] | 5/181 |
| Lost or stolen drugs | Lost or stolen drugs may reduce the compliance[^59,78,153,etc] | 4/181 | Morbidly obese | People who have morbidly obese may have worse compliance[^36,118,etc] | 2/181 |
| Disease | | | | |
| Patient's condition[^*] | Patient with severe illness have higher compliance than those with less severe illness. But they may also withdraw due to the worsening of their condition[^30,46,47,etc]. | 39/181 | Types of diseases | Different types of diseases also affect patient compliance. For example, patient with cancer have higher compliance in clinical trials compared to chronic diseases[^28,157,168,etc] | 22/181 |
| Attitude towards disease | People who have positive attitude to disease may have higher compliance[^35,97,109,etc] | 16/181 | Wanting more information about their illness | Patient who want more information about their illness may have higher compliance[^30,107,145,etc] | 13/181 |
| Environment | | | | |
| Support from surrounding people | The more support from surrounding people (family, friends, patient groups), the higher the compliance[^28,31,60,etc] | 70/181 | Traffic | The more convenient the transportation, the higher the compliance[^61,124,165,etc] | 54/181 |
| Distance | Patients who live closer to the study site have higher compliance[^28,58,177,etc] | 46/181 | The environment of treatment | The better the treatment environment, the higher the compliance. The compliance of inpatients is higher than outpatients[^58,75,154,etc] | 28/181 |
| Support from private doctors | The more support from private doctors, the higher the compliance[^35,51,53,etc] | 23/181 | Media | Positive guidance from the media may improve compliance[^60,63,89,etc]. | 13/181 |
| Protocol | | | | |
| Safety concerns | The higher the security, the higher the compliance[^12,13,16,etc] | 59/181 | Effect | The better and clearer the effect, the better the compliance[^37,81,87,etc] | 49/181 |
| Compensation | Patient compliance is higher in studies that have compensation[^159,171,etc] | 48/181 | Frequency of inspection | The higher the frequency of the inspection (blood draws, etc), the worse the compliance[^28,58,61,etc] | 48/181 |
| Frequency of treatment | The higher the frequency of the treatment, the worse the compliance[^100,149,158,etc] | 36/181 | The complexity of the study protocol | The more complex the study protocol, the higher the compliance[^98,146,149,etc] | 35/181 |
| Frequency of follow-up | The higher the frequency of the follow-up, the worse the compliance[^216,29,74,etc] | 34/181 | Drug / Product | Patients who are dissatisfied with drug/product (taste, smell, etc) have worse compliance[^119,126,161,etc] | 30/181 |
| Duration of treatment | The longer the duration of treatment, the worse the compliance[^3,15,43,etc] | 28/181 | Randomly assigned | Patients who are dissatisfied with randomization have worse compliance[^132,146,173,etc] | 22/181 |
| Different recruitment methods and locations | The compliance of patients recruited online is lower than that of patients recruited by private doctors[^37,56,101,etc] | 15/181 | Different study sites | Due to factors such as the treatment environment or the investigator, the compliance of patients in different research sites also varies[^158,172,180,etc] | 15/181 |
| Feeling to be cured | Patients who are consciously cured are more likely to withdraw[^52,81,87,etc] | 14/181 | Intervention | Patients who are dissatisfied with intervention (medication, drip, surgery, etc) have worse compliance[^15,16,24,etc] | 9/181 |
|-------------------|-------------------------------------------------|-------|---------------|-------------------------------------------------------------------------------------------------|------|
| The way of inspection | Patients who are dissatisfied with the way of inspection have worse compliance[^55,80,134,etc] | 8/181 | The level of study | High level study can improve patient compliance because of patient trust[^71,157,161,etc] | 6/181 |
| Investigators | | | | | |
| Researchers' skills on communication | The better the investigator's communication skills, the higher the patient compliance[^9,52,82,etc] | 75/181 | The adequacy of informed consent | The more informed consent, the higher the patient compliance[^28,81,93,etc] | 71/181 |
| Researchers' attitude | The better the researcher's attitude, the higher the patient compliance[^10,18,61,etc] | 62/181 | The relationship between researchers and participants | The closer the relationship between the investigator and the patient, the higher the patient compliance[^10,18,21,etc] | 51/181 |
| Researchers' experience | The richer the researcher's experience, the higher the patient compliance[^9,18,105,etc] | 38/181 | The mastery of the study protocol | The better the investigator's mastery of the protocol, the higher the patient compliance[^113,130,139,etc] | 30/181 |
| 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[^90,52,120,etc] | 29/181 | Researchers' understanding of participants | The more researchers understand the patient, the higher the patient compliance[^108,139,145,etc] | 24/181 |
| Researchers' race | Keeping the researcher's race consistent with the patient's race can improve patient compliance[^92,142,164,etc] | 13/181 | The harmony of research team | The more harmonious the research team, the higher the patient compliance[^37,76,126,etc] | 4/181 |

*Explanations derived from information rich studies*

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

**Table.2 Potential approaches to improve compliance**
| Potential approaches                                                                 | Frequency | Potential approaches                                                                 | Frequency |
|-------------------------------------------------------------------------------------|-----------|--------------------------------------------------------------------------------------|-----------|
| The phase of protocol design                                                       |           | Training researchers in advance (such as study protocol, communication skills, the quality of service) | 22/181    |
| Develop simple and convenient research or questionnaire design to make them conform to the patient's lifestyle | 43/181    | Recruiting full-time researchers                                                     | 18/181    |
| Determining the frequency of follow-up reasonably                                    | 19/181    | Improving the screening table based on factors (such as table 1) that affect patient compliance | 11/181    |
| Determining outcomes reasonably                                                    | 17/181    | Considering the compliance, determining the period of study reasonably               | 9/181     |
| Conducting Nominal Group Meeting to explore measures to improve compliance         | 10/181    | Considering the rate of dropout when calculating the sample size                     | 9/181     |
| Reducing the frequency of harmful inspection (such as blood draws, etc)             | 9/181     | Reducing the number of research files                                                | 9/181     |
| Providing multiple forms of research documents (online or on-site)                  | 3/181     | Making full use of predictive factors                                                | 2/181     |
| Setting up a methodology team to explore measures to improve compliance            | 3/181     |                                                                            |           |
| The phase of recruitment and informed consent                                       |           |                                                                            |           |
| Full implementation of informed consent(safety concerns, effect, study protocol, the time they may take, etc) | 54/181    | Expanding the channels of recruitment                                               | 47/181    |
| Pre-compliance assessment                                                           | 38/181    | Emphasizing participants’ contributions and commitment to research                   | 23/181    |
| Conduct psychological consultation in advance to determine whether the patient is suitable for enrollment | 7/181     |                                                                            |           |
| The phase of the trial implementation period                                         |           |                                                                            |           |
| Paying attention to the changes on participants’ psychological and building good relationships | 75/181    | Money, gifts and other compensation                                                  | 68/181    |
| 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)) | 65/181    | Providing online reminder (phone, email, etc)                                       | 53/181    |
| Recording 3-4 contact information of participants or their family                   | 45/181    | Establishing the table of follow-up, follow up on time                               | 44/181    |
| Flexible study time and location                                                    | 41/181    | Handle adverse reactions timely during the study                                     | 40/181    |
| Researchers should adhere to the basic ethical principles                           | 32/181    | The drug package should be accompanied by information about the process of trials, the use of medication, and adverse reactions | 27/181    |
| At each visit, checking compliance by counting the remaining medications with participants | 26/181    | Online data collection                                                              | 25/181    |
| Emphasizing the importance of the participants’ diary and checking in time          | 21/181    | Fixed researchers and healers                                                       | 21/181    |
| Improving the environment of treatment                                             | 17/181    | Intervention by pharmacists during the study (strengthening medication guidance and supervision, designing reasonable individual treatment plans, and improving the quality of medical services) | 13/181    |
| Establishing a record system to dispense medicines and packing medicines according to the system | 13/181    | Intervention by nurses during the study                                              | 11/181    |
| Reimbursement of traffic                                                            | 10/181    | Conducting motivational interviews                                                   | 7/181     |
| Paying in cash                                                                     | 6/181     | Establishing a record system to remind doing inspection                              | 4/181     |
| Reporting the effects at any time during the study to allow patients to dynamically understand their progress | 4/181     |                                                                            |           |

**Appendix**

**Appendix table 1 Studies included in the review**
| Study ID                        | Health conditions specified | Funding | The country of first author | Sample population | Design                          | Sample size | Data source (for Secondary studies only) |
|--------------------------------|----------------------------|---------|-----------------------------|-------------------|---------------------------------|-------------|----------------------------------------|
| Soumya J. Niranjan2019[9]      | Cancer                     | No      | USA Researchers             | Adults            | Interview                       | 91          | Not applicable                         |
| Eleanor Ladd Schneider Leavens2019[10] | NR                         | No      | USA NR                      | Implementation research | 42                      | Not applicable |
| Laura A. Novak 2019[11]        | Post-traumatic stress disorder(PTSD) | No      | USA Adults                  | Survey            | 666                             | Not applicable |
| Zhou Q2019[12]                 | Cancer                     | Public  | USA Adults                  | Survey            | 110                             | Not applicable |
| Wisk LE2019[13]                | Diabetes                   | Industrial | USA College students        | Survey            | 227                             | Not applicable |
| JS Liang2019[14]               | NR                         | Public  | China NR                    | Retrospective analysis of RCTs | 82                      | 8 RCTs     |
| MK Yu2019[6]                   | NR                         | Public  | China NR                    | Literature Review  | NR                              | Not applicable |
| Henshall C 2018[15]            | Diabetes                   | Public  | England Adults              | Interview         | 20                              | Not applicable |
| Rachel Schoor2018[16]          | Multiple sclerosis         | Public  | USA Adults                  | Motivational interview | 75                      | Not applicable |
| Grace Cannard K2018[17]        | Parkinson                  | Industrial | USA Adults                  | Survey            | 29                              | Not applicable |
| Annette Grape2018[18]          | Asthma                     | Public  | USA Children                | Implementation research | 373                     | Not applicable |
| Anne Daykin2018[19]            | NR                         | Public  | England NR                  | Interview         | 22                              | Not applicable |
| Arame Thiam-Diouf2018[20]      | HIV                        | Public  | USA NR                      | Systematic review and meta-analysis | 964                     | 10 Studies |
| YS Xu2018[21]                  | NR                         | No      | China NR                    | Survey            | 22                              | Not applicable |
| Joshua Wynne2018[22]           | HIV                        | No      | England Women               | Implementation research | 322                     | Not applicable |
| Sophie G 2018[23]              | HIV                        | Public  | USA Adults                  | Interview         | 25                              | Not applicable |
| Chhatre S2018[24]              | Cancer                     | Public  | USA Adults                  | Implementation research | 551                     | Not applicable |
| Rosalind J 2018[25]            | Ebola                      | Public  | USA Healthcare providers, or Ebola front-line workers | RCT | 7979                     | Not applicable |
| H xiong2018[26]                | NR                         | No      | China Adults                | Retrospective analysis of RCTs | 371                     | Not applicable |
| Okhomina V2018[27]             | Cardiovascular disease     | Public  | USA Adults                  | Cohort study      | 375                             | Not applicable |
| Rios-Romenets S2018[28]        | Alzheimer                  | Public  | Colombia Adults             | Implementation research | 252                     | Not applicable |
| Ulrich C M2018[29]             | Cancer                     | Public  | USA Adults                  | Retrospective analysis based on RCTs | 27443               | 134 RCTs |
| Hepatitis                      | Public                     | China   | Adults                       | Retrospective     | 620                             | 1 RCT       |
| Author                  | Number | Country  | Age Group    | Research Design          | Sample Size | Notes                  |
|-------------------------|--------|----------|--------------|--------------------------|-------------|------------------------|
| JX Tao2018[30]          |        |          |              | Retrospective analysis based on RCTs | 90          | Not applicable         |
| JH Liu 2018[31]         | NR     | No       | China        | Adults                   | 56          | 4 RCTs                 |
| J Yang2018[32]          | NR     | No       | China        | NR                       |             |                        |
| Joanna C Crocker 2018[33]| NR   | No       | England      | NR                       | 2222        | 6 Studies              |
| Boada M 2018[34]        | NR     | No       | Spain        | NR                       |             |                        |
| HL Duan 2018[35]        | NR     | No       | China        | NR                       |             |                        |
| Babatunde O A 2017[36]  | NR     | No       | USA          | Seniors                  | 412         | Not applicable         |
| Julia Lawton 2017[37]   | NR     | No       | England      | Researchers              | 22          | Not applicable         |
| J. Lloyd 2017[38]       | NR     | No       | England      | Children                 | 1324        | Not applicable         |
| David A. Rorie 2017[39] | NR     | No       | England      | NR                       | 31695       | Not applicable         |
| HM Wang 2017[40]        | NR     | No       | China        | Adults                   | 15          | Not applicable         |
| Pfammatter A F 2017[41] | NR     | No       | USA          | Adults                   | 150         | Not applicable         |
| Kati A K 2017[42]       | NR     | No       | Finland      | Adults                   | 1139        | Not applicable         |
| Anna Kearney 2017[43]   | NR     | No       | England      | Researchers              | 75          | Not applicable         |
| Paul A. Leighton 2017[44]| NR    | No       | England      | Adults                   | 26          | Not applicable         |
| Theresa A 2017[45]      | NR     | No       | South Africa | Pregnant women           | 1354        | Not applicable         |
| Beishuizen C R L 2017[46]| NR    | No       | Netherland   | Seniors                  | 2994        | Not applicable         |
| Megan Comerford 2017[47]| NR     | No       | India        | Adults                   | 387         | 1 RCT                  |
| Robert S. Ware 2017[48] | NR     | No       | USA          | Adolescent with mental retardation | 556         | Not applicable         |
| ZC Cai 2017[49]         | NR     | No       | China        | Adults                   | 70          | Not applicable         |
| JJ Jin 2017[50]         | NR     | No       | China        | NR                       | 200         | 19 RCTs                |
| YW Zhang 2017[51]       | NR     | No       | China        | NR                       | 828         | 38 RCTs                |
| Y Jin 2017[52]          | NR     | No       | China        | NR                       | 405         | 24 RCTs                |
| Kadam R A 2016[53]      | NR     | No       | Industrial   | Researchers              | 73          | Not applicable         |
| Ashley Salazar 2016[54]  | NR     | No       | USA          | Pregnant women           | 9 RCTs      |                        |
| Authors | Disease | Study Type | Country | Group | Setting | Study Method | Sample Size | No. of RCTs |
|---------|---------|------------|---------|-------|---------|--------------|-------------|------------|
| CJ Feng 2016[55] | Diseases of the endocrine system | No | China | Adults | Retrospective research from RCT | 410 | 15 RCTs |
| Thayabaranathan T 2016[56] | Stroke | No | USA | Nurse | Interview | 2 | Not applicable |
| Atherton P J 2016[57] | Cancer | Public | USA | Adults | Retrospective research from RCT | 1640 | 14 RCTs |
| HB Zhang 2016[58] | Cancer | No | China | Adults | Retrospective research from RCT | 36 | 1 RCT |
| Miguel AQ 2016[59] | Cocaine dependence | Public | Brazil | Adults | RCT | 65 | Not applicable |
| ComeliA 2016[60] | HIV | Public | China | Women | Interview | 212 | Not applicable |
| HY fan 2016[61] | Hypertension | Public | China | Adults | Retrospective research from RCT | 614 | 18 RCTs |
| HY Li 2016[62] | Cancer | No | China | Adults | Implementation research | 60 | Not applicable |
| H Zhang 2016[63] | NR | Public | China | NR | Theoretical research | NR | Not applicable |
| GX Chen 2016[64] | NR | No | China | NR | Theoretical research | NR | Not applicable |
| Louise Robinson 2016[65] | NR | No | England | Children | Systematic review and meta-analysis | 154 | 28 RCTs |
| Eivind Berge 2016[66] | Stroke | No | Norway | NR | Survey | 46 | Not applicable |
| Thomas M 2016[67] | NR | No | USA | NR | Retrospective research from RCT | NR | Not applicable |
| Erica EM 2016[68] | Schizophrenia | Public | Canada | NR | Literature Review | NR | 48 Studies |
| V C Brueton 2015[69] | Smoking/Headache/Asthma, etc | Public | England | NR | Systematic review and meta-analysis | 4751 | 38 Studies |
| Natalie A. Johnson 2015[70] | Alcohol addiction | No | USA | Adults | Retrospective research from RCT | 837 | 1 RCT |
| Boden-Albala 2015[71] | Stroke | No | USA | Adults | Mixed methods approach | 93 | Not applicable |
| Blaha Robert Z 2015[72] | Traumatic Brain Injury | No | USA | Adolescent | Implementation research | 132 | Not applicable |
| Barbro L 2015[73] | Diabetes | No | USA | Children | Retrospective research from RCT | 8677 | 1 RCT |
| Amy Corneli 2015[74] | HIV | No | USA | Women | Mixed methods approach | 312 | Not applicable |
| Langford D P 2015[75] | Fracture | Public | Canada | Seniors | RCT | 30 | Not applicable |
| David olds 2015[76] | NR | Industrial | USA | Adults | Focus group interview | 5969 | Not applicable |
| XX wang 2015[77] | Cancer | No | China | Adults | Single-arm clinical research | 80 | Not applicable |
| L Zhang 2015[78] | NR | No | China | NR | Retrospective research from | 1351 | 40 RCTs |
| Researcher          | Year | Study Type | Country        | Population/Setting                        | Methodology                                                                 | Study Size | Study Details                      |
|---------------------|------|------------|----------------|-------------------------------------------|-----------------------------------------------------------------------------|------------|------------------------------------|
| M Yang              | 2015 | NR         | China          | NR                                        | Theoretical research                                                        | NR         | Not applicable                     |
| Joseph A            | 2015 | Cancer     | USA            | NR                                        | Theoretical research                                                        | NR         | Not applicable                     |
| L Mood              | 2015 | NR         | Public Portland| Persons with physical disabilities       | Literature Review                                                            | NR         | Not applicable                     |
| Anjanette A         | 2015 | Major depressive disorder | USA | No | Interview | 9 | Not applicable |
| Florence Clark      | 2014 | NR         | USA            | Seniors                                   | Retrospective research from RCT                                             | 460        | 1 RCT                              |
| Marjorie C          | 2014 | Hearing loss | USA            | Farm operators                            | RCT                                                                          | 709        | Not applicable                     |
| Mary Fischer       | 2014 | Osteoporosis | USA            | Women                                     | Interview                                                                   | 43         | Not applicable                     |
| W Wang              | 2014 | Chronic obstructive pulmonary disease | China | Seniors | RCT | 150 | Not applicable |
| XW Qiao             | 2014 | Respiratory diseases | China | Adults | Interview | 52 | Not applicable |
| Busisiwe Magazi     | 2014 | HIV        | South Africa   | Women                                     | Focus Group Interview                                                       | 102        | Not applicable                     |
| Olubukola T Idoko   | 2014 | NR         | Gambia         | Children                                  | Retrospective research from RCT                                             | 300        | 1 RCT                              |
| Romina Kim          | 2014 | Smoking    | USA            | Patients with mental illness              | Retrospective research from RCT                                             | 100        | 1 RCT                              |
| LP Mai              | 2014 | NR         | China          | NR                                        | Retrospective research from RCT                                             | NR         | 10 RCTs                            |
| Q Zhang             | 2014 | NR         | China          | NR                                        | Theoretical research                                                        | NA         | Not applicable                     |
| YG Li               | 2014 | Diabetes   | China          | NR                                        | Retrospective research from RCT                                             | 51         | 14 RCTs                            |
| P Huang             | 2014 | NR         | China          | NR                                        | Theoretical research                                                        | NA         | Not applicable                     |
| YG Li               | 2014 | NR         | China          | NR                                        | Theoretical research                                                        | NA         | Not applicable                     |
| J Wei               | 2014 | NR         | China          | NR                                        | Theoretical research                                                        | NA         | Not applicable                     |
| Wenke Zheng         | 2014 | NR         | China          | NR                                        | Retrospective research from RCT                                             | NR         | Not applicable                     |
| Lopes R T           | 2014 | Major depressive disorder | Portugal | Adults | RCT | 63 | Not applicable |
| S Knippschild       | 2013 | Cataract   | Germany        | NR                                        | Literature Review                                                           | 2834       | 18 Studies                         |
| Plummer M           | 2014 | HIV        | England        | Women                                     | Retrospective research from RCT                                             | 1305       | 1 RCT                              |
| Warner E            | 2013 | Overweight/Hypertension | USA | Adults | Implementation research | 474 | Not applicable |
| Murphy E            | 2013 | Major depressive disorder | USA | NR | Retrospective research from RCT | 3222 | 1 RCT |
| Author                  | Condition                                | Location | Population | Setting | Study Type                          | Methods | Subjects | Outcomes | Year |
|-------------------------|------------------------------------------|----------|------------|---------|-------------------------------------|---------|----------|----------|------|
| Margaret Pribulick 2013 | Cardiovascular disease                   | Public   | USA        | Rural women | Retrospective research from RCT | 167     | 1 RCT    |          |      |
| V C Brueton 2013        | NR                                       | No       | England    | Researchers | Interview                          | 29      | Not applicable |          |      |
| CC Xia 2013             | Stroke                                   | No       | China      | Adults    | Implementation research            | 68      | Not applicable |          |      |
| Lewis AL 2013           | Smoking                                  | Public   | USA        | Adolescent| Retrospective research from RCT   | 98      | 1 RCT    |          |      |
| SY Liu 2013             | Cancer                                   | No       | China      | Women     | Implementation research            | 20      | Not applicable |          |      |
| SJ Hu 2013              | Asthma                                   | No       | China      | Adults and Children | Retrospective research from RCT | 68      | 1 RCT    |          |      |
| Atassi N 2013           | Amyotrophic lateral sclerosis            | Industrial | USA      | NR       | Literature Review                  | 1815    | 55 Studies |          |      |
| Koog Y H 2013           | Arthritis                                | No       | Korea      | NR       | Systematic review and meta-analysis | 13593   | 266 Studies |          |      |
| Gatehouse C S 2012      | Oral ulcer                               | Industrial | USA     | Adults   | Retrospective research from RCT   | 160     | 1 RCT    |          |      |
| YY Kou 2012             | Cancer                                   | No       | China      | Adults   | Implementation research            | 68      | Not applicable |          |      |
| QW Rao 2012             | NR                                       | No       | China      | NR       | Theoretical research               | NR      | Not applicable |          |      |
| YM Hu 2012              | NR                                       | No       | China      | NR       | Retrospective research from RCT   | 954     | 48 RCTs  |          |      |
| Vellas B 2012           | Alzheimer                                | Public   | France     | NR       | Theoretical articles               | NR      | Not applicable |          |      |
| Hui D 2012              | Cancer Palliative Treatment              | Public   | USA        | NR       | Retrospective research from RCT   | 1214    | 18 RCTs  |          |      |
| Y Zhang 2012            | NR                                       | No       | China      | NR       | Theoretical research               | NR      | Not applicable |          |      |
| Bradley N Collins 2011  | Smoking                                  | Public   | USA        | Pregnant women | Implementation research | 279     | Not applicable |          |      |
| Deborah A 2011          | Tuberculosis prevention trial            | No       | USA        | Adults   | Interview                          | 355     | Not applicable |          |      |
| Sue Penckofer 2011      | Diabetes                                 | No       | USA        | Women    | Theoretical research               | NR      | Not applicable |          |      |
| Brubaker L 2011         | Pelvic floor disorder                    | No       | USA        | Women    | Focus group interview              | 105     | Not applicable |          |      |
| L J Burgess 2011        | NR                                       | No       | South Africa | Adults   | Survey                            | 302     | Not applicable |          |      |
| Kalkhuis-Beam S 2011    | Smoking                                  | Public   | USA        | Adolescent | RCT                            | 710     | Not applicable |          |      |
| XN Wang 2011            | Stroke                                   | No       | China      | Adults   | Retrospective research from RCT   | 92      | Not applicable |          |      |
| J Xiong 2011            | Asthma                                   | No       | China      | NR       | Retrospective research from RCT   | NR      | 1 RCT    |          |      |
| Lesley J Burgess 2010  | NR                                       | No       | South Africa | NR       | Retrospective research from RCT   | 1386    | 50 RCTs  |          |      |
| Anne-Marie              | End-stage renal disease                  | Public   | USA        | Adults   | Implementation                      | 58      | Not applicable |          |      |
| Study ID            | Research Area                  | Country   | Setting    | Sample Size | Study Design          | Result  | Applicable |
|---------------------|--------------------------------|-----------|------------|-------------|------------------------|---------|------------|
| Shields 2010        | Heart failure                  | No        | China      | NR          | RCT                    | 64      | Not applicable |
| CM Zhai 2010        | Alzheimer                      | Industrial| USA        | NR          | Literature Review      | NR      | Not applicable |
| Grill J D 2010      | Diabetes                       | Public    | USA        | Adults      | Implementation research| 276     | Not applicable |
| Magner R 2010       | NR                             | No        | USA        | Adults      | Retrospective research | NR      | Not applicable |
| Gul B R 2010        | Smoking                        | Public    | Sweden     | Adults      | Interview              | 30      | Not applicable |
| D. Lindström 2010   | Cancer                         | No        | China      | Adults      | Interview              | 20      | Not applicable |
| YJ Huang 2010       | NR                             | No        | China      | Adults      | Theoretical research   | NR      | Not applicable |
| DC Fan 2010         | NR                             | No        | China      | NR          | Theoretical research   | NR      | Not applicable |
| DC Fan 2010         | NR                             | No        | China      | NR          | Theoretical research   | NR      | Not applicable |
| GD Lu 2009          | Cancer/Chronic obstructive pulmonary disease/Asthma | No        | USA        | NR          | Retrospective research | NR      | 1 RCT     |
| Merran Toerien 2009 | NR                             | Public    | England    | NR          | Literature Review      | NR      | Not applicable |
| HY Liu 2009         | Digestive diseases             | No        | China      | Adults      | Survey                 | 112     | Not applicable |
| LJ Tian 2009        | NR                             | Public    | China      | NR          | Survey                 | 326     | Not applicable |
| SX Wang 2009        | NR                             | Public    | China      | Adults      | Survey                 | 632     | Not applicable |
| Guzmán Anglica 2009 | Overweight                     | No        | USA        | Children    | RCT                    | 123     | Not applicable |
| Claire S Leathem 2009 | Coronary heart disease      | No        | Ireland    | Doctors and patients | Survey | 903     | Not applicable |
| Chang MW 2009       | Overweight                     | Public    | USA        | Women       | Retrospective research | NR      | 1 RCT     |
| Cox LE 2009         | HIV                            | Public    | USA        | Adults      | Survey                 | 238     | Not applicable |
| X Zhang 2009        | NR                             | No        | China      | NR          | Theoretical research   | NA      | Not applicable |
| XX Wang 2009        | NR                             | Public    | China      | NR          | Theoretical research   | NA      | Not applicable |
| YP Bao 2009         | NR                             | Public    | China      | NR          | Literature Review      | 2831    | 18 RCTs   |
| SM Xue 2009         | Orthopaedics                   | NO        | China      | NR          | Theoretical research   | NR      | Not applicable |
| Sharika Gappoo 2009 | HIV                            | No        | South Africa | Women      | Implementation research| 5045    | Not applicable |
| Higginson Irene 2008 | Multiple sclerosis palliative care service | No        | England    | Adults      | Interview              | 52      | Not applicable |
| Siddiqi A 2008      | Cancer                         | No        | USA        | Adults      | Implementation research| 713     | Not applicable |
| GD Lu 2008          | NR                             | No        | China      | NR          | Retrospective          | 1181    | Not applicable |
| Author et al.                     | Type          | Country  | Region       | Description                                                                 |
|----------------------------------|---------------|----------|--------------|-----------------------------------------------------------------------------|
| GD Lu2008                        | Theoretical   | China    | NR           | Research from RCT                                                          |
| SS Bull2008                      | Implementation| USA      | NR           | Research from RCT, 2623                                                     |
| Victoria Villacorta2007           | Implementation| Peru     | Esquineros/Men/Movidas | Research from RCT, 1263                                                |
| Russell E Glasgow2007             | Overweight    | USA      | Adults       | Research from RCT, 2311, 1 RCT                                              |
| J Xiao2007                        | Theoretical   | China    | NR           | Research from RCT                                                          |
| Andrew Maurice2006                | Cancer        | England  | Women        | Research from RCT                                                          |
| Mor M2006                         | Intestinal polyps | USA    | Adults       | Survey, 31, Not applicable                                                  |
| Lynette Dias2005                  | Myopia        | USA      | Children     | Research from RCT                                                          |
| Constance M 2005                  | Sexually transmitted infections | USA | Women       | Research from RCT, 376, 1 RCT                                              |
| Avins A L2005                     | Cancer        | USA      | Adults       | Case report, 1, Not applicable                                              |
| Steven K2005                      | Major depressive disorder | Portland | Adults  | Interview, 31, Not applicable                                              |
| J Li2005                          | Theoretical   | China    | NR           | Research from RCT                                                          |
| Raymond E G2004                   | Pregnancy     | USA      | Women        | Research from RCT, 1514, 1 RCT                                              |
| Mazzuca S A2004                   | Arthritis     | USA      | Women        | Research from RCT, 432, 1 RCT                                              |
| de Bruyn G2004                    | HIV           | USA      | Adults       | Research from RCT, 3033, 48 RCTs                                            |
| Sears S R2003                     | Cancer        | USA      | Women        | Research from RCT, 558, 1 RCT                                              |
| Bruce G2003                       | Asthma        | USA      | Children     | Research from RCT, 1041, 1 RCT                                              |
| Adubato S 2003                    | Lead-exposure | USA      | Children     | Research from RCT, 780, 1 RCT                                              |
| J Zeng 2003                       | Theoretical   | China    | NR           | Research from RCT                                                          |
| Sonawalla Shamsah B2002           | Major depressive disorder | USA    | Adults       | Research from RCT, 119, 1 RCT                                              |
| Bulpitt CJ2001                    | Hypertension  | England  | Seniors      | Research from RCT, 4695, 1 RCT                                              |
| David C Mohr1999                  | Multiple sclerosis | USA | NR          | Mixed methods approach, 939, Not applicable                                 |
| G Jónasson                       | Asthma        | Norway   | Children     | Research from RCT, 163, 1 RCT                                              |
| Year   | Title                                      | Country | Study Type          | Participants | Study Design                                                                 | N  | Type   |
|--------|--------------------------------------------|---------|---------------------|--------------|-------------------------------------------------------------------------------|----|--------|
| 1999   | Cancer Palliative Treatment                | Public  | Norway              | Adults       | Survey                                                                        | 434| Not applicable |
| 1999   | Panic Disorders                            | No      | USA                 | Adults       | Retrospective research from RCT                                               | 162| 1 RCT  |
| 1999   | Asthma                                     | No      | USA                 | Adults and children | Retrospective research from RCT                                               | 362| 1 RCT  |
| 1999   | Periodontal disease                        | No      | USA                 | NR           | Implementation research                                                        | 70 | Not applicable |
| 1999   | Cancer                                     | Public  | USA                 | Women        | Retrospective research from RCT                                               | 55 | 1 RCT  |
| 1999   | Alcohol addiction                          | Public  | USA                 | Men          | Retrospective research from RCT                                               | 105| 1 RCT  |
| 1999   | Cancer                                     | Public  | Canada              | Adults       | Retrospective research from RCT                                               | 280| 1 RCT  |
| 1999   | Smoking                                    | No      | USA                 | Adults       | Retrospective research from RCT                                               | 73 | 1 RCT  |
| 1999   | HIV                                        | Public  | USA                 | Adults       | Retrospective research from RCT                                               | 40 | 1 RCT  |
| 1983   | Arthritis                                  | Industrial | Norway         | Adolescent  | Implementation research                                                        | 80 | Not applicable |
| 1982   | Hypertension                               | No      | USA                 | Adults       | Retrospective research from RCT                                               | 1012| 1 RCT  |

**Note**

USA: the United States of America

RCT: Randomized controlled trial

Not Reported: NR

**Figures**
Figure 1

Study flow diagram

Figure 2

Annual outputs of publications regarding participants compliance in clinical trials from 1982 to 2019.
Figure 3

The word cloud about factors affecting the compliance

Supplementary Files

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- PRISMA2009Checklist.pdf