The Conduct of Randomised Controlled Trials in China: Quality of Trial Reports and Stakeholders' Views

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Abstract

China is an emerging force in undertaking randomised clinical trials. The quality of trials from China may affect not only its own substantial population but also potentially contribute to health policy throughout the world. However, little is known about the quality of clinical trials conducted there. In this thesis, I will evaluate the quality of published Chinese randomised controlled trials (RCTs) by comparing them with Indian RCTs as well as a set of 'gold standard' trials reported in leading European and North American journals. I will also describe and contrast the quality and biases within Chinese RCTs. I then explore the reasons for these differences from the point of view of the major RCT stakeholders: Chinese clinicians and patients. The potential influences from Chinese traditional culture is also evaluated.

I conducted both quantitative and qualitative research in this thesis. The first systematic review was about randomised controlled trials (RCTs) conducted in China and published in 2004. This was undertaken to describe their characteristics, assess the quality of their reporting, and where possible, the quality of their conduct. The second systematic review was to undertake a comparative empirical analysis of RCT reports published in selected Chinese, Indian and European or North American medical journals. Quality was assessed against a subset of criteria from the CONSORT statement. I compared the rate of reporting of positive outcomes in clinical trials to describe potential bias. I also conducted qualitative research in 3 hospitals of Guangzhou, interviewing clinicians and patients to explore their understanding,

attitude and personal experiences toward conducting and participating in RCTs.

Three hundred and seven Chinese papers, 117 Indian papers and 304 Western papers were included. In the Chinese papers, 199 (64.8%) failed to report methods of randomization and 254 (82.4%) did not report blinding of either participants or investigators. Reporting of baseline characteristics, primary outcome and length of follow-up was inadequate in a substantial proportion of studies. Fewer than 11% of RCTs described ethical approval and only 18% adequately discussed informed consent. However, dropout rates were favourable, with nearly 44% of trials reporting a zero dropout rate. Reports of Indian trials were slightly better than Chinese papers on trial reporting quality indicators and much better than Chinese papers on reporting patients' ethical issues. However Western trial reports scored considerably higher on all quality criteria. Non-linear mixed models with a logit link and binomial/ normal error inferred that Chinese papers were substantially more likely to report statistically significant results (OR=2.96, 95% CI 2.23 to 3.94; P<0.0001). Indian trials reported a similar rate of positive results to the gold standard Western papers (OR=0.92, 95% CI 0.69 to 1.24; P=0.59).

The RCT as a research method was developed in Western countries and exported to China. This created potential conflict within the traditional Chinese medical system, including the doctor-patient relationship and issues of ethics. Chinese clinicians have the dilemma of being either a clinical doctor or of being a medical researcher. Chinese culture and the current Chinese medical system block doctors' understanding of and participation in RCT research.

Chinese patients place extreme trust in their clinicians, therefore Chinese clinicians find it easy to recruit patients to RCTs and this is also reflected in the good compliance rate. However, the uncertainty from involvement in? RCTs affects the trust between clinicians and patients.

The reporting of trials in major Chinese and Indian journals is inadequate, and may reflect underlying inadequacies in the design and conduct of these trials. Chinese trials appear biased and may selectively report positive outcomes while ignoring neutral or negative outcomes. In order to improve the quality of RCT reporting and conduct, the Chinese medical system needs to make changes at a systemic level. Research work should be considered as an important part of being a modern Chinese clinician. Journal editors in China and India should adopt the CONSORT reporting guidelines, should ensure that a primary outcome is prespecified and reported, and should ensure that analysis is conducted according to the intention to treat principle. Ethical questions in the conduct of trials in China must be addressed.

Four years after my first study of the quality evaluation of Chinese RCTs, I also updated my review of the quality of Chinese trials and compared it with my previous systematic review result, hoping to detect an improvement in the quality of Chinese RCTs

Two hundred and forty-two papers were included. Compared to my previous research, Chinese published RCTs had a significant improvement on their description of informed consent, ethical committee approval and the reporting of a primary outcome. 11 (4.6%) RCTs reported adequate concealment of

patient allocation, and, 100% of the papers used P value to describe the results from statistical tests. Compared to 2004, the positive result rate OR= 1.01, 95% CI 0.81 to 1.27, P=0.93.

Ethical committee approval and reporting of participants' informed consent have been improved significantly. However, reporting of RCTs in China needs substantial improvement to meet the target of the CONSORT statement.

Chinese medical journal editors need to undertake more training on the reporting of RCTs; all medical societies should take more concern about doctors' research work; the Chinese public media should help the general population to understand more about RCT principles.

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Chapter 1. INTRODUCTION

Outline

In this chapter, I will introduce the basic knowledge and important theory relating to the conduct and reporting of Randomised Controlled Trials.

Randomized controlled trials (RCT) are considered the 'gold standard' for assessing the effectiveness of pharmacological and other interventions in the field of medicine[1-4], which provide the best evidence on the effects of health care interventions. They are widely accepted as the best research design because they distribute both known and unknown prognostic factors between treatment groups by the play of chance thereby minimising the possibility that any treatment effect is due to bias or confounding (that is, other factors which are systematically different between the treatment groups), and providing the basis for valid statistical comparison[5-8]. Reports of RCTs provide evidence for health care providers and policy makers to make decisions on whether to use new health technologies in their patients. However, RCTs vary in their methodological rigour, and it is well known that poor quality studies tend to produce systematically different results from larger, better quality studies; often erroneously showing larger treatment effects.[9;10] Many medical journals now expect authors to adhere to internationally agreed standards of reporting thus allowing the reader to assess the conduct of each trial[11]. In order to maximise the benefits from increased knowledge, a high-quality publication should always report the characteristics and results of a RCT. Previous work has indicated that the methodological quality of an RCT is reflected in the

quality of such reports[12;12;13] Through the RCT publications I can thus evaluate the trial's conduct and quality in developing research contexts.

1.1 Clinical trial

Evaluation of the effectiveness of treatments for diseases has historically been fraught with problems and was often not conducted in a systematic way. It is now generally accepted that well conducted clinical trials are the most reliable means for evaluating the efficacy and safety of new treatments.

1.2 Clinical trials and statistics

Statistics play an important role in medical research, including generalizing observations and combining knowledge. Randomised controlled trials are considered to be the best combination of clinical observation and statistics[14] .

A clinical trial is an experiment testing medical treatment on human subjects. Sir Austin Bradford Hill described clinical trials elegantly I[15]:

In the assessment of a treatment, medicine always has proceeded and always must proceed, by way of experiment. The experiment may merely consist in giving the treatment to particular patient or series of patients and of observing and recording what follows- with all the difficulty of interpretation. Of distinguishing the propter hoc from the post hoc. Nevertheless, even in these

circumstances and in face of unknown a question has been asked of nature, and it has been asked by means of trial in human being. There can be no possible escape from that. This is human experimentation of one kind at least. Somebody must be the first to exhibit a new treatment in man. Some patient, whether for good or ill, must be first to be exposed to it.

1.3 Bias and Bias control

'Bias' is a deviation that is not a consequence of chance alone[16]. The direct consequences of bias may be impossible to see. However, some biases, such as patient selection effects, appear to be strong compared with the modest size of many treatment effects. Cochrane handbook had summarised different types of biases in clinical trials in table, which I used partly in table 1.1 ,

Table 1.1. Bias categories and effects[16] (part of Cochrane handbook for system reviewers of interventions)

Type of bias	Description
Selection bias.	Systematic differences between baseline characteristics of the groups that are compared.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.
Attrition bias.	Systematic differences between groups in withdrawals from a study.
Detection bias.	Systematic differences between groups in how outcomes are determined.
Reporting bias.	Systematic differences between reported and unreported findings.

There are many types of bias in medical studies. In randomized trials, selection bias may not be as serious a problem, because it affects each group equally and therefore does not influence the estimated treatment difference. Selection bias is not the only one which made effect to clinical studies, Treatment administration, outcome assessment and counting endpoints can be biased either.

Statistical biases are those that arise from using certain methods, test and analysis procedures and selection from alternative procedures. A preferential selection of positive study result rather than neutral or negative results leads to reporting bias. Another strong bias in data analysis is from inappropriate exclusion of eligible study subjects, that is called attrition bias. Usually, there are some excellent clinical reasons for making these exclusions, therefore this kind of bias is difficult to eliminate.

Detection bias is another potential difficulty. Patients and clinicians' self-assessments and report will not be objective if they have personal expectation on treatment. Therefore trial designs that use subjective assessment are necessary and important.

There were studies indicating that in trials with subjective outcomes effect estimates were exaggerated when there was inadequate or unclear allocation concealment or lack of blinding[17]. There was little evidence of bias in trials with objective outcomes. The average bias associated with defects in the conduct of randomised trials varies with the type of outcome.

1.3.1 Randomization

Randomization is the principal method to reduce selection bias. It is effective because it guarantees the differences between the treatment groups are only attributable to chance, the effect from chance can be accounted through statistics. Therefore, the remaining differences can be attributed to the treatment. The benefit of randomization is that it prevents confounding, even if the investigator is unaware that the effects exist or has not measured them.

Chance was explained in many ways which relative to God or chaos, which is an unpredictable issue, As Barrow said in his brief but interesting discussion[18]

'Dabbling with random devices was serious theological business. Not something to be trifled with [or] merely studied for the fun of it.'

In WesternWestern science, randomization was used in medical studies by Bradford Hill and Richard Doll in Great Britain in the 1940s[14], Randomisation is widely used for preventing bias in allocating treatments in comparative clinical trials. Randomization does not secure complete objectivity in a trial and must be combined with other design strategies to reduce bias[14].

1.3.2 Blinding

Blinding is an important mean to reduce assessment bias. 'Single blind' means that the participants in the study are unaware of which treatment they receive. 'Double blind' means both participators and clinicians are unaware of treatment. In order to make blinding work properly in practice, placebo is usually helped to make sure the treatment which look, taste and feel same to participants. A masked placebo control is different from a no-treatment control. In the latter case, the difference of treatment will include 'placebo effect' which is from participants' personal expectation of the treatment. For example, in studies comparing analgesics[16], patients might overstate the benefit if they know they are receiving a new drug. Thus, blinding can improve objectivity among participants and investigators.

Double blinding further increases the usefulness of subjective endpoints, because investigators can also be influenced by their expectations[16]. This is especially true if the investigator has been exposed to seemingly favourable pre-clinical data, believes strongly in the biological basis on which the therapy was developed, or has professional or financial interest in the success of the study. Effective treatment masking is essential in such cases.

1.3.3 Objective assessments

In clinical trials, the methods of evaluating study endpoints should be objective in order to minimize assessment bias and increase the reproducibility of findings.

1.3.4 Active follow-up and endpoint ascertainment

Attention should be given to methods of assessing endpoint, even if these endpoints can be objectively defined, such as disease recurrence and death. If a trial relies only on passive reporting of such events, the chance for bias is increased.

1.3.5 Concealment

Proper allocation concealment helps to ensure the random allocation in trials. Without adequate allocation concealment, the effectiveness of random, unpredictable assignment sequences can be compromised[9;19;20]. In practice, in taking care of individual patients, clinical investigators often find it difficult to maintain impartiality. In order to dictate the allocation of their next patient, investigators hold up sealed envelopes to lights[21]. This introduces selection biases and confounding to the results of the study.

Piantadosi suggested the following standard methods of ensuring allocation concealment include[16]:

- Sequentially-Numbered, Opaque, Sealed Envelopes (SNOSE)
- Sequentially-numbered containers
- Pharmacy controlled
- Central randomization, Central allocation （Which has become the most commonly used in large RCTs approach these days）

1.3.6 Intention-to-treat

Intention-to-treat (ITT) was consider as a principle that patients should be analysis in randomised controlled trial. All randomised patients should be involved in analysis, 'regardless of their adherence with entry criteria, regardless of the treatment they actually received, regardless of subsequent withdrawal from treatment'[22].

1.4 Ethical issues

1.4.1 The Helsinki Declaration

Helsinki declaration is widely adopted all over the world, which includes full issues of ethics for clinician engaged in clinical research[23]. It strengthen that individual patients' interest is prior to any biomedical and clinical research. It outlines some principles; including those research involving human subjects must conform to generally accept scientific principles, having a written protocol, be conducted only by qualified individuals and include written informed consent from the participants.

1.4.2 Clinician's new role

Statisticians have long played a significant role in clinical trials, in purely clinical tasks, there is relatively little need for statistical and reasoning[14]. Clinical researches require clinicians taking researcher's roles including critical and quantitative views of research designs and data, which are different to clinician's traditional role in clinic. Clinicians are required to

perform, report, and interpret clinical research studies requires statistical modes of reasoning.

1.4.3 Ethic issue of clinical research

Ethical considerations should be of continuing concern through the design and conduct of clinical trial. The general ethical requirements of clinical research world wide are outlined in the declaration of Helsinki issued by the World Medical Association. This brief document has been accepted internationally as the basis for ethical research[23].

1.4.3.1 Individual versus collective ethics

Individual ethics imply that each patient should receive that treatment which is best benefit to his health condition. This is the clear aim of good clinical practice in which the patient and his doctor decide together on what is the best course of action. Usually clinicians would determine therapy on the basis of his knowledge, experience and opinion with appropriate acknowledgement of patient's wishes.

Collective ethics is concerned with achieving medical progress as efficiently as possible so that all patients may subsequently benefit from superior therapy. One could argue that collective ethics is aimed at future patients while individual ethics is about that patient who requires treatment now. 'Exclusive adherence to collective ethics is an unacceptable stance to adopt'[24]. However, There is research demonstrating that patients in trials are better cared for than those in general clinical practice.[25]

1.4.3.2 Informed consent

The declaration of Helsinki states that in clinical research 'the doctor should obtain the subject's free-given informed consent, preferably in writing'.

Informed consent is a vital concern in clinical trials[23]. There are numerous examples of studies where patients have been exposed to potentially or definitely harmful treatments without being fully appraised of the potential risks. Sick or dying patients and their families are vulnerable and it is questionable how much technical information about new treatments they can truly understand, especially when it is presented to them quickly or at a time of crisis. This problem arises when using treatments already know to be effective as well as when testing experiments ones. It is interesting that informed consent procedures, originally developed to protect research subjects from exploitation, are now viewed by many practitioners as devices to protect themselves from litigation[23].

1.5 The quality standard of RCT publications

Study, design, conduct and writing up are closely related. We conduct studies not only to test hypotheses but also to share the results to broaden the community's knowledge. A good report will give details on how the study was conducted so the reader may consider the applicability of the study's population, intervention and results to his or her own patients. It follows that a study then needs to be conducted in a way that captures important reporting details----descriptors of the study population and appropriate documentation

of outcomes. Thus, it is appropriate to consider the details and article will report while the study is being designed.

In Chan's study,[ref] they found there were some differences between the study protocol and the final research publications on the report of outcomes. Outcomes with negative results were more often 'ignored' in final publications, which was considered a publication bias. However, there is limited research on detecting differences of RCT quality issues between reporting and what actually happened.

1.5.1 The CONSORT statement

In 1996, a group of scientist, editors and statisticians assembled to objectively evaluate what elements of an article were necessary for reader to assess the validity of a study's background, conduct, results and conclusions[11]. The Consolidated Standards for Reporting Trials (CONSORT) statement was developed to guide the reporting of randomized controlled trials (RCTs). The original 50 items detailing essential reporting elements of the title, abstract, introduction, method, results and discussion were simplified to 22 in 2001 and have become the standard of reporting in most major medical journals for RCTs[27]. More than 25 % of the CONSORT statement focuses on methods of randomization, masking and follow-up of the large cohort in RCTs[10].

The publication of CONSORT statement in 1996 was an important step toward improving, reporting, standards. That year, Ophthalmology and several

other medical journals adopted the CONSORT standards and subsequently the revision in 2001[27]. The first study of CONSORT standard compliance in the reporting ophthalmology RCT from 1991 to 1994 was published by Scherer and Crawley[28]. In 2001, Sanchez-Thorin and colleagues conducted a similar analysis and found that the quality of RCT reporting had improved since the adoption of the CONSORT standards, but still left 'room for improvement'.[29] Nowadays, standards of scientific reporting have evolved from very beginning of scientific reporting. Virtually all journals now publish instructions for authors and most medical journals adhere to certain standards of publication. The CONSORT statement have been promoted by international groups such as the International Committee of Medical Journal Editors (ICMJE) and Committee on Publication Ethics (COPE), which is the general RCT requirement of all leading medical journals[30].

1.5.2 ICH-E9

ICH-E9 was the first comprehensive document of its kind to create a single global reference for a broad range of statistical principles in clinical trials[31]. It also helped establish a foundation for the practice of statistics in clinical trials for statisticians and non-statisticians worldwide. While statisticians have long played a significant role in clinical trials in some parts of the world, ICH-E9 gave a credible voice to statisticians who need an authoritative reference on topics of great relevance for the scientific design, conduct, analysis and interpretation of clinical trials[31]. In that sense, it brought statistical considerations to a broad audience of scientists involved in clinical trials. Although ICH-E9 served us very well over the last decade, and its principles

are as valid today as ever, it may be time to supplement the document with current issues and thinking.

ICH-E9 has achieved much of its overarching goal of harmonization of statistical practice in regulated clinical research for drug development, there are evidence show that protocol development, statistical analysis planning and even the role of the statistician have changed in many positive regards[32] ICH-E9 has also served as an excellent educational tool for statisticians embarking on a career in clinical trials. It is widely known and referenced by pharmaceutical statisticians.

ICH –E9 put in one place a wide range of major topics for consideration and defined consensus opinions for the underlying statistical and scientific principles relevant to those topics. Besides definitive statements on well-worn topics such as bias, randomization and multiplicity, it brought greater focus and clarity to[33]:

- Intention-to- treat (ITT) and defined a new concept termed the full analysis set, which allowed the proper use of ITT principles in a typical trial of new medicine.
- Confirmatory versus exploratory trials, although the latter garnered limited discussion and was defined by exclusion.
- Interim analysis and Interim Data Monitoring Committees.
- Superiority and non-inferiority, although it fell short on the issue of the definition of effect ‘margin’.

- Pre-specified statistical analysis plans and the need to stipulate not only the analysis methodologies, but also the handing of protocol deviations/violation that impact analyses.

1.6 Research background

1.6.1 General introduction

Chinese medical authors and chief medical editors appear all to be clinicians. The Chinese Medical Association is the main medical organization of Chinese medical doctors, which includes 82 branch associations on different disease areas and 430,000 members across mainland China[34]. The journal series of the Chinese Medical Association includes 71 journals, which comprise the core medical journals in Mainland China. The Chinese Medical Association is an academic and non-government organization and its members are all qualified medical professionals. The journal series includes the most influential medical journals, which should represent the highest quality of Chinese medical research. The leading Medical editors are all clinicians; they view and make comments on medical publications for the journal series of the Chinese Medical Association. Therefore, I concentrate on clinicians as my research group as the most important group who influence the conduct and reporting of Chinese randomized controlled trials.

I searched in both Chinese and English language but found no similar research had been done before on a Chinese population. Therefore, I conducted a series of qualitative research interviews with clinicians and patients, including personal interviews of senior doctors and patients and focus group meetings of junior doctors in order to explore their knowledge and attitude towards randomized controlled trials. The purpose of this was to explore the reasons for Chinese medical authors producing unsatisfactory RCT papers and to attempt to identify the barriers to conducting and reporting better RCTs, as well as exploring what could be done to improve the quality of RCTs.

1.6.2 Health in China and Guangzhou

China is one of the largest countries in the world. It expands to over 9.6 million square kilometers and houses a population of more than 1.3 billion people. It consists of 23 provinces, 5 autonomous regions, 4 municipalities and Hong Kong and Macao special Administrative regions.

The rapid economic development after the reform and opening up policy, especially the economic transformation in recent years, has resulted in improved living conditions, nutrition and health care. The birth rate has decreased from 33.43‰ in 1970 to 12.40‰ in 2005[35].The death rate has decreased from 7.6‰ in 1970 to 6.51‰ in 2005. Infant mortality decreased

from 47.0‰ in 1970's to 32.2‰ in 2000[36]. Life expectancy increased from 66.4 to 69.6 in men and from 69.3 to 73.3 in women during 1981 to 2000[37].

Figue 1.1 location of Guangzhou

Guangdong is a big province in south China with a population of 91,940,000.(2005 projection from China Ministry of Health). Guangzhou is the provincial capital of Guangdong province. (Figure 1.1) It is a city of more than 10 million population. The birth rate and the death rate in Guangzhou are 9.56‰ and 5.74‰ respectively in 2004, which are slightly lower than the national level. Guangzhou is the leading economic and cultural city in southern China.

1.6.3 General introduction of medical doctor

A physician, medical practitioner or medical doctor is a person who practices medicine and is concerned with maintaining or restoring human health through the study, diagnosis and treatment of disease and injury[38].

Medical doctors are traditionally considered to be members of a learned profession because of the extensive training requirements and also because of the occupation's special ethical and legal duties. Physicians are often members, or fellows of local professional organizations.[38]

In ancient history medical issues were strongly connected to magic. All human societies have medical beliefs that provide explanations for birth, death, and disease. Throughout history illness has been attributed to witchcraft, demons, adverse astral influence, or the will of the Gods[39]. These ideas still retain some power with faith healing and shrines still used in some places, although the rise of scientific medicine over the past millennium has altered or replaced many of the old beliefs. The practice of medicine has ancient associations with religion and magic; healers were treated as a god to save people from ailments, for example, in China, famous ancient doctors are all named as ‘medical god’ or ‘magic doctor’. The traditional relationship between the doctor and patient is like the relationship between a magic saint and a normal person; patients consequently have extreme respect for doctors[40].

In China, medical doctors belong to the upper-social class[41], even in poor rural areas. Most hospitals are located in downtown areas due to people's reliance on public transportation in China. More than 80% of Chinese medical resources are concentrated in urban areas, and the rest in rural areas. Medical doctors are considered scientific professionals and are representatives of modern science.

1.6.4 Chinese hospital system

Chinese hospitals are classified as three general levels, with level 3 at the top and level 1 at the bottom[41]. Each level has sub-levels of A, B and C. Some elite hospitals are 3As. Physicians used to be hired as full-time and lifetime employees at a government controlled hospital. But both physicians and hospitals now have more freedom in choosing each other.

For a government-controlled hospital[42], the hospital is still operated and managed by a management team under the leadership of the president of the hospital, who is usually nominated and appointed by the healthcare department of a province, a city or a county. However, for a private hospital or a publicly traded hospital, the ownership is the same as that of a private company or a public company. Medical doctors usually have an employment contract with the hospital they work with, and a person can quit at will. The hospital can also terminate the individual's employment if they are not satisfied with the employee's performance or morality.

Not all Chinese hospitals could currently conduct clinical trials. The Chinese Food and Drug Administration had a strict regulation for all the hospitals on clinical trial activities. Only those hospitals considered to provide superior medical techniques and with clinicians with adequate clinical trial knowledge which pass the evaluation from CFDA will have the approval to conduct clinical trials. For different phases of clinical trial, the required standards vary. Through gaining appropriate qualification, the hospital could participated in medical research, especially those multi-centre, international randomised controlled trial are which may appear quite attractive. Therefore, this qualification is consider as an honour to many hospitals. The requirements are more like to be achieved by those 3A hospitals, those big hospitals with a large number of clinicians. There are 449 hospitals in Guangzhou, 28 of them are 3A hospitals.

1.6.5 RCT in Chinese medical education

RCT Research is a new word to traditional Chinese clinicians[43], but methodological courses of medical research are now required by medical school. Therefore, current Chinese medical school graduates have the basic knowledge of medical research methods, including clinical trials.

However, the RCT as an experimental method is new to those clinicians who graduated from medical school 20 years ago or more. There was subject discrimination in medical school which derives from Chinese culture and

society, with the clinical course the principal concerned of the teacher and students. Clinicians were expected to do their work with patients to improve patients' health condition in previous times. Surgeons as a group received most respect among doctors, because they could perform operations and save a patient's life, even in the war they could join the army immediately. Surgeons are followed in prestige by physicians, who are considered as highly skilled people who could help patients in daily life, old (that means experienced) physicians also may be particularly admired by patients. These groups are followed in prestige by the third kind of people who work in hospitals but do not conduct clinical jobs, such as epidemiologists or medical statisticians.

Non-clinical students are still the group of students with lowest entry scores in medical school. Therefore it is hard to say this discrimination has disappeared totally. Another reflection of this discrimination is the difference in incomes. Due to the direct link between clinical work and financial income, Surgeons have the most opportunity to receive grey income, because they would be the direct person to make effect on patients' bodies. The term grey 'income' was coined in China after 1978 when the country implemented its policy of reform and opening-up. It describes the significant portion of urban residents' income that is outside the scope of state supervision and control. Second come physicians, but not epidemiologist or statisticians. Therefore, those people who are potentially skilled in research design and research conduction do not work in hospitals, and thus could not help professional clinicians when conducting research work.

Summary

In this chapter I introduced randomized controlled trial and all of its essential items, which are the theoretical principles of this thesis. In chapter 2 and 3, I will evaluate the quality of Chinese RCT publication and compare with leading WesternWestern medical journals and Indian medical journals on the basis of these principal items. In chapter 4 and 5, I will try to explain the reason of difference from RCT stakeholders: Chinese clinicians and patients, by presenting the fieldwork result. In chapter 6, I will review 2008-09 Chinese RCT and compared with previous research, in order to see any change on Chinese RCT publication quality. In chapter 7, I will explore the intension of Chinese clinicians and patients' behaviours through multi-aspect.

Chapter 2. An assessment of the quality of randomized controlled trial conducted in China in 2004 and an updated assessment on 2008-09

Outline

In this chapter, I conduct a systematic review largely derived from the CONSORT statement, to evaluate the quality of main published Chinese RCTs. I found the quality of Chinese published RCTs needs to improve in many items.

China is a developing country with the biggest population of any country in the world. Research in China has been rapidly gaining momentum, but as yet there has been no systematic evaluation of the current standard of trials conducted there. Evaluations of the quality of Chinese RCTs have been restricted to a few selected journals and a limited list of quality indicators[44-46] . For example, a recently published systematic review of the effectiveness of hyperbaric oxygen using Chinese RCTs found that the published papers reported inadequate information and were generally of poor quality.[47]

I present a critical evaluation of randomised controlled trials conducted in China and published in 2004. My aim was to infer the general level of research in China and make suggestions for improvements in the design, conduct and reporting of Chinese RCTs.

2.1 METHODS

2.1.1 Search strategy

Search strategy

Randomised controlled trials published in 2004 were identified through two broad sources:

1. Using the PubMed database. PubMed includes MEDLINE and OLDMEDLINE[48] but papers published in many non-English Journals are not listed. I searched PubMed for Chinese randomised controlled trials published in 2004 using the textwords 'chin*' and the PubMed filter for randomised controlled trials.

2. Since many of the main medical journals in China are not indexed in PubMed, or in any electronic database, I also accessed the online versions of each journal in the Journal Series of the Chinese Medical Association. The Journal Series of the Chinese Medical Association includes 71 journals, which comprise the main core medical journals in Mainland China and additionally the Chinese version of the British Medical Journal.

I used the same search strategy as we used for our previous study

For both sources, reference lists of included studies were checked. No language or other limitations were imposed. I translated Chinese text into English, and another Chinese author helped me in some cases. Titles were initially scanned for relevance and abstracts read if titles were unclear. The full text of papers with no abstract was viewed and checked for eligibility.

2.1.2 Inclusion and exclusion criteria

I included any papers reporting randomised controlled trials on all disease groups and all types of interventions, which were published in 2004, took place in China and included Chinese citizens. I excluded reports that did not include any participants from Mainland China. I excluded papers from Hong Kong and Taiwan where research and clinical practice may be different from those from the Mainland.

Same inclusion and exclusion criteria were applied on the research of 2008-09.

2.1.3 Assessment of quality

The quality of each trial was assessed using a standard checklist based on the CONSORT statement, an internationally agreed standard for reporting RCTs.[11] I also added some customised indicators in order to extract further information specific to the Chinese papers. I did not use overall quality scores or categories to judge each paper because the use of summary scores is known to be problematic and often obscures individual aspects of quality.[49]

Table 2.1. Indicators used to describe and evaluate included randomised controlled trials

I**ndicator**		**Description**
Descriptive indicators		
1	Publication language	Chinese or English
2	Nationality of authors	Chinese, international or collaboration
3	Funding source	As reported
4	Disease area	Simple categories
5	Choice of comparator interventions	Placebo/alternative treatment/no treatment
6	Size of trial	Number of participants
7	Ethical committee approval	Yes/No
8	Informed consent from participants	As reported
Quality of reporting: CONSORT indicators		
9	Sample size	How was sample size determined?
10	Randomisation	Was the trial randomised?
11	Allocation concealment	What method was used to implement the random allocation sequence?
12	Blinding	Whether or not patients and/or investigators were blinded to group assignment
13	Baseline characteristics	Were the baseline demographic and clinical characteristics of each group reported
14	Primary outcomes	Did they report which outcome was designated as the primary outcome?
15	Length of follow-up	As reported
16	Loss to follow-up	As reported
17	Statistical reporting	Were confidence intervals or p values reported to indicate precision?

2.1.4 Data extraction and analysis

One reviewer extracted data from all included papers. A second reviewer independently checked a random sample of 26% of the papers. Discrepancies were resolved where possible by discussion, and the sample results compared with the full results using Kappa scores. Data on the quality of the included papers were presented in tabular format accompanied by a critical description.

2.2 RESULTS

2.2.1 Search results

Figure 2.1 describes the results of the search and the identification of eligible trials. Among 372 identified papers 29 papers were initially excluded as they were duplicate publications. Of the remaining 343 studies 307 (89%) clearly described that their patients were allocated randomly to treatments and therefore were included as confirmed RCTs. Thirty-six studies were excluded as they either were not, or could not be confirmed as, RCTs (table 2.2).

271 papers were identified from Pubmed and 104 papers were from journal series of the Chinese medical association. 25 duplicate papers were excluded, 108 papers were excluded on the basis of the abstract. 242 papers were included in the study. (figure2.2.)

Figure 2.1. Flow chart of selection decisions of 2004

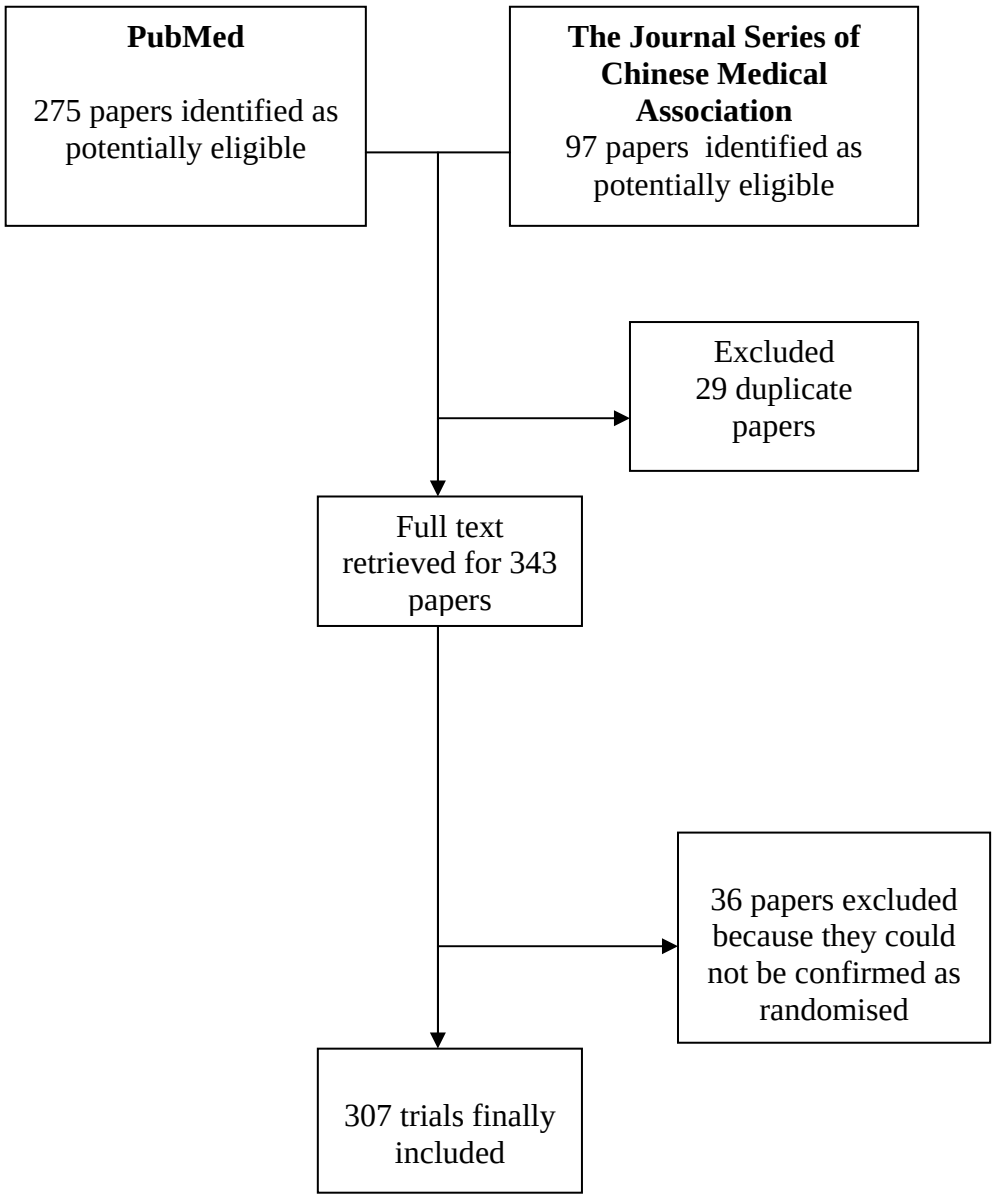

Figure 2.2. Flow chart of selection decisions of 2008-09

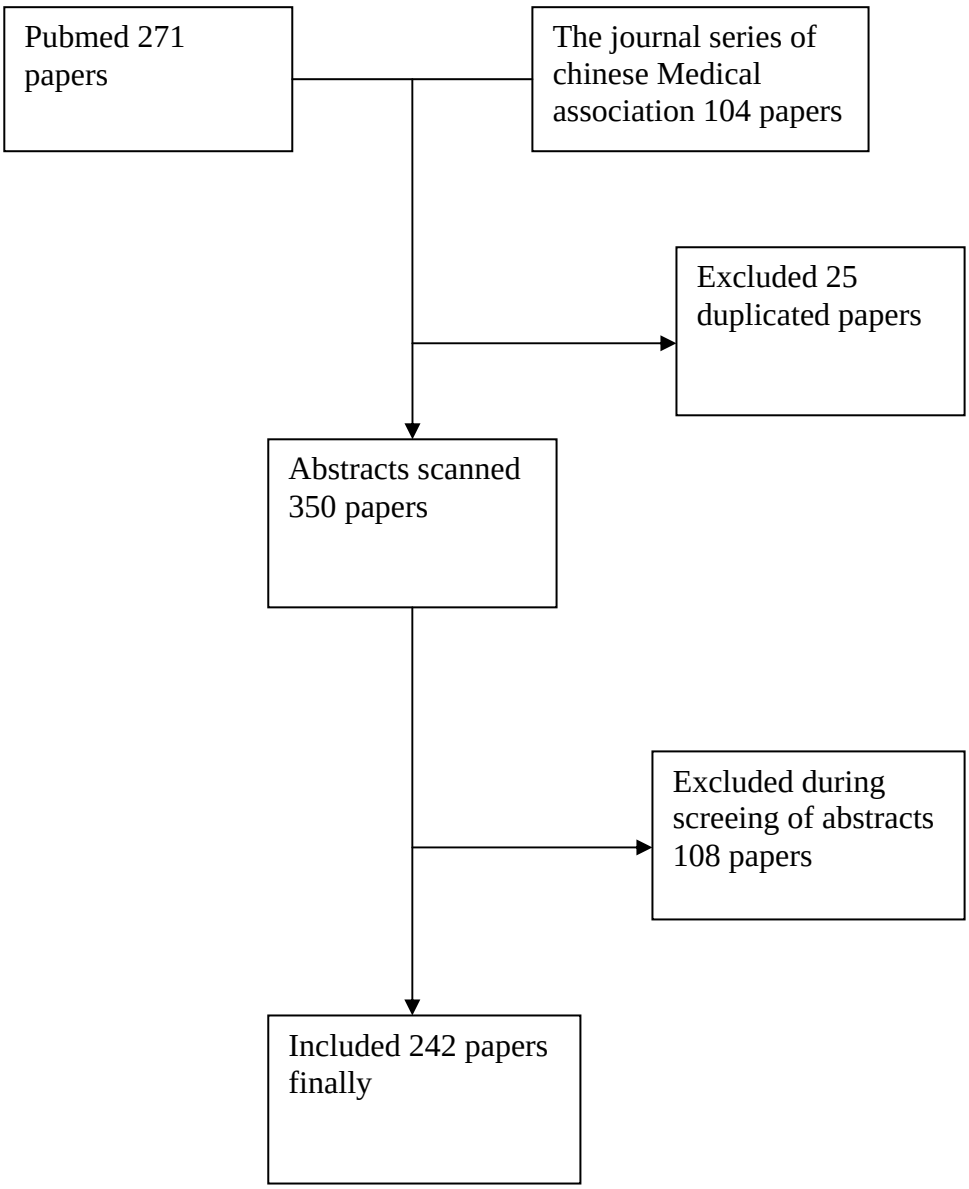

Table 2.2 Reasons for excluding papers

Reason for exclusion	Number of papers
Before/after studies	17
Brief report given only	6
Case control study	5
No control arm	4
Randomisation not mentioned in full text	2
Allocated by patients' choice	1
Allocated by patients' economic status	1
Total	36

2.2.2 Agreement between reviewers

Agreement between the reviewers was good with a kappa score of greater than 0.7 for the main indicators (Funding source 0.73, disease area 0.8, choice of comparator interventions 0.75, ethical committee approval 0.72, informed consent from participants 0.73, sample size 0.86, randomisation 0.76, allocation concealment 0.78, blinding 0.75, baseline characteristics 0.75, primary outcomes 0.8, loss to follow-up0.6, length of follow-up 0.62, statistical reporting 0.71)

2.2.3 Characteristics of the included trials in 2004

2.2.3.1 Publication language

Of the 307 included RCT papers, 259 (84%) were written in Chinese. The remaining 48 papers were published in English.

2.2.3.2 Nationality of authors

292 (95%) included papers were written by authors based in Chinese research institutes; the remaining papers were collaborations between Chinese and foreign researchers. There were no trials conducted or reported only by foreign researchers.

2.2.3.3 Funding source

Of the 307 papers, 232 (75.6%) did not report their sources of funding. Funding was from provincial/municipal and national sources in 38 trials (12.4%) and 23 trials (7.2%) respectively. Foreign pharmaceutical companies, universities, international research agencies and the military financed five or fewer trials each.

2.2.3.4 Disease area

Fifty (16.3%) of the RCTs focused on diseases of the digestive system (Table 3). The second most published disease area was disease of the circulatory system with 48 papers (15.6%), followed by tumours with 42 papers (13.7%) and diseases of the urogenitary system (37 papers (12.1%)). Central nervous

system, motor system and respiratory system diseases each had approximately 5% share of the total number of trials as did the category of primary prevention or health promotion. One hundred and twenty-two of the included papers (39.7%) reported studies of traditional Chinese treatments such as traditional Chinese medicine (TCM), massage and acupuncture.

Table 2.3 Disease area of included trials

Disease area	*Number of papers*	*Percent*
Digestive system diseases	50	16.3
Circulatory system diseases	48	15.6
Tumours*	42	13.7
Urogenital system diseases	37	12.1
Nervous system diseases	16	5.2
Motor system diseases	16	5.2
Healthy population	15	4.9
Respiratory system diseases	15	4.9
Endocrine system diseases	12	3.9
Immune system diseases	9	2.9
Others	47	15.3
Total	307	100

2.2.3.5 Choice of comparator interventions

Thirty-nine (12.7%) of the included trials compared active treatment with a placebo group. Three of these were randomised controlled crossover trials where participants were blinded to the order of drug taken. In 179 (58.3%) trials the new treatment being tested was compared with an alternative active treatment, and in 79 (25.7%) trials the new treatment was compared with a treatment described as the "standard", but with no specific details. Seven additional studies included a control group receiving no treatment: three of them were health education and promotion projects, two of them were health rehabilitation and two drug trials. A further three papers described trials with three different treatment arms: active treatment, standard treatment and no treatment.

2.2.3.6 Size of the trials

The number of participants in each included trial ranged from 3 to 19200, with a median of 78.

2.2.3.7&8 Ethical issues (Ethics Committee Approval and Informed Consent)

Only 33 (10.8%) of the included Chinese trials reported approval by an ethics committee. The majority of the study reports (249 or 81%) did not provide any information about informed consent although 54 (17.6%) of papers stated that the participants did give consent. The remaining four studies stated that participants were included in the trial of their own free will.

2.2.3.9 Sample size

Only nine (2.9%) of the 307 papers mentioned sample size calculation.

2.2.3.10&11 Methods of randomisation & allocation concealment

Table 2.4 Methods of randomisation

Methods of randomisation	Number of papers (%)
Not clear	199 (64.8%)
Random number sheet	73 (23.8%)
Random allocation card	13 (4.2%)
Sealed envelope	11 (3.6%)
Computer allocation	7 (2.3%)
Toss of a coin	4 (1.3%)
Total	307 (100%)

In nearly two-thirds of the included trials (Table 2.4) the authors failed to report details of their methods of randomisation. Seventy-three (23.8%) of the trials reported using a random number table to allocate participants; 13 (4.2%) a random allocation card; 11 (3.6%) a sealed envelope; 7 (2.3%) computer allocation and 4 (1.3%) the toss of a coin. Twenty-four trials allocated participants using visit order that were included in the "not clear" group. No trial mentioned allocation concealment.

2.2.3.12 Blinding

254 (82.7%) papers provided no information about blinding of either participants or investigators. In 39 (12.7%) trials, both the investigators and participants were blinded. In 9 (2.9%) trials the participants were not blind,

and in 5 (1.6%) the investigators were not blinded to the participants' treatments.

2.2.3.13. Reporting of baseline characteristics

Eighty-nine (29%) of the included papers fully reported the baseline characteristics of the participants in a separate table. Two hundred and nine (67%) of the papers described baseline characteristics using either text or mixed tables, which also included results. In 9 papers (2.9%) only age was given in the baseline information, and in two papers no information was given other than a statement that the baseline characteristics matched in both arms.

2.2.3.14. Reporting of primary outcomes

Only 11 (3.6%) of the included trials indicated which measure was used as the primary outcome; the remainder merely reported a list of results from which it was not possible to distinguish which outcome was the primary.

2.2.3.15. Length of follow-up

Table 2.5 Length of follow up of included RCTs (days)

Days of follow-up	Number of papers (%)
Not clear	105 (34.2%)
0-30	85 (27.7%)
31-90	43 (14.0%)
91-365	43 (14.0%)
366-3650	31 (10.1%)
Total	307 (100.0%)

Table 2.5 details the distribution of length-of-follow-up for participants in the included studies. In 105 (34.2%) of papers, there was no information about the length of time for which participants were followed. The mean length of follow-up (where stated) was 166 days, although the median (interquartile range) was 56 (8 to 360) days.

2.2.3.16. Loss-to-follow-up

Table 2.6 Dropout rate of included trials

Dropout rate (%)	Number of papers	Percent	Cumulative Percent
0	165	53.7	53.7
less than 5%	32	10.4	64.1
> 5% but < 10%	23	7.5	71.6
>10% but < 25%	18	5.9	77.5
More than 25%	12	3.9	81.4
Not clear	57	18.6	100.0
Total	307	100.0	

Over half of the trials (165 studies – 53.7%) reported that no participants had dropped out (Table 2.6). Sixty-four percent of all the clinical trials showed a drop out rate of 5% or less by the end of the study, and overall 70% of all the trials had a drop out rate lower than 10%. Fifty-seven (18.6%) studies failed to report dropout rates.

2.2.3.17. Statistical reporting

The majority of the papers (298 trials or 97.1%) conducted and reported test for statistical precision rather than calculating and reporting confidence intervals. In only 20 papers (6.5%) did the authors use confidence intervals to describe the uncertainty around their estimates?

2.2.3.18 Subgroup analysis

The main quality indicators of trials included double blinding, allocation concealment, report of primary outcome, ethical approval and informed consent. In the subgroup analysis I explored the differences in trials quality and their associations with individual trials' characteristics.

Publication language

Of the 307 included RCT papers, 259 (84%) were written in Chinese. The remaining 48 papers were published in English.

Chi-square tests were used. There are significant differences on double blinding, type of treatment, ethical approval and informed consent between different publication languages.

Table 2.7 Statistical analysis for publication language associated to RCT papers characteristics

	RCT papers characteristics				
	Double blinding	Traditional Chinese treatment	Primary outcome	Ethical committee approval	Informed consent
Chi-square	10.85	17.6	3.7	20.11	79.1
P value	0.002	<0.0001	0.054	<0.0001	<0.0001
OR	3.26	0.18	2.7	5.2	16.4
95% CI	1.57-6.80	0.07-0.43	0.92-11.68	2.39-11.36	7.9-33.3

*OR= 1 means compared with papers published in English, Chinese RCT papers have the same rate on reporting those characteristics.

OR > 1 showed that Chinese papers denoted a lower rate of reporting those characteristics, with worse quality.

- Authorship

Of the 307 included RCTs, 292 (95%) were written by authors based in Chinese research institutes; the remaining papers were collaborations between Chinese and foreign researchers. There were no trials conducted or reported only by foreign researchers.

There are significant difference between different author ship on double blinding, type of treatment, ethical approval and informed consents.

Table 2.8 Statistical analysis for authorship associated to RCT papers characteristics

	RCT papers characteristics				
	Double blinding	Traditional Chinese treatment	Primary outcome	Ethical committee approval	Informed consent
Chi-square	13.96	4.59	0.43	4.16	62.4
P value	0.0002	0.032	0.51	0.04	<0.0001
OR	0.16	4.5	2	0.30	0.01
95% CI	0.06-0.47	1.0-20.4	0.24-20	0.09-1.02	0.001-0.09

*OR= 1 means compared with papers written by Chinese authors, combined authors' RCT papers have the samrate on reporting those characteristics.

OR < 1 showed that combined authorship denoted a higher rate of reporting those characteristics, with good quality.

- Size of the trials

The number of participants in each included trial ranged from 3 to 19200, with a median of 78.

In statistical analysis, Trials were allocated to 5 different groups for the trials size: 3- 100, 101-500, 501-1000, 1001-5000, 5001-19200, There are significant differences among different trial size groups on primary outcome and ethical committee approval.

Table 2.9 Statistical analyses for trial size associated to RCT papers characteristics

	RCT papers characteristics				
	Double blinding	Traditional Chinese treatment	Primary outcome	Ethical committee approval	Informed consent
Chi-square	7.2	6.75	13.33	22.6	6.4
P value	0.12	0.15	0.01	<0.0001	0.16

- Western vs. traditional Chinese medicine

One hundred and twenty-two trials were about traditional Chinese medicine, the rest 185 were about Western medicine. There was significant difference on report of double blinding, primary outcome, ethical committee approval and informed consent.

Table 2.10 Statistical analyses for different treatments associated to RCT papers characteristics

RCT papers characteristics				
	Double blinding	Primary outcome	Ethical committee approval	Informed consent
Chi-square	9.32	7.5	11.7	22.4
P value	0.002	0.006	0.001	<0.0001
OR	3.3	1.06	5.49	7.1
95% CI	1.49-7.7	1.03-1.1	1.89-16.1	2.78-16.6

*OR= 1 means compared with those about Western treatment papers, traditional Chinese papers have the same effect size on reporting those characteristics.

OR > 1 showed that traditional Chinese treatment papers denoted a lower rate of reporting, those characteristics, with worse quality.

- Pubmed vs Non-Pubmed

Two hundred and thirty-nine trials were included from Pubmed, the rest 68 were from Journal series of Chinese Medical Association. There are significant difference between Pubmed and non-Pubmed papers on report of double blinding and informed consent.

Table 2.11 Statistical analyses for Pubmed papers associated to RCT papers characteristics

RCT papers characteristics					
	Double blinding	Traditional Chinese treatment	Primary outcome	Ethical committee approval	Informed consent
Chi-square	4.7	3.84	0.1	3.65	8.26
P value	0.03	0.051	0.74	0.056	0.004
OR	0.32	0.58	0.77	0.31	0.25
95% CI	1.07-9.06	0.33-1.0	0.16-3.67	0.91-10.5	1.47-12.18

OR= 1 means compared with Pubmed papers, Non-Pubmed papers have the same rate on reporting those characteristics.

OR < 1 showed that Pubmed papers denoted a higher rate of reporting those characteristics, with good quality.

2.2.4 Characteristics of the included trials of 2008-09

2.2.4.1 Publication language

Of the 242 included RCT paper, 148 (61%) were written in Chinese. The remaining 94 (39%) were written in English.

2.2.4.2 Funding source

Of the 242 paper, 149 (62%) did not report their source of funding. funding was from provincial/municipal and national source in 42 (17%) trials and 36 (15%) trials respectively. The pharmaceutical industry funded 8 (3%) trials, international research agencies funded four trials and universities funded three trials.

2.2.4.3 Disease Area

Sixty-four (26.5%) of the RCTs focused on diseases of the circulatory system. Motor system disease was the second most commonly represented disease with 32 trial reports (13.2%), followed by urogenital system disease with 26 papers (10.7%), digestive system disease 25 papers (10.3%), oncology with 24 papers (9.9%) and nervous system diseases with 15 papers (6.2%).

Papers reporting trials concerned with the respiratory system, endocrine system, immune system disease and primary prevention or health education each had approximately 5% share of trials.

Table 2.12 Disease area of include trials

Disease area	Number of papers	percent
Circulatory system disease	64	26.5
Motor system disease	32	13.2
Urogenital system	26	10.7
Digestive system disease	25	10.3
Tumours	24	9.9
Nervous system disease	15	6.2
Healthy population	12	5.0
Respiratory system disease	10	4.1
Endocrine system disease	6	2.5
Immune system disease	6	2.5
Others	22	9.1
Total	242	100

2.2.4.4 Size of trials

The number of participants in each included trial ranged from 9 to 30283, with a median of 80.

2.2.4.5&6. Ethical committee approval and informed consent

Of the 242 paper, 107 reported approval by ethical committee, 133 reported they have participators' informed consent for the trial.

Quality of reporting

2.2.4.7. Methods of Randomisation

Table 2.13 Methods of Randomisation

Method	Number of papers (%)
Not clear	139(57.4%)
Random number table	39(16.1%)
Patient visit order	29(12.0%)
Computer allocation	24(9.9%)
Sealed envelop	7(2.9%)
Toss coin	4(1.6%)
Total	242 (100%)

One hundred and thirty-nine (57.4%) papers failed to report the method of method of randomisation. 39 (16.1%) of the trials reported using random

number table to allocate participants, 29 (12.0%) patients visiting order, 24 (9.9%) computer allocation, 7 (2.9%) sealed envelop and 4 (1.6%) toss coin.

2.2.4.8. Blinding

One hundred and seventy-five (72.3%) papers provided no information about blinding of either participants or investigators. 29 (12.0%) papers reported they did double blind in their trial. 18 (7.4%) papers reported they did single blind. The remaining 20 papers reported they were open trials.

2.2.4.9. Allocation Concealment

Of 242 included paper, 11(4.6%) mentioned they used allocation concealment clearly in text. 24(9.9%) trials allocated participators by computer and 39 (16.1%) by random number table, but they did not have a clear statement of using them as allocation concealment.

2.2.4.10. Reporting of baseline characteristics

One hundred and sixty-two (66.9%) of the included papers reported the baseline characteristics of participators in a separate table. 48 (19.9%) papers describe baseline characteristics using mixed table or text. 32 (13.2%) papers only describe participators' age and sex as baseline characteristics.

2.2.4.11. Report of primary outcomes

Only 28 (11.6%) papers indicated which measurement was used as their primary outcome. In the remaining 214 (88.4%) trials, it is not clear which one (if any) was prespecified to be the primary outcome.

2.2.4.12. Statistical reporting

All the included RCTs report their statistical result by using statistical tests and P-values. Only 24 (9.9%) papers used confidence interval to describe the uncertainty around their estimates of treatment effect.

2.2.4.13. Length of follow up

The mean length of follow-up was 221 days, the median (interquartile range) was 32 days.

2.2.4.14. Loss to follow up

181 (74.8%) of include trials reported they have no participators drop out. 82.2% of all included papers showed a drop out rate of 5% or less, and 90.1% of all the trials had a drop out rate lower than 10%.

2.2.4.15. Intention-to-treat

Two of 242(0.8%) of included papers described ‘intention-to-treat’ as their data analysis principle.

2.2.5 Change between 2008-09 and 2004

I compared trials from the 2008-09 and 2004 cohorts on the main trial quality indicators. Compared to 2004, 2008-09 Chinese published RCTs had a significant improvement on their description of informed consent, ethical committee approval and report the reporting of a primary outcome. In 2008-09 period, 11 (4.6%) RCTs reported they did concealment on the patient allocation, and 100% of the papers used P value to describe the statistical result from statistical tests.

Table 2.14 The results comparison between 2004 and 2008-09 period

	N=307 number of reported (%)2004	N=242 number of reported (%) 2008-09	2008-09 OR (compared with 2004)	95% CI	P
Concealment	0	11(4.6%)	999	-	<0.001*
Double blind	39(12.7%)	29(12.0%)	0.94	0.559-1.566	0.80
Informed consent	54(17.6%)	133(55.0)	4.14	3.79-8.24	<0.001*
Ethical committee approval	33(10.8%)	107(44.2%)	6.36	4.1-9.87	<0.001*
Primary outcome	11(3.6%)	28(11.6%)	3.52	1.71-7.25	0.0007*
P-Value	298(97.1%)	242(100%)			<0.01*
Confidence interval	20(6.5%)	24(9.9%)	1.58	1.18-2.94	0.1489
Intention- to-treat	11(3.6%)	2(0.8%)	0.22	0.05-1.03	0.0542

2.2.6 Exploring Sub-groups

Papers from 84 different journals were included in the research on journal quality in 2004 and 114 journals included in 2008-09. 26 journals were represented in both data sets. I did an additional supportive analysis on these 26 journals, in order to examine whether there is evidence of the difference in reporting quality in the same journals between different periods.

In this sub-group exploratory model, I also considered the individual journals as the random effects. I found, the report of ethical committee approval was improved significantly. However surprisingly, the report of double blinding and confidence interval was decreased significantly.

The positive outcome reporting rate over time

Through the result from non-linear mixed model, I found no evidence of change in the reporting of the rate of positive results from all included journals between different time periods. The trials from 2008-09 have the similar positive result rates to trials published in 2004, (OR= 1.01, 95% CI 0.81 to 1.27, P=0.93). In the sub-group analysis of the 26 journals reporting trials in both time periods we also found no evidence of a reduction in the high rate of positive result reporting (OR=1.20, 95% CI 0.80 to 1.80, P=0.3766).

Table 2.15 The results comparison between 2004 and 2008-09 on 26 journals

26 journals	2004 N=86 number of reported (%)	2008/9 N=89 number of reported (%)	2008-09 OR (compared with 2004)	95% CI	P
Concealment	0	1(1.1%)			0.9
Double blind	18(20.9%)	5(5.6%)	0.22	0.078-0.646	0.0059
Informed consent	20(23.3%)	32(36.0%)	1.8526	0.947-3.62	0.0714
Ethical committee approval	13(15.1%)	26(29.2%)	2.317	1.087-4.939	0.0297
Primary outcome	6(7.0%)	1(1.1%)	0.1515	0.017323-1.325	0.0876
P-Value	84(97.7%)	89(100%)			0.47
Confidence interval	11(12.8%)	3(3.4%)	0.2378	0.0628-1.109	0.0348
Intention- to treat	7(8.1%)	2(2.2%)	0.259	0.05118-1.3152	0.1026

2.3 Discussion

2.3.1 Key results

The study of trial quality is rare in developing countries, and tends to focus on limited clinical areas[50;51] . Although among Chinese publications there are a

few papers which describe trial quality in specific journals or fields[47;52-57], this is the first systematic study to evaluate the quality of trial conduct and reporting in a sample which is likely to be more representative of Chinese RCTs in general.

My review revealed that the standard of reporting of trials was generally poor, which concurs with the other published reports on Chinese trials[47;52;55;57]. For example, nearly two-thirds failed to report any information on their methods of randomisation, reinforcing previous work[55;57] . In the remainder there were various methods of random allocation, of which about a quarter reported using a computer-generated method or a random number table, which are the usually acceptable ways of randomisation. None of the trials discussed allocation concealment. If the allocation of the patient is not adequate and fully independent of the enrolling investigator, then this may allow either conscious or unconscious selection of participants into the trial, or into particular arms of the trial, thus introducing selection bias and undermining randomisation. The internal validity of a randomised controlled trial has been shown to be directly associated with a clear description of appropriate methods of random allocation of participants, and concealment of their allocation[58].

Over 80% of trials provided no information about blinding of either participants or investigators. This confirms the result observed in a review of RCTs of traditional Chinese medicine[57]. Without blinding the groups may have been treated differently by the investigator and the outcomes not measured objectively, thus creating further assessment bias. Participants aware of their

treatment may behave differently or have particular expectations[8] , thus affecting the results.

Interestingly, among the included Chinese studies in this review, over half stated that none of their participants dropped out. This is unusual compared with trials in countries with more established research programmes, where a drop-out rate of below 5% is generally considered a very good result. Over 60% of the trials in this review reported a drop-out rate of less than 5%, and two-thirds less than 10%. The reasons behind these very low rates warrant further investigations.

The reporting of ethical issues was inadequate in the Chinese RCTs. Fewer than 11% of the trials reported having ethical committee approval, although the latter is a legal requirement in China[59] . Also, only a minority of the Chinese studies (17.4%) gave adequate details about informed consent procedures; a few mentioned that participants attended of "their own free will" but the remainder made no mention of consent. However, this level appears better than in a recent review of traditional Chinese medicine trials[57] .

Compared with many published trials in developed countries[60], the standard of reporting in China is lagging behind, although there are still many fields in Western countries which have inadequate standards of reporting[61] . However, the application of the CONSORT statement has demonstrated benefits in improving reporting[29] and could be expected to do the same in China.

My review revealed that compared to our 2004 review, the ethical committee approval and reporting participants' informed consent have been improved significantly. In 2005, the Chinese Food and Drug Administration published

the instruction of ‘Ethical requirement in conduct of randomised controlled trials’. In this regulation, GCP and Helsinki Deceleration were promoted as the basic regulation in the RCT ethical area. This may be one of the explanations for the improvement on these measures.

The Primary outcome in particular has much invested in it, because it is normally the outcome alone that indicates whether or not the trial provides evidence at an acceptable level that the treatment is efficacious.[62] The choice of outcome measure is an important design consideration.. Chinese RCTs have significant improvement on the reporting of primary outcome between time periods. However, in 2008-09, only 28(11.6%) RCTs identified a primary outcome, which rate is still very low and undermines the trial interpretability. The primary outcome as an essential indictor should be presented much more clearly.

There are several studies which concentrate on Chinese published RCT quality. All of them suggest that Chinese trialists should use CONSORT as their basic reporting check list. In order to improve overall the quality of published RCTs, the Chinese medical journals should take the responsibility to ensure that CONSORT is followed. We assess all the journals from the journal series of the Chinese medical association on their ‘instruction for authors’. Unfortunately, only one journal ‘Chinese Medial Journal’ was found to refer to the CONSORT statement.

The quality of published RCT papers in Chinese was significant different from those published in English, on double blinding, type of treatment ,ethical approval and informed consent. Authorship was significantly associated with double blinding, type of treatment and ethical committee approval. Traditional Chinese treatment RCTs are significant different with Western treatment RCTs on double blinding, primary outcome, ethical committee approval and informed consent. In addition, pubmed papers were significant different from non-pubmed papers on the double-blinding, and informed consent. All of these results showed that Chinese RCT authors need to improve the quality of RCT conducting and report writing. The involvement of Western medical authors might also help to improve the quality of Chinese RCT reports.

A paper written by Chinese Cochrane Centre published in May 2008, which is titled 'Chinese authors do need CONSORT…' the main recommendation of this paper is Chinese medical author should use CONSORT to improve their reporting of RCTs. We identified all the papers published 6 month after Chinese Cochrane Centre's publication. However, the quality of reporting of RCTs is still at an unsatisfactory level. It is clear that Chinese medial journals were not taking advice from medical researchers and the CONSORT statement has not been accepted in practice.

2.3.2 Strengths of this study

My research is a prospective study of the quality of published Chinese RCTs. I used the same search strategies to search the same data resources, and

therefore the difference from search strategies is decrease to minimum. The difference is from all the included journals individually.

2.3.3 Limitations

Although I undertook a thorough search for eligible studies using both PubMed and the Journal Series of the Chinese Medical Association, I may have missed relevant studies not included in the databases. The Journal Series of 71 Chinese journals comprises the core of the Chinese medical journals, but only approximately 20% of the total. RCTs which were not described as such in the abstract would have been excluded; however it is not clear how many such false negatives there would have been. Indeed failure to mention correctly the study design in the abstract is a mark of poor quality.

My research for Chinese Trials through Pubmend and Journals Series of the Chinese Medical Association may have included journals which are unrepresentative of all Chinese journals, although because of our research strategy these may be considered the highest status journals publishing the most influential trials reports.

2.4 Conclusion

Reporting of RCTs in China requires substantial improvement to meet the targets of the CONSORT statement. The conduct of Chinese RCTs cannot be directly inferred from the standard of reporting; however without good

reporting the methods of the trials cannot be clearly ascertained. Research bodies in China should ensure that the reporting of RCTs is improved to meet internationally agreed standards, thereby allowing the conduct of their studies to be monitored and encouraging high quality standards. Ethical committee approval and reporting of participants' informed consent have been improved significantly in 2008-09. However, reporting of RCTs in China needs substantial improvement to meet the target of the CONSORT statement.

Summary

In this chapter, I reviewed all published Chinese RCTs of 2004, and find Chinese RCT publications need to be improved in many items of CONSORT statement. In chapter 3, I will compare Chinese RCT publications with Western leading medical journals and Indian medical journals, in order to locate the status of Chinese RCT research in world medical society. I also evaluated Chinese updated published RCT papers by using the same evaluation strategy, and made comparison with my previous research. Although there are significant improvements in some indicators, the quality of Chinese published RCT still need substantial improvement. In addition, the positive result rate remained as high as it was in 2004.

Chapter 3. Are Randomized Trials Conducted in China or India biased? A comparative empirical analysis

Outline

In this chapter, I make comparisons between Chinese, Indian and a contemporaneous 'gold standard' sample of Western RCT publications, in order to develop an understanding of the status of Chinese RCT publications among the world medical research area.

China and India are the two potentially important countries undertaking RCTs given their substantial populations. They are also potentially important users of the results of high quality trials. As well as investigator led trials, the international pharmaceutical and device industries increasingly conduct their development programmes for new products in lower income countries. Therefore, trial quality in low-income countries affects not only the substantial local population but also potentially influences health policy in other regions. In this thesis I examine aspects of the quality of the reports of trials conducted in China, and contrast these with India and a "gold standard" set of trials conducted in Europe and North America. A better understanding of the quality of trials is important both to aid current interpretation but also to inform any future methodological work on the quality of RCTs in those countries.

I present a critical evaluation of randomized controlled trials conducted in China and published in 2004. The aim was to appraise the general level of research in China and make suggestions for improvements in the design, conduct and reporting of Chinese RCTs. Furthermore, I examine whether published reports of Chinese or Indian trials exhibit a high proportion of positive results compared to a “gold standard” selection from high quality European and North American journals. I also examine the extent to which any difference in the rate of positive results in trials may be due to trials examining traditional Chinese medicine treatments which form a particular subject of investigation in Chinese trials, or whether it may be due to markers of trial quality.

3.1 Method

3.1.1 Derivation of study material

Relevant Indian papers were identified through PubMed,and 'ISI Web of Sciences' databases. PubMed includes MEDLINE and OLDMEDLINE[48] but many non-English Journals are not listed. I searched Pubmed for Indian randomised controlled trials published in 2004 using the textwords ‘india*’ and the PubMed filter for randomised controlled trials. No language or other limitations were imposed.

Relevant Western papers were also identified though Pubmed, where the search was limited to six journals: JAMA, BMJ, New England Journal of

Medicine, Annals of Internal Medicine, Lancet and Circulation. (Circulation was selected because of the following reasons: Cardiac & Cardiovascular system disease is the top 1 health killer in Western population. Impact factor of circulation is 12.755- Ranks #1 among journals in the Cardiac & Cardiovascular Systems category, #1 among journals in the Haematology category, and #1 among journals in the Peripheral Vascular Disease category.)

I used the Pubmed filter for randomised controlled trials to identify RCT publications in 2004. That year was selected because I already had comparable data from China from conducting a systematic review of Chinese RCT papers published in 2004. In order to have similar number of Western RCT papers as Chinese or Indian ones, I reviewed the 2nd, 3rd and 4th issues of each month, if they published weekly. For 'Annals of Internal Medicine' which publishes bimonthly, I reviewed the 2nd issue of each month.

3.1.2 Inclusion and exclusion criteria

I included full reports of randomised controlled trials on all disease groups and all types of interventions. For Chinese papers, I excluded reports that did not include any patients from Mainland China. I excluded papers from Hong Kong and Taiwan as they are under the jurisdiction of independent governments with separate medical budgets and thus may not be representative of Mainland China. Papers published in Indian journals were excluded if they did not include any Indian patients.

3.1.3 Assessment of quality

The quality of each trial was assessed using a checklist derived from the items included in the CONSORT statement, an internationally agreed standard for reporting RCTs. I added some further items in order to extract further information specific to my research papers.

3.1.4 Outcome measures

I derived the 'positive outcome rate' from each included trial to describe the potential for bias. The positive outcome rate was defined as the number of outcomes reported to have a statistically significant result divided by the total number of outcomes reported for the trial. Apart from the potential confounding effect of Chinese medicine trials (which I hypothesised could have systematically different treatment effects) I did not identify potential systematic confounding factors at the level of the country a priori. However I did recognise that a systematic difference in the mix of disease areas investigated (analogous to the concerns about Chinese Medicines) might lead to an apparent difference between regions (eg China, India, or Western). These were explored in supportive analyses.

3.1.5 Statistical analysis

Comparative rates of quality indicators were summarised by country, and differences between countries on these scores were assessed using Chi Squared tests. I used non-linear mixed models with a logit link and binomial / normal error to examine the effect of country on the rate (r/n) of positive

results as a proportion of all outcomes reported in clinical trials. In the principal analysis I examined the effect of country, and defined the individual trials as random effects, thus accounting for study level differences (extra binomial variability)[63]. Further potential confounders (eg disease area, industry sponsorship, double blinding, concealment of allocation, and the 'intent to treat' principle) were prespecified to be considered in an additional exploratory analyses, to identify a parsimonious model in which candidate variables were selected for final inclusion on the basis of backward selection, with an α level for inclusion of he model of .05. Multivariable analyses were conducted using the statistical package SAS (SAS Institute, Cary, NC).

3.2 Results

Among 372 identified Chinese papers 29 papers were initially excluded as they were duplicate publications. Of the remaining 343 studies 307 clearly described that their patients were allocated randomly to treatments and therefore were included. Thirty-six studies were excluded as they either were not, or could not be confirmed to be, RCTs.

My search for Indian Trials revealed 340 reports, identified by the use of the key term 'India*'. Of these, 124 papers were not Indian trials, 20 papers were brief reports or short communications and full-text was not available for 79 papers. As a result, 117 Indian papers were included.

I identified 310 Western papers; six of them were brief reports, which were excluded from my final database, leaving a total of 304 papers.

239 Chinese RCT papers were selected from Pubmed, all 117 Indian papers and 304 Western papers were selected from Pubmed.

Table 3.1. Indicators used to describe and evaluate included randomised controlled trials

I**ndicator**		**Description**
Quality of reporting: CONSORT indicators		
1	Allocation concealment	What method was used to implement the random allocation sequence?
2	Blinding	Whether or not patients and/or investigators were blinded to group assignment
3	Primary outcomes	Did they report which outcome was designated as the primary outcome?
4	Statistical reporting	Were confidence intervals reported to indicate precision?
Descriptive indicators		
5	Intent- to-treat	Did they describe 'intent to treat' as their data analysis principle?
6	Kind of treatment	Whether it is traditional Chinese treatment?
7	Funding source	Whether it is sponsored by industry?
8	Ethical committee approval	Yes/No
9	Informed consent from participants	Yes/No

3.2.1. Allocation concealment

None of Chinese RCT publications described 'allocation concealment' in the trial reports and only 1 Indian paper mentioned it; 132 of 304 (43%) Western papers described concealment of allocation clearly in their study reports (P < 0.0001).

Comparison among Pubmed papers

None of Chinese RCT publications describe 'allocation concealment' in the trial reports.

3.2.2. Blinding

One hundred and sixty-three of 304 (54%) Western trial reports described that they used double blinding in their studies; while, only 39 (13%) Chinese papers and 40 (34%) Indian papers clearly described the use of double blinding in reports of their trials (P < 0.0001). However, 83% of Chinese papers and 61% of Indian papers were unclear in their reporting of blinding.

Comparison among Pubmed papers

28 (12%) of 239 Chinese papers described the use of double blinding in the report of their trials, compared to Indian and Western papers, P<0.0001.

3.2.3. Primary outcomes

Eleven (4%) of 307 Chinese and 14 (12%) of 117 Indian papers specified a primary outcome, 268 (88%) of Western papers specified a primary outcome (P < 0.0001).

Comparison among Pubmed papers

Eight (3%) of 239 Chinese papers specified primary outcome, compared to Indian and Western papers, P<0.0001.

3.2.4. Statistical reporting

Twenty (7%) of Chinese papers and 19(16%) of Indian papers reported confidence intervals, 251(83%) of Western papers reported confidence intervals (P < 0.0001).

Comparison among Pubmed papers

Sixteen (7%) of Chinese papers reported confidence interval, compared to Indian and Western papers, P<0.0001.

3.2.5. Intention-to-treat

Eleven of 307 (3.6%) Chinese and 44 Indian trials (38%) described 'intention to treat' as their data analysis principle, while 238 of 304 (78.3%) Western trials described it as their principle (P < 0.0001).

Comparison among Pubmed papers

Eight (3%) of 239 chinese trials described 'intention to treat', compared to Indian and Western papers, P<0.0001.

3.2.6. Type of treatment

One hundred and twenty-two (39.7%) Chinese papers described a Chinese treatment trial, such as Chinese traditional medicine, acupuncture or other kind of traditional therapy. None of the Western and Indian trial reports described Chinese treatment.

Comparison among Pubmed papers

Ninety-three (38%) of 239 Chinese papers described Chinese treatment.

3.2.7. Funding source

Seventy-eight of 304 (25.7%) Western trial reports described receiving support from industry funding; only 5 (2%) Chinese and 5 (4%) Indian trial reports stated that they received industry funding (P < 0.0001). However, 232 (75.6%) of 307 Chinese papers and 99 (85%) of 117 Indian papers did not report their funding source.

Comparison among Pubmed papers

Five (2%) of 239 Chinese papers reported they received industry fundings, compared to Indian and Western papers, P<0.0001.

3.2.8. Ethical approval

Thirty-three (11%) of Chinese and 91 (77%) Indian papers reported they had gained ethical committee approval, 296 (97%) of Western trial reports stated that they had received ethical committee approval (P < 0.0001).

Comparison among Pubmed papers

Twenty (8%) of Chinese papers reported they had gained ethical committee approval, compared to Indian and Western papers, P<0.0001

3.2.9. Informed consent from participants

Fifth-four (18%) of Chinese papers and 93 (79%) of Indian papers stated that the participants provided their consent. 291(96%) of Western papers reported they had gained participant's signed consent (P < 0.0001).

Comparison among Pubmed papers

Thirty-five (15%) of Chinese papers reported they had participant's informed consent, compared to Indian and Western papers, P<0.0001

There were substantial differences in numbers of outcomes reported in different studies by country (Table 3.2). The mean outcomes reported for Western papers and Indian papers were 15.79 and 15.09; for Chinese papers the mean was 4.13. The median number of Western and Indian papers were 12 and 8 respectively; The Chinese median number of outcomes reported was 3.

Table 3.2. Number of papers' outcomes by paper derivations

	Median number of reported outcomes	Range
Western	12	2 to 85
Chinese	3	1 to19
Indian	8	2 to 74

Comparison among Pubmed papers

The median number of reported outcome of Chinese papers was 4, range was from 2 to 19.

Table 3.3. Number of papers' outcomes by paper derivations of Pubmed papers

	Median number of reported outcomes	Range
Western	12	2 to 85
Chinese	4	2 to19
Indian	8	2 to 74

Table 3.4. Univariate effect analysis of potential predictors

Predictor	Odd ratio (95 %CI), P-Value
Chinese Indian Western	3.70 (2.89 to 4.74) P<0.0001 0.92 (0.69 to 1.24) P=0.59 1
Traditional Chinese treatment	4.28 (3.02 to6.06) P<0.0001
Double blinding	0.65 (0.51 to 0.82) P=0.0004
Whether concealment	0.56 (0.42 to 0.74) P<0.0001

*OR=1 means compared with Western papers, Chinese papers have same effect size on presenting positive result rate.

ˆ OR=1means compared with Western papers, Indian papers have the same effect size on presenting positive result rate.

˜ OR=1 means among all reviewed papers (Western, Chinese and Indian papaers), compared with Western treatment papers, traditional Chinese treatment papers have the same effect size on presenting positive result rate.

˚ OR=1 means among all reviewed papers (Western, Chinese and Indian papers), compared with non-double blinding papers, double blinding papers have the same effect size on presenting positive result rate.

˙ OR=1 means among all reviewed papers (Western, Chinese and Indian papers), compared with non-concealment papers, dconcealment papers have the same effect size on presenting positive result rate.

Table 3.4 reports the univariate results for each potential predictor in the model. In each case a random effect describing the individual trial report was included in the model, with country of origin included as a three level factor. I found Chinese papers substantially more likely to report statistically significant results (odds ratio (OR) 3.70, 95% CI 2.89 to 4.74; P<0.0001). Indian papers had a very similar result to Western papers (OR=0.92, 95%CI 0.69 to 1.24; P=0.59). Traditional Chinese treatments were also significantly more likely to report positive results than other treatments, although in a univariate model this result may be confounded by country. Because of the high rate of missing data I did not include funding source in univariate or subsequent multivariable models. Double blinding and concealment were both associated with a lower rate of positive results.

Table 3.5 Univariate effect analysis among Pubmed papers

Predictor	Odd ratio (95 %CI), P-Value
Chinese Indian Western	3.20 (2.47 to 5.69) P<0.0001 0.92 (0.69 to 1.24) P=0.59 1
Traditional Chinese treatment	4.02 (2.94 to6.82) P<0.0001
Double blinding	0.64 (0.51 to 0.82) P=0.0004
Whether concealment	0.56 (0.42 to 0.74) P<0.0001

Chinese papers were substantially more likely to report statistically significant results (odds ratio (OR) 3.20, 95% CI 2.47 to 5.69; P<0.0001). Indian papers had a very similar result to Western papers (OR=0.92, 95%CI 0.69 to 1.24; P=0.59). Traditional Chinese treatments were also significantly more likely to report positive results than other treatments, although in a univariate model this result may be confounded by country. Because of the high rate of missing data I did not include funding source in univariate or subsequent multivariable models.

Table 3.6.Principal multivariable analysis and supportive analyses

Predictor	Model 0	Model 1	Model 2	Model 3	Model 4
Chinese/Western	2.54 (0.79-8.21) P=0.1185	2.84 (1.59-5.08) P=0.0004	3.07 (2.11-4.46) P<0.0001	3.13 (2.20-4.46) P<0.0001	2.96 (2.23-3.94) P<0.0001
Indian/ Western	0.65 (0.32-1.32) P=0.2295	0.90 (0.64-1.28) P=0.5682	0.91 (0.66-1.26) P=0.5839	0.93 (0.69-1.26) P=0.6492	0.92 (0.69-1.24) P=0.5906
Chinese treatment	0.93 (0.16-5.54) P=0.9398	2.10 (0.65-6.74) P=0.2137	1.82 (1.22-2.72) P=0.0035	1.82 (1.22-2.72) P=0.0035	1.81 (1.21-2.7) P=0.0038
Intention to treat	0.84 (0.56-1.26) P=0.4053	1.07 (0.78-1.47) P=0.6725	1.08 (0.81-1.44) P=0.5935	1.08 (0.81-1.44) P=0.5980	
Whether Concealment	0.95 (0.67-1.35) P=0.7848	0.96 (0.69-1.35) P=0.8252	0.95 (0.70-1.29) P=0.7402		
Double blinding	1.18 (0.84-1.66) P=0.3314	1.01 (0.76-1.33) P=0.9676			
Industry sponsor	0.73 (0.03-21.38) P=0.8564				

*Values in the brackets are 95% CIs.

I used backwards selection to identify the best fitting parsimonious statistical multivariable model. The final model included country of origin and traditional Chinese treatments. Chinese trials were associated with an increased rate of positive results (OR=2.96, 95% CI 2.23 to 3.94; P<0.0001), Indian trials reported a similar rate of positive results to Western papers (OR 0.92, 95% CI

0.69 to 1.24, P=0.59). Traditional Chinese treatments were associated with a higher rate of significant results (OR=1.81, 95% CI 1.21 to 2.7; P=0.004).

Comparison among Pubmed papers

Chinese trials were associated with an increased rate of positive results (OR=2.46, 95% CI 2.00 to 4.16; P<0.0001). Traditional Chinese treatments were associated with a higher rate of significant results (OR=1.67, 95% CI 1.05 to 3.04; P=0.004).

3.3 Discussion

I compared Chinese and Indian RCTs with Western Trials from high quality journals because I considered that there were some important similarities between these two countries. Both are developing countries with very large populations and they are undergoing rapid socioeconomic transition. They are also recognised as potentially the two largest markets for pharmaceutical trials in the world, which can contribute important data on medical research and development.

I found reports of Indian trials to be slightly better than Chinese papers on the trial reporting quality indicators: concealment, double-blind, intent-to-treat, reporting of primary outcomes, confidence intervals; and much better than Chinese papers on reporting patients' ethical issues: informed consent and ethic committee approval. However Western trial reports scored considerably higher than both Indian and Chinese trial reports on all quality criteria.

The rate of positive results was substantially different between Chinese and non-Chinese reports of randomised trials. Reports of trials of Chinese Traditional Treatments included a higher proportion of positive outcomes than trials of conventional treatments.

Although the pubmed papers are significant different from non-pubmed papers on many quality characteristics, however, on many quality characters, Chinese RCTs are still

significant different to Western and Indian RCT papers. Therefore, the overall Chinese RCT report quality need to be improved.

3.3.1 Strengths of this study

To my knowledge, this study presents the first empirical comparison among Chinese, Indian and Western RCT publications. I found poor reporting of all quality measures among Chinese and Indian trials, and strong evidence of bias in the reported results of Chinese trials.

3.3.2 Methodological evaluation

Essential details of trial design and quality need to be reported more clearly in Chinese and Indian RCT papers. In my comparison, I found significant differences on those methodological details across countries. Schultz et al found inadequate reporting of concealment of allocation and the absence of double blinding were associated with exaggerated estimates of treatment effect in RCTs. [9]

The prior specification of a primary outcome measure is an important measure for the interpretation of a trial since this can avoid the statistical problems of multiplicity as each test conducted increases the probability of a false positive finding and thus increases the studywise type 1 error rate. The failure to prespecify a primary outcome measure or α spending strategy may lead to inappropriate application of apparently positive results from trials when in fact chance alone may often provide an adequate explanation for the observed results.[62]

I appreciate that important methodological details may be omitted from published reports despite having been appropriately implemented within trials. For example, Soares found that authors of RCTs frequently used allocation concealment and blinding, but fail to report these methods[12]. Journal editors, especially those who handle large number of trial reports from China and India, are important players in improving the quality of reports of trials through the active implementation of the CONSORT recommendations[62].

3.3.3 Ethic issues

I observed significant shortcoming in the reporting of ethical issues in Chinese papers. Informed consent and ethic committee approval are widely accepted as fundamental requirements of conducting RCT in China but not all hospitals involving in trials have institutional ethical committees[64] .

3.3.4 Publication bias

Chan et al found a substantial difference between RCT protocols and the final publication of their outcomes in many trials.[26] Those outcomes with non-significant result were frequently omitted in the final report. In my study, I found Chinese papers reported fewer outcomes than Indian or Western trials, which could be the explanation for the high rate of positive results reported. Indeed, in some Chinese RCT papers I found the outcomes described in the methods and results sections did not match. For example in a paper describing a trial of the effects of somatostatin on intestinal obstruction published in a Chinese medical journal, the operation rate was the only

outcome described in the methods section, but in the results section a further five outcomes were presented.[65] In another trial report published in another medical journal which examined the effects of oxymatrine in the treatment of chronic hepatitis B, 22 indicators were described as outcome measures in the methods section. However, only 6 outcomes were reported in results section, with 5 out of 6 of the reported outcomes indicating a significant result.[66]

3.3.5 Limitations

The sample of Indian trials may not have been representative; my search would not have located all published trials although it seems likely that I identified the highest status journals through my searches of Pubmed and ISI web of science. But trials are published in many journals which are not indexed by Pubmed and ISI. Similarly, my search for Chinese trials through Medline and the Journal Series of the Chinese Medical Association may have included journals which are unrepresentative of all Chinese journals although because of my search strategy these may be considered the highest status journals publishing the most influential trial reports.

Seventy-nine Indian papers were not available despite attempts to secure copies. This level of missing data could affect the final analysis and comparison results. However, it is reasonable to expect that the quality of papers published in those journals that do not produce electric versions or are not included in British inter library loan would be inferior than those that are more readily available. Therefore, if I was able to include papers

from the former journals, it is very likely that the average quality of Indian papers would come out worse. Further research is needed to verify this.

I wished to investigate the effects of industry support in medical trials. However, I did not find enough information from Chinese and Indian trial reports to allow us to explore this issue properly.

3.4 Conclusions

My study focussed on the reporting of randomised trials, which may not exactly follow the conduct of trials. I used the CONSORT recommendations for reporting of trials as a template for my evaluation. This may mediate against trials from China and India as CONSORT may have less influence on trial reporting in those regions than in the West where it was developed and actively promoted by several major journals included in my work. Thus the trials from China and India could be well conducted, but inadequately reported. However the difference in positive results reported between Chinese trials and Western or Indian trials cannot plausibly be explained by the play of chance or the a priori identified confounding factors, and may be associated with the selective publication of outcome measures which showed statistically significant results.

Summary

In this chapter, I compared Chinese and Indian RCTs with a gold standard sample of Western RCT publications. I found that Chinese RCTs are biased in many items, and on average Chinese RCTs present a higher proportion of positive results than Indian and Western RCTs. In addition, on many quality and ethical indicators, Chinese RCTs showed worst results, not individually, but systematically. What are the reasons why Chinese RCT publications are at such a low quality level? I will explore it though clinicians and patients' knowledge and attitude in the next two chapters.

Chapter 4. Barriers of Chinese clinicians to participation in randomized controlled trials

Outline

In this section I used questionnaires, focus group meeting and semi-structured interviews to describe Chinese clinicians' Knowledge and attitude toward RCTs. They are the direct executors of randomized controlled trial, whose understanding and attitude will influence RCT and RCT publications' quality. Results from quantitative research (questionnaires) and qualitative research (focus group meetings and personal interviews) are reported separately.

In the previous chapter, I reviewed and evaluated Chinese RCT publications and found Chinese randomized controlled trial papers were not well reported, which is likely to be a reflection of the quality of trial conduct. There is a substantial gap between leading Chinese and Western RCT publications in many issues, which may lead to Chinese RCT research being unconvincing among the international medical community. An RCT report with inadequate information and uncertain description risks being rejected by readers for quality reasons, and may not be included in meta-analysis. Meta-analysis combines the results of several studies which address similar research hypothesis, providing a more powerful estimate of the true effect size than those derived in a single study.

Furthermore, from the previous systematic review, I discovered the substantial problem does not just exist in individual journals, but appears to affect the whole Chinese medical journal system, because the main source of evaluated papers is from the journal series of the Chinese medical association, and which is the well known medical journal series in Mainland China.

The success of RCTs depends on the participation of clinicians. To achieve this, clinicians must agree to participate when invited, must recruite patients who are eligible (including offering participation to eligible patients) and must follow the trial protocol. Each of these stages represents a potential barrier to participation which varies from trial to trial.

There are studies which have shown that trial participants' failure to understand information about randomisation, even the provision of clear and readable trial information[67]. As a consequence, patients may create their own incorrect interpretations and consent that would influence their behaviours in RCTs and further the quality of RCTs. Clinicians' understanding and attitude made effect on their behaviour of conducting RCTs[68]. The insufficient of RCT reporting on the main quality items are reflecting some practical problems, such as the ethical problems or patients' allocations. Therefore, I would like to identify whether poor reporting reflects poor quality trials, or merely deficiencies in the medical paper writing. I would like to access the real RCTs conductors and participatants through focus group meetings and interviews, to assess

their understanding and attitude toward RCTs, and try to explain the reasons for poor quality RCT reporting,

Research question

What is the Chinese clinicians' experience of conducting RCT? Do they have a correct understanding and positive attitude toward RCT? What are the barriers which may affect their conduct of RCTs in practice?

I address several sub-questions: What is clinicians' understanding and attitude towards randomized controlled trials? What are clinician's clinical and research work profiles? Why they like or not like participating in RCT research? What are the barriers which block them from conducting better RCTs? Are there any characteristics from the Chinese medical system which may affect clinicians' RCT work?

I conducted a qualitative study to access Chinese clinicians, attempting to describe their working profile in practice and with patients, and analyze clinicians' attitudes to the randomised controlled trial in depth.

- **The reason of using multiple research methods**

Questionnaires are perhaps one of the most popular data gathering tools, but there are a number of situations in which the interview is the most logical research technique. Both questionnaires and interviews have their advantages and disadvantages; questionnaires are low cost in terms of both time and money, the inflow of data is quick

and from many people, which is fit for detecting attitudes, motivation, opinions[69]. Focus group could be employed to explore same information, but potential for explore answers in more depth; personal interviews provide more detailed and in-depth information[70]. The dialogue between interviewer and respondent allows for nuances to be captured and for questions to be clarified and adopted or improvised; in questionnaire surveys, nuances of the respondent's voice cannot be heard and questions cannot be modified once printed. Therefore, in my research, I used questionnaire, focus group meeting and interviews to examine Chinese clinician's attitude and knowledge of RCT research. With those high status 'big man' in the department, I conducted personal interview, which is more flexible and provide more in-depth information.

4.1 Part One. Quantitative research: Physician Orientation Profile

RCT research requires clinicians to take the role of being an investigator, a dilemma which cannot be avoided. We have to understand their attitude of being an investigator in a clinical setting and what the difficulties are that they met in practice, then I could prescribe effective solutions on policy making or improvement.

The Randomized controlled trial was developed as a new research method by Western scientists and has been used widely in Western countries. There have been significant improvement in health care as a result of findings from clinical trials, but practical conduct problems are common, may cause delays, increased costs or lead to the failure

to complete trials[71]. Doctor-related factors have been cited as one of the primary reasons for poor conduct for clinical trial[72]. Barriers to trial participation for doctors[71;73;74], as currently we known, include personal conflicts between the roles of clinician and scientist[75]; lack of rewards[75], discomfort with random allocation of patients to treatment[76]; difficulty with ethics requirements and informed consent[72]; concerns about patients' wellbeing and effects on the doctor-patient relationship[76;77]. However, when RCTs arrived in China, there have been some Chinese specialized barriers which hinder Chinese clinicians in conducting randomized controlled trial properly. Some of the reasons are from traditional Chinese culture; some are from the current Chinese medical system which I indentified from my quantitative and qualitative work of Chinese clinicians.

The Physician Orientation Profile is a questionnaire which is based on the different roles of clinician and investigator, designed for clinicians to describe their attitude toward randomised controlled trials. It was used in main Western countries, such as US, UK, Canada, France, Australia and Poland.[78;79] however, it had not yet been used with Chinese clinicians. A translated physician orientation profile was used with all participating clinicians.

I translated Physician Orientation Profile into Chinese by myself. I also had a pilot study of Chinese version in July 2006, 28 Chinese clinicians involved. Their comments and suggestions were taken for the words correction. The final version of Physician Orientation Profile in Chinese was revised 4 times before it put in practice.

4.1.1 Method

I would have liked to select research hospitals randomly among all the hospitals in the Guangzhou area, however, that was not practical because without the agreement from Guangzhou Public health bureau, selected hospitals would reject any access about their RCT conduct. I informed Guangzhou public health bureau of my research plan and discussed hospital involvement with them. I required participating hospitals to have substantial experience in conducting clinical trials. After initial meetings, 3 hospitals were nominated by Guangzhou Public health bureau which were First Municipal People's hospital of Guangzhou, Guangzhou Red Cross hospital and Guangzhou Brain hospital. These 3 hospitals are all 3A+ hospitals with a clinical trial base and under the control of the Guangzhou public health bureau.

First Municipal People's hospital of Guangzhou and Guangzhou Red Cross hospital are both general hospitals, which Provide medical service to local communities and treat various types of diseases and injuries. Guangzhou Brain hospital is a special hospital for nervous system disease, which has conducted clinical trials for more than 10 years. These 3 hospitals were selected because they are typical hospitals with RCT experience, their clinician and patients are also typical.

With the help of hospital research administrator, I sent questionnaires to all clinicians if he or she has the experience of participating RCT research within these 3 hospitals.

4.1.2 Analysis for Quantitative study

Demographic variables were reported, practice variables and responds to individual questions were compared between Chinese and Western clinicians, using Z test for testing differences in proportions. Because the data from literature of Western clinicians[79] are presented in percentage, so I presented corresponding percentages as well, and made comparison by giving Z and P-value. The SAS statistical program (SAS ver 9.2, Cary, NC) was used for data analysis.

4.1.3 Result

Questionnaire survey, performed between July 2007 and May 2008**,** in 247 Chinese clinicians from 3 hospitals of Guangzhou. With their hospital administrator's help, I achieved a response rate of 95%, 234 of 247 clinician returned completed questionnaires. My study involved only those clinicians with experience of conducting randomized controlled trials, therefore not every clinician was eligible in a hospital. I tried to include every eligible clinician in the questionnaire study. As I mentioned before, this is the first study to investigate Chinese clinicians' attitude of RCT, and the questionnaire was translated into Chinese language. Considering the substantial Chinese medical doctor population, this study only involved a small proportion of doctors within one city.

4.1.3.1 Clinicians demographic characteristics

Table 4.1 presents included Chinese clinicians' demographic information.

Among 234 Chinese clinicians,158 (67%) were less than 40 years old, 108 (46%) were males. 124 (55%) had Bachelor degree, 94 (39%) had Master degree, 16 (6%) had PhD or MD degree. 74 (32%) were based ininternal medicine departments, 38 (17%) were in surgery, 50 (21%) were from mental health department (because the brain hospital was involved). 162 (70%) had no academic appointment, 44 (18%) were associate professors, 28 (12%) were professors. Only 24 (10%) clinicians reported that they spend more than 50% time on research, and only 34 (15%) clinicians had more than 3 papers published every year.

Table 4.1 Characteristics of included clinicians

	Number	Percent
Age		
30 years or less	74	31%
31-40	84	36%
41-50	56	24%
51-60	18	8%
More than 60	2	1%
Sex		
Male	108	46%
female	126	54%
Education		
Below Bachelor Degree	0	0%
Bachelor Degree	124	55%
Master Degree	94	39%
PhD or MD Degree	16	6%

Department		
Surgery	38	17%
Internal medicine	74	32%
Radiology	12	5%
Paediatrics	12	5%
gynaecology and obstetrics	18	7%
dentistry	2	1%
Mental health	50	21%
others	28	12%
Hospital setting		
1000 beds or fewer	158	68%
More than 1000 beds	76	32%
Income		
Primarily fee for service	22	9%
Primarily salaried	212	91%
Academic appointment		
No appointment	162	70%
Associate professor	44	18%
Professor	28	12%
Activities		
50% research time or less	210	90%
More than 50% research time	24	10%
Authorship		
More than 3 articles/year	34	15%
3 or few articles/ year	200	85%

4.1.3.2 Chinese clinicians' responses on Physician Orientation Profile

The results from Chinese physician Orientation Profile were reported and compared with Western clinicians' answers together, in order to show the difference between Chinese and Western clinicians.

Because the data from literature of Western clinicians[79] are presented in percentage, so I presented corresponding percentages as well, and made comparison by giving Z and P-value.

Table 4.2. Physicians' Responses to the Binary-Option Questions of the Physician Orientation Profile

	Chinese clinicians'' responds N=234	Western clinicians' responds[79] N=250	Chi-square	P	OR and 95% CI
1. although many physicians are expected to perform both tasks, as a physician my primary allegiance is to					
a. future patient (society)	28	27	0.07	0.79	1.12 (0.64-1.97)
b. present patient (individual)	206	223			
2.if I had to choose, I would say my primary task is:					
a. caring for individual patients	187	225	8.93	0.002	0.44 (0.26-0.75)
b. contributing to scientific knowledge	47	25			

3.I would like to assess how successful I was as a physician by					
a. my research contribution	16	36	188.4	<0.001	
b. how I helped individual patients	56	192			
c. both	162	22			
4. Although physicians strive to achieve an optimal balance, would you rather become somewhat too involved with your patient or somewhat to detached?					
a. too involved	186	212	1.99	0.158	0.69 (0.43-1.11)
b. too detached	48	38			
5. if a patient refuses to participate in the study, I :					
a. take him off the study	204	248	26.37	<0.001	0.05 (0.01-0.23)
b. refer him to another physician	30	2			
6. I would rather be known for:					
a. my interpersonal skills with patients	206	194	8.46	0.003	2.12 (1.3-3.48)
b. my research accomplishments	28	56			
7. Overall I feel the quality of patients care					

a. in creases in when a patient is in a clinical trial	164	113	34.07	<0.001	
b. decreases when a patient is in a clinical trial	12	11			
c. does not change when a patient is in a clinical trial	58	126			
8. Randomised controlled trial restricts my ability to individualise patient care:					
a. true	32	69	13.6	0.001	0.42 (0.26-0.66)
b. make no different	202	181			
9. I think the patient's right to select treatment option is always more important than advancement of scientific knowledge					
a. yes	88	175	49.8	<0.001	1.9 (1.32-2.74)
c. no	146	75			
11. When there is controversy in the literature as to which treatment is best:					
a. I enter the patient in a clinical trial if one exists	120	89	11.48	<0.001	1.9 (1.32-2.74)
b. I personally select a treatment for the patient	114	161			
12. When making critical and controversial decisions, I usually:					

a. seek major input from my patients	13	240	392	<0.001	0 (0-0.01)
b. do not seek major input from my patient	221	10			
13. When published data and my clinical judgement conflict, I am more likely to rely on:					
a. my clinical experiences	156	112	22.5	<0.001	2.46 (1.7-3.56)
b. published data	78	138			
14. When a protocol includes a treatment that is more aggressive than I would usually give to similar non-trial patients:					
a. I am often reluctant to participate	151	128	8.26	0.04	1.73 (1.2-2.5)
b. it makes no different	83	122			
15. when a protocol includes a treatment that is less aggressive than I would usually give to similar non-trial patients:					
a. I am often reluctant to participate	151	100	28.16	<0.001	2.73 (1.89-3.94)
b. it makes no different	83	150			
16. I am reluctant to participate in a trial that may randomise the patient to a 'no treatment' group					

a. yes	149	70	60.6	<0.001	4.51 (3.07-6.62)
a. no	85	180			
17. when I am personally uncertain as to which treatment is best, I am likely to:					
a. enter the patient in a randomised clinical trial if I am aware one exists	175	138	19.45	<0.001	2.41 (1.64-3.54)
b. personal select a treatment	59	112			
18. when a potential eligible patient chooses not to enrol on a trial that I have suggested:					
a, I often feel disappointed	121	72	25.5	<0.001	2.65 (1.82-3.85)
b, I seldom feel disappointed	113	178			
20. ideally I would like to refer or enter the following proportion of my potential eligible patients into randomised controlled trial					
a. none	14	8	18.96	<0.001	
b. some	145	135			
c. half	14	13			
d. most	55	63			
e . all	6	31			
21. the time I devote to publications, lectures and research commitments, compared to clinical work, is relatively:					

a. totally clinical work	22	27	8.84	0.065	
b. mainly clinical work	155	153			
c. clinical and research equally	47	45			
d. mainly research	10	19			
e. totally research	0	6			
22. Frequent publications are important to my career advancement:					
a. yes	198	117	74.4	<0.001	6.25 (4.05-9.64)
b. no	36	133			
23. I am more likely to attend a conference that focuses on					
a. Clinical issues	155	186	3.48	0.06	0.68 (0.46-1.00)
b. research issues	79	64			
24. in my hospital, doctors are given more reward for:					
a. clinical skills with patients	99	166	27.35	<0.001	0.37 (0.26-0.54)
b. contributing to scientific knowledge	135	84			
25. If written informed consent was not required, I would approach more patients to enter clinical trails					
a. true	113	24	87.26	<0.001	8.79 (5.37-14.39)
b. make no	121	226			

difference					
26. the need for detailed monitoring of my management of trial patients by trial staff deters me from participating in randomised controlled trial					
a. yes	62	26	19.98	<0.001	3.11 (1.89-5.12)
b. no	172	224			
27. The increased paper work involved in treating patients on trials deters me from participating in randomised controlled trials:					
a. yes	77	94	0.97	0.32	0.81 (0.56-1.18)
b. no	157	156			
28. the thought of having to spell out all the details of a trial to eligible patients discourages me from approaching them to participate					
a. true	89	49	19.26	<0.001	2.52 (1.67-3.79)
b. false	145	201			
29. a major reason for my participation in randomised controlled trials is that it financially benefits my institution or department					
a. agree	67	26	24.72	<0.001	3.46 (2.11-5.67)
b. not agree	167	224			
30. Overall, involvement in randomised controlled trials					
a. enhances my reputation	101	111	0.03	0.85	0.95 (0.66-1.36)
b. does not enhance my	133	139			

reputation					
31. if research activities were to enhance my income, I would enter more patients in randomised controlled trials					
a. agree	101	63	16.61	<0.001	2.25 (1.53-3.31)
b. not agree	133	187			
32. when I participated in a randomised controlled trial, it is more likely that:					
a. I increase my patient population	73	13	56.67 <0.001		
b. I lose patients I might otherwise keep	14	15			
c. It makes no difference to my patient population	147	222			
33. my income rely on my research work					
a. yes	20	26	0.29	0.589	0.81 (0.44-1.49)
b. no	214	224			
35. in my hospital the pressure to participate in a randomised controlled trial is relatively					
a. low	131	222	64.29	<0.001	0.16 (0.1-0.26)
b. no	103	28			

4.1.3.3 Responses to the five indices of doctors' attitudes to involvement in RCTs

- **Primary allegiance[79]**

Chinese clinicians orientation, is towards the care of individual patients.(Q1, Q2) Chinese clinicians are more likely to take both clinical and research tasks at the same time, recognising that clinical practice is not their only requirement in the current medical community. A qualified modern clinician should connect clinical experience with medical research in their daily practice. (Q3) most clinicians thought that the overall quality of patient care increased.(Q7) Compared with Western clinicians, less Chinese clinicians thought that RCTs restricted their ability to deliver individual patient care.(Q8)

- **Decision making under conditions of uncertainty[79]**

When published data and clinical experiences conflicted, 67% of Chinese clinicians claimed they would rely on their clinical experience. However, Chinese clinicians are less willing to refer a patient if they were personally uncertain about treatment than their Western colleagues (Q11), and less likely to seek a major input from their patients.(Q12) this is the significant difference between Chinese and Western clinicians, which maybe caused by Chinese traditional culture and the clinicians' special status that I will discuss later. Chinese clinicians are more reluctant to put their patients in a trial involving a protocol that included a treatment that was more or less aggressive than their usual treatment.(Q14,Q15)

- **Professional activities**[79]

Research plays a small role in most Chinese clinicians' professional activities. Only 2.6% Chinese clinicians would enter all of their potentially eligible patients into a research trial, whereas 23% would enter most patients.

- **Perceived rewards**[79]

Chinese clinicians perceived that they would gain more rewards for research contribution than clinical skills (Q24), and thought that trial participation made no difference to their patient population (Q32). The laborious recruitment process (Q25 Q28), detailed monitoring of their management of patients (Q26), increased paperwork (Q27), and lack of financial reward (Q29, Q31) were significant deterrents for clinician participation in clinical trials. These results suggested that Chinese clinicians need more direct and indirect rewards from RCT research. Therefore, Chinese clinicians' incentive system needs to be improved to enhance clinicians' research interests.

- **Peer-group influence**[79]

Most Chinese clinicians perceived little pressure from their hospital to participate in trials (Q35). There is a strong culture for conducting research but not RCTs.

4.1.3.4 Some response with significant different results between Chinese and Western clinician

Western clinicians believe patients' right to select treatment option is prior to scientific knowledge advancement, but Chinese clinicians do not think so (Q9). Western clinicians seek major input from patients when making critical and controversial decision, but Chinese clinicians do not (Q12).

When published data and clinicians' personal judgment conflict, Western clinicians rely on published data, but Chinese clinicians prefer to rely on their personal experience (Q13).

Frequent publications benefit to Chinese clinicians' career much more than Western clinicians'. (Q22) Western clinician would get more reward for clinical skill with patients, but Chinese clinician would not.

4.1.4 Discussion

Conflict: Clinical doctor and researcher

In the past, the traditional dichotomy of physician either as researcher or as clinician was useful in categorizing groups of doctors and predicting their behaviour. Clinician's

reluctance to participate may be a significant behavioural consequence of the implication of randomized controlled trial[79]. The intensity of the physician's response to the formal integration of conflicting roles suggests that physicians themselves have begun to question and ardently defend their definition of their core task.[78] The Physician Orientation Profile is developed to gain a better understanding of clinicians who are expected to be both scientific investigator and primary caregiver. Therefore, two opposite groups were classified, one group is 'therapist' and the other is 'experimenter'.

Experimenters declared a primary allegiance to generating scientific data, interpreted medical uncertainty as justification for randomized controlled trials, saw patient care as an outgrowth of research, altered their current practice on the basis of published data, emphasized the rational and technical dimensions of medicine and expressed a willingness to share data with colleagues. In contrast, therapists claimed that their primary allegiance was to the individual patient, believed that it is the physician's obligation to reduce medical uncertainty by using personal clinical skills, viewed research as a possible outgrowth of patient care, gave priority to personal clinical experience rather than to published data, professed a loyalty to medical tradition, and declared a preference for individual patient care. The Declaration of Helsinki states that 'In medical research on human subjects, considerations related to the well-being of the human subject should take preference over the interests of science and society', which is the basic requirement for all medical professionals.'

Compared to Western clinicians, Chinese clinicians are significantly more willing to be seen as a medical doctor rather than a researcher. Chinese clinicians all have substantial experience of clinical practice; indeed every senior clinician could be called an expert in their own specialism. Compared with conducting research, clinical practice brings clinicians more praise from patients and greater financial returns, which are direct and visible benefits.

Chinese clinicians are used to instructing patients, and making decision for patients, rather than follow their opinion. This is a substantial difference between Chinese and Western clinicians. Chinese clinicians consider themselves as leaders in the relationship with patients, which are different to Western medical relationship. In Western countries, clinician and patient are considered more equal in their relationship, and the Helsinki Declaration emphasizes that patients' right of treatment selection is more important than scientific research. However, it is certain that Chinese clinicians are not taking concern about these issues.

4.2 Part Two. Qualitative research: focus group meetings and personal interviews

Semi-structured interview and personal interview are also conducted to detect Chinese clinicians' attitude toward RCTs. Furthermore, I tried to find the in-depth reason through clinicians' daily work.

4.2.1 Method

A preliminary study, included focus group meeting, interviews and in-depth observation of 3 grand hospitals in Guangzhou. This is a study to detect clinicians' knowledge and attitude. As I mentioned, there is no relative study conducted in China before, therefore my research is trying to collect frontline information as much as possible, both quantitative and qualitative research method are used to gather wide information.

I had a formal meeting with research administrators of those hospitals and discussed with them the best way to access clinicians and patients. As a result I decided to post an advertisement on the hospital website; both clinician and patients were free to participate. In case of a low response rate, each hospital research administrator nominated a group of clinicians to participate in my research, which was considered part of their routine training programme.

4.2.1.1 Focus group meeting

Focus groups are unstructured interviews with small groups of people who interact with each other[80]. They have the advantage of making use of group dynamics to stimulate discussion, gain insights and generate ideas in order to pursue a topic in greater depth. It is a useful technique for exploring cultural values and beliefs about health and disease.

An understanding of group processes and models of small group behaviour is helpful to offer insight into what can happen in focus groups and why. This can inform appropriate strategies to facilitate the group as it goes through different phases of the group process.

I conducted 14 focus group meetings in these 3 hospitals, 5 in The No.1 hospital, 4 in the Red Cross hospital and 5 in the Guangzhou Brian hospital. Following the principle of maximizing information, I repeated my focus group meeting among the eligible clinicians until I could not find any new information from the group meeting. The focus group meetings lasted 65-85 mins each, and were conducted in each hospitals' meeting room.

4.2.1.2 Personal interview

Semi-structured interviews are used for getting more specific information, by asking open-ended questions[80]. The data obtained from qualitative interviews are used to increase our insight into social phenomena rather than assume representativeness. None the less, the issue of non-representativeness of people, and hence the limitations upon generalisability of results, is a criticism that is frequently encountered.

30 senior clinicians were interviewed, 12 from No.1 hospital, 8 from Red Cross hospital, 10 from Guangzhou Brain hospital. The interviews last 20 to 40 minutes each and take placed in senior clinicians' offices. All the interviewed clinicians are nominated by each hospital; all of them have the experience of conducting RCTs.

4.2.1.3 Focus group and personal interview questions

1. What is a randomised controlled trial?
2. What is your personal experience of randomised controlled trials? And what is your attitude towards conducting RCTs, positive or negative?
3. What are the difficulties in conducting RCTs?
4. Are there any benefits of conducting randomised controlled trials, personally or collectively?
5. Based on your experiences, what do you think is the job of ethics committees in conducting randomised controlled trials? And what is the reality?
6. What is your suggestion of improving RCTs conducted in China?

4.2.2 Procedure

Every Wednesday and Thursday afternoon were the regular training time of clinicians in these hospitals. That is the time for health professionals to learn updated information about their medical area. Although 100% of the participants were nominated by the hospital they were interested in the study when they heard about the research questions, because this study is the first time experienced clinicians had come together to discuss RCT problems, especially some of the more practical problems. The focus group meetings provided professional medical doctors a good opportunity to discuss practical problems with their colleagues in the same medical area or in different medical areas.

The focus group consisted of 8 participants each time, that all had experience of conducting RCTs. I, as the facilitator, introduced myself and gave a brief background to my research at the beginning, then asked them to introduce themselves one by one. This was followed by a discussion using open ended questions and a semi-structured questionnaire.

At the beginning of the focus group, I introduced myself and welcomed all participators warmly, in order to put them at their ease by friendly conversation. I introduced some basic information about randomised controlled trials and my research background with the following words: Randomised controlled trials are known as the gold standard of medical research, every new drug and treatment needs to establish certain information from a RCT before it can be used widely. However, in recent years researchers found there are many problems in RCT conduct, which would relate to RCT participatants, including clinicians and patients. We would like to hear from you, as an experienced clinicians about the problems you encounter as a researcher / participant in RCTs. We hope you could share your experiences with your colleagues and us, in order to make RCT conducted in China more effective and efficient.

Following this I asked the group to introduce themselves, with the aim of them getting to know each other and to build up a degree of familiarity. However, I found that participants did not like to do introduce themselves, because they felt they already knew each other within the group and I was the only one they needed to be introduced to. Since they were all the clinicians of the same hospitals, it is understandable that they

already knew each other. Therefore, if they did not want to introduce themselves to each other then I would omit this part of the focus group.

It is impossible to gather all senior doctors together to conduct a focus group meeting, therefore I arranged a personal interview for those senior doctors unable to attend the focus group. The senior doctors were nominated by the hospital study administrator. I was introduced to the senior doctors by the hospital study administrator and made the appointments myself. The questions in the personal interviews were similar to the questions asked at the focus group meetings. Questionnaires were left with senior doctors if they did not feel able to complete them immediately. Personal interviews lasted 10 to 15 minutes each. I introduced the same information as when conducting the focus group meeting.

4.2.3 Analysis

I am using 'thematic content analysis', which is the most basic type of qualitative analysis. It is to an analysis of the content of the data to categorize recurrent or common 'themes'.

Using the transcript from all my interview recordings, I categorized interviewees' accounts in ways that can be summarized. It is essentially a comparative process, by which the various accounts gathered are compared with each other to classify those 'themes' which recur.

Analysis must be purpose driven[81] and the style of analysis must be directed towards answering the research questions. My analysis, therefore, was based on selective coding that focused on normative claims that were relevant to the research questions. Coding was carried out as a method of organizing and managing meaningful segments of data[82], and was the first stage in the formal analytic process. Codes were attached to the data, and multiple codes were often attached to same segment. Multiple coding is warranted when a coded segment is both descriptively and inferentially meaningful[70], and the data was generally rich in both kinds of meaning.

In order to keep the segments in context, I refrained from coding small segments of speech and coded larger sections, often including the parts of discussion prior to and immediately after the segment of interest. This made coded segments very substantial but ensured that the context was not lost upon retrieval.

Coding as the first stage in formal analysis, was selective and focused on the meaning of the data rather than on the word used[70] As such, the coding itself was an interpretive process, in which meaning was elucidated through my own understanding of the significance of the context in which the words were uttered[69].

Coding was performed in two streams. The first stream was ‘free coding’, in which the data was taken at face value and codes were attached without particular reference to previous data sets. This simply means that the ‘primary coding’ was conducted in an

unstructured way, focusing on the data set and generating codes solely in reference to that. The second stream was performed based on those free codes and aimed at standardising the codes so that the groups could be compared and analysed using the same conceptual framework. No attempt was made to limit the number of codes used in the first stream only those codes that had been replicated or could be replaced by an existing code were removed.

This method was chosen because the very large data set meant that too rigid a coding framework from the start would inhibit full analysis, but not enough of a framework would make the data uncontrollable. The two stream system compromise was labour intensive, but was advantageous insofar as it allowed sufficient conceptual freedom to ensure the analysis did not become conceptually bound by what had gone before, but it also provided enough of a framework to ensure that coding was performed consistently. The two stream coding also helped to reduce the possibility of bias, and helped me to maintain a sense of objectivity during coding. Using standard codes from the start would have increased the temptation to use existing codes that did not quite fit, rather than produce new codes and increase the workload. By giving free reign to start with and the standardizing later, I allowed the creation of new codes as and when necessary. I found multiple codes that were unnecessary, which I subsequently removed and re-coded using the previous standard.

Excel was employed as a tool to help manage and organize data under categories, facilitating easy retrieval of coded segment and providing efficient way to store the data.

4.2.4 Results

The focus group meeting and personal interview were taken placed from July 2007 to May 2008.I divided clinicians into two groups: a senior clinician group and a junior clinician group, because I found their working characteristics varied from my interviews. Senior doctors were defined as an associated chief and chief doctor; junior clinicians were defined as clinicians in charge, or resident clinician. Although these two groups work together in the same department, their duties derived from their positions are different. In the RCT context, senior clinicians are in charge of administrative work, but junior clinicians are the people who execute the trial in practice. I tried to describe their different working characteristics in detail, which would help understand clinician's behaviours, and found different way to investigate their RCT work. 30 senior doctors and 112 junior doctors participated in my interviews. Each hospital has conducted a number of randomised controlled trials in different departments including digestive, respiratory, urinary, incretion and surgery.

In my study junior clinicians are defined as clinicians in charge and also resident clinicians. These two different groups of clinicians were grouped together because of their common characteristics and similar working status in randomized controlled trials.

- **Age and sex**

Most senior doctors interviewed already had PhD or MD degrees (25 of 30); the remaining 5 have a Masters degree and are currently completing their PhD studies. Their age ranges from 39-65, with a mean age of 52, and median age of 49, 24 of the interviewees were male, whilst 6 were female.

In comparison to senior doctors, junior doctors are of course younger; in my study I interviewed 112 junior doctors, whose age ranged from 26 to 36, (mean is 29.3, median is 28). Their clinical work experience ranges from 1 to 12 years. Male clinicians (64) were more common than female clinicians (48).

- **Knowledge and experience of clinical practice**

Senior doctors interviewed all have at least 20 years of clinical experience. The number of patients' seen is a reflection of this experience. I asked senior clinicians how many patients they had seen and most of them said 'that is hard to say, it is certainly a big number.' On the other hand, senior doctor are all clinical experts, they are often invited to consult for difficult cases among different hospitals. As senior doctors they have a low complaint rate from patients and the expectation is that they are highly skilled in clinical treatments.

An academic degree is increasingly important to Chinese clinicians, especially for professional clinical doctors. Ten years ago, a medical school graduate could start his clinical work with a bachelor degree, however, now it would be difficult to find a medical job in a hospital with only a bachelor degree. Increasingly hospitals require their medical

employees to have good bachelor degrees upon entrance, and then encourage junior clinicians to study part-time for higher degrees. Therefore, from my research, I found junior doctors in these 3 hospitals all either have, or are aiming to obtain, master degrees on clinical science.

- **Experience of conducting randomized controlled trial**

The senior doctors interviewed all have experience of being the director or coordinator of randomized controlled trials. From discussions in the interviews they are knowledgeable about conducting randomized controlled trials, especially on a practical level. They were aware of good practice standards of RCTs; what the barriers are, and the best ways to solve them.

Senior doctors have much experience of managing RCTs, but junior clinicians have more experience on recruiting participatants. They are participating in RCTs as frontline researchers. Their works also includes talking to patients, obtaining informed consent and collecting data. However, from my research, I found that they often had not had the opportunity to look though the whole study completely. Therefore, few of them have a comprehensive understanding about randomized controlled trials.

When asked the question 'have you participated in randomized controlled trials as a researcher?' all junior doctors responded 'yes'. They described their jobs in randomized controlled trials, for example '*when the chief doctor (senior doctor) of my department agreed to do a randomized controlled trial, a project manager would come to our*

department and have an introductory meeting. They explained their research proposal to make us understand what kind of patients they are looking for' (J17).

'My job is to find the right patients for them to conduct research.'(J5) 'I talk to patients, introduce the research project, and seek their agreement to join the research.'(J12) 'When they have agreed to participate, I would let them sign their name in documents.'(J34) 'Some specific body-examination would be required for a randomized controlled trial; I record the result.'(J56) ' If the participating patients are not feeling well during the research processing, I have to take care of them. Most participating patients are in-patients; I have to watch them all the time. Anyway, any in-patients would be taken care of by our clinicians.' (J58) 'There is some monitoring from the pharmaceutical company; they would come to the hospital to view patients and data quality. At last I hand in all data to him.' (J24)

When I asked, 'after handing in all data to the monitor, what you will do next?' Junior Clinicians answered for example, *'usually, my job is then finished. Later they will inform us about the trial result.*' (J1) Most of the junior doctor responses were similar in this regard; they only participated in patient recruitment and not the other stages of randomized controlled trials. Junior clinicians' understanding of clinical trials is mostly around patient recruitment. However, one junior clinician told me he was willing to do some data analysis for the trial, but due to some contract regulation, he was not allowed. Some junior doctors need to have publications for their academic degree or working promotion and they would like to have some publications from their daily work; however

this is hard to put into reality. From my interviews, I was told that some randomized controlled trial projects had already decided who and how to deal with the data analysis before hand; so after the project started, they would not allow others to join the analysis group.

- **Busy working hours but limited research time**

Senior doctors state that they are very busy. Their working hours are from 8am to 5pm, including a two hour lunch break. Usually they arrive in the hospital before 8am, and see all patients on the ward, listen to junior doctor's updates of each patient's disease information, and prescribe treatment. Each senior doctor would take responsibility for a small group of patients; usually between 10 and 20. Therefore, from my personal observation, senior doctors knew each of his/her patients quite well.

Senior doctors are required to work in clinic at least three day per week. Their clinic working time is fully booked. They are required to see a certain number of patients, usually 20, in the morning section or in the afternoon section. On the other hand, there is often a waiting list of patients wishing to make appointments with senior doctors, and there are always some patients waiting outside of senior clinicians' offices hoping to see the clinician as soon as possible. Therefore, senior clinicians' workload can be substantial, the bigger hospital the bigger the workload.

Although many senior doctors work more than 8 hours per day, they find only limited time in which to do research. This is especially true for famous surgeons, who spend

almost all of their working time on clinical practice. On the other hand, their clinical works were praised by patients, as from an individual patient's point of view; they are seeking the best doctor in clinical practice, not in medical research. It is maybe therefore quite understandable for clinicians to have more interest in clinical activities and not research.

On the other hand, hospital regulations state that clinicians are required to work in clinic or take time with patients; and there is not any requirement for clinicians to do research. Therefore, overall clinicians' patient requirements mean that they have little time for research. To participate in an RCT, they could recruit patients from their clinical work, however other tasks that form part of a randomised controlled trial, are time consuming and difficult to create time for.

Junior clinicians often work long and inflexible hours, with shifts at unsociable times, and may earn less than other professionals whose education is of comparable length. They have at least 2 overnight shifts every week, and their working hours totals over 55 per week. In some departments a shortage of formal employed staff means they may work even longer hours. When they are on duty, they are in charge of all in-patients; any emergency incident would be treated immediately.

However, not all duty time is spent treating patients, Some of the time will be spent recording disease information, making diagnoses, dealing with prescriptions and updating their in-patients' medical records. Junior doctors spend most of their time on

seeing patients and writing medical records. In my study I found 62% of junior doctors are aiming to obtain higher academic degrees by attending part-time courses. The higher degree is required in order to achieve promotion, and Publication is required to obtain the degree. It is stated clearly by the medical school that postgraduate students need to publish a certain number of papers in Chinese core medical journals in order to receive their Masters degree and varied but more strict publication requirement for PhD or MD degrees. The requirement of quantity and quality of publication varied in different medical schools.

- **Relationship with local medical community**

Chinese senior doctors all develop and maintain good relationships with the local medical community. There are a number of medical associations at national and provincial level. In addition, they are all alumni of medical schools. In each large and middle-sized city in China, there are at least 2 medical schools, and the medical schools are attached to local hospitals. When medical school students graduate, they tend to prefer to work in their local hospitals with only a small amount of graduates migrating to other hospitals. Thus most doctors within a hospital graduated from the same medical school and therefore they tend to have similar backgrounds.

In China, each specific disease area has its own association at a national, provincial and municipal level. Senior doctors all hold important positions in the medical associations. There are many opportunities for senior doctors to study, such as conferences or short training courses.

- **Relationship with local community**

In order to keep good relationships with the local community, hospitals frequently introduce free consultations or treatment to the public. Hospitals, as a professional medical unit, have an important responsibility for the health promotion and education of their local communities. Senior doctors are always the main organizers of these activities. The hospitals require each department to do some consulting or health promotion activities, and the senior doctor's name is utilized as the best advertisement.

On the other hand, the good relationship is from their occupational position, not from their personal characteristics. As previously mentioned, doctors were considered as 'representative of God' or 'God' in ancient China[39]. During the last 100 years, China has suffered war, poverty and disease and an extreme shortage of professional medical doctors. As a result, healers and 'magic' came back to Chinese rural areas. When the Peoples' Republic of China was founded, the government introduced scientific treatment to citizens, and banned healers from treating patients. Medical doctors were described as 'representatives of science' and replaced the magic healers. Therefore, medical doctor as an occupation was linked with terms such as 'professional' 'advanced' and 'authority'.

Junior clinicians concentrate on their personal routine works, however, in addition, they are keen to enhance their personal reputation in the medical and local community as well. A high quality of clinical service and an abundance of medical publications are the

two substantial elements contributing to a clinicians' reputation. Junior clinicians are taught this; therefore they work hard in their clinical practice and seek any possible opportunity to participate in medical research. The good reputation of a clinician would encourage patients to choose them with more confidence, which would bring more direct and indirect benefits to clinicians in terms of honours and incomes.

In my research, junior doctors recognized the need to enhance their personal reputations in order to achieve their ambitions and career progression, for example *'I am only a tiny guy in my department. My department director, Dr XX, he is the expert in this area. He is famous, not only in medical area, but also in the local community. I need to work about another 20 years, I hope I could reach his level.(J23)'* I recognized that they respect the senior doctors in their department and wish to emulate their careers by becoming famous clinicians themselves.

- **Are Doctors Satisfied with their Income?**

In all RCT research, the participated investigators will get financial award for their work, those incomes is not included in their salary. The amount of this income is depending on their workload, more work means more income.

In my research, I found that Chinese senior doctors are generally satisfied with their income. Their incomes included basic salary from the hospital, research work rewards and grey incomes. Grey incomes include ‘red envelopes’ from patients and prescription bonuses from pharmaceutical companies. (The original meaning of Red envelop[39] is the gift money which was given in holiday or special occasions, which is also used to deliver bribes.) Senior doctors have the power to allow or forbid junior doctors to prescribe a certain drug. There is no specific regulation to restrict clinicians’ prescription bonuses which is still a substantial part of clinician’s income.

For many physicians, in particular those at big hospitals, specialty hospitals or hospitals with large reputations, physician incomes can be larger than regular hospitals. Physicians, and in particular, surgeons, can augment their hospital salaries by operating surgeries at hospitals other than the one in which they are employed. Many physicians also receive commissions from prescribing prescription drugs and get “red envelopes” from patients or from sales representatives of drug companies. However, a new regulation issued by the Health Ministry removes physicians from the practice of medicine if they are found to have taken "red envelopes" from patients, and a hotline has been set up to monitor physicians.

Another big part of their income is the bonus from prescriptions. As we know, the competition between pharmaceutical companies is fierce, especially in China. The Chinese medical market is large and there are a number of medicines with similar curative effects but that are produced by different pharmaceutical companies.

Pharmaceutical Sales Representatives attempt to access clinicians, especially the senior doctors, in order to make them understand their products and prescribe these to patients rather than other opponent pharmaceutical companies' drugs. Financial encouragement is still a substantial way to stimulate sales volume. There is no relative regulation from hospital to forbid these activities and more and more pharmaceutical companies accepted this 'sub-principle' in medicine sales, then clinicians would like to take this bonus from their daily work. Furthermore, as the senior member, those doctors would be more concerned with pharmaceutical companies than junior doctors, more advanced gifts may additionally be sent to senior doctors, such as free shopping vouchers or free family holidays.

When I asked junior clinicians about their incomes, most of them responded that they were 'not satisfied' 'I am poor in this city'. Like other clinicians, their incomes include a basic salary, department bonus and prescription bonuses. The prescription bonus is a substantial part of a clinician's financial income. There is some research that suggests that prescription bonuses take the leading part of clinicians income[83]**.** In addition, Guangzhou is one of the most developed cities, both the average income level and consumption level are higher than in other Chinese cities. Usually, junior clinician's salary level in comparison to their years of education is not considered satisfactory. Junior clinicians have more financial pressure than senior doctors, because junior clinicians are younger and have the pressure of having their own family, getting married and buying a house. Therefore, junior doctors are motivated to work hard in the hope of

gaining a promotion, because a higher position in the hospital would bring them more financial return.

- **Ethical approval**

Senior clinicians have a good understanding about getting ethical approval before starting the research. Some of the senior doctors are members of ethics committees of the hospital, local medical association or provincial ethics committee. There are many different kinds of people involved in ethics committees, for example, lawyers, nurses, lay people and experts in certain disease areas. Senior doctors joined ethic committees as medical experts, and their opinions carry great weight in the committee.

'When we received a research proposal, each of our committee members would judge whether to take it in on from our personal professional view. The research manager would come to give a presentation, and then we discuss the project within committee, and then all of our members vote to have the final decision.' 'Normally, when the research manager come to us and give the presentation, I already have an idea about whether to give approval or not. I am a senior person in this area. I think I understand about all the disease principles in this area. I know what kind of treatment would make patients feel better, and some of the medicines side effects; I know how bad it is. If I feel the research design is not good enough, I mean, if there is some good treatment, but they choose placebo as a comparison group, I would certainly say no to them, whatever

they pay us for doing research.' 'There are many researchers, especially those multi-centre, large, randomised controlled trials, which got ethical approval from the committee of Beijing or from provincial level ethic committee. When we see the approval from upper level, we have to give approval as well.'

Ethics committees are not a new concept to Chinese clinicians. Although Chinese medical professionals have conducted their research since the Peoples' Republic of China was founded, no research work is conducted in mainland china without getting ethical approval before hand. With the development of medical ethics, Chinese medical professionals have recognized that there should be ethics committees in our medical systems. Therefore, in just a few years, almost every grade 3 hospital, medical schools and medical research institution has their own ethics committees. However, there are still some problems on ethic committee's working mechanisms such as the lack of a medical ethicist and working experiences.

- **Informed consent**

Informed consent is the way we introduce the research to patients and get their agreement to participate in the randomised controlled trial. Senior doctors do not usually handle informed consent. They usually send informed consent to junior doctors, and then await their reply with the patients' signature. Without the patient's signature the senior doctors would not allow those patients to be involved in the randomised

controlled trial. ‘Without patients signature we could not put the patient into our clinical trial, which is the routine procedure of clinical trial. We have to comply with the regulation.’

From senior clinicians view, they think it is not difficult to get informed consent from participators. ‘Usually, if we clinicians asked patients to join the research, most of them would agree to participate.’ ‘I don’t think getting patients signature is difficult, at least from my experience, our department always could have enough patient participants for research.’

Junior doctors describe the ethical issues of randomized controlled trials as:
‘Our hospital has an ethics committee, without their agreement, research can’t start, not only randomized controlled trial, but also other types of research.’(J34) ‘ I know ethic committee’s agreement is quite important for trial start, without it, it is illegal.’ (J35) ‘When our department accepted to do this research, I think this research had already passed ethics committee approval.’(J43) ‘We are in the executive level, about ethics issues, which is conducted by senior doctors and administrative staffs in our hospital.’ (J45)

From my research it appears that junior clinicians in Chinese hospitals know it is necessary to obtain ethical approval for research (including randomized controlled trials), which is the preliminary procedure of doing research. Although junior clinicians have no idea about how ethics groups produce approval for the research.

- **Attitude to participate in research**

From the personal interviews which I undertook, I found that Chinese senior doctors are willing to participate in research, regardless of the research topic. Senior clinicians are also the senior staff at medical school so to achieve and maintain an advanced academic title not only requires clinical skill and diverse experiences, but also the ability to conduct research.

They prefer to lead research rather than participate in research, which requires financial support from national, provincial, municipal or school level. However, the competition for rewards is fierce; therefore, most of them are involved in joint-leadership of many research projects.

A Chinese clinician is very busy in his clinical work everyday as they manage a large patient population. However, if a clinician would like to do some medical research, it is not easy to find an opportunity; they are often passive in medical research. Usually when a research project is accepted by senior doctors in the department, then several junior clinicians would be required for the project team. Then junior doctors would be invited to study. In most of these studies, junior clinicians will not get a publication at the end of it, thus junior clinicians are not enthusiastic of participating in the study and it is just treated as an order from senior clinicians.

Junior clinicians cannot connect medical research they have participated in to their promotion achievements. From my study, all junior clinicians told me that in big research studies (such as randomised controlled trials), it is unusual for them to achieve authorship of a publication. Due to their hospital promotion requirement, these non authored publications of research in which they played a part do not contribute to their promotion aspirations.

Many junior clinicians feel that this process is unfair. They all carried out trivial but important jobs with patients but the rewards of this were limited. For example, 'I spend much time on patients for those researchers, but there is no record of my hard work, only my supervisor knows how hard I worked.' Therefore, if their work could be related to their promotion, that would help to increase their enthusiasm for medical research.

4.2.5 Clinicians' Knowledge of randomized controlled trial

- **Definition of randomized controlled trial**

The definition of randomized controlled trial is as follows,

'Randomized controlled trial' is an experiment for new drug and new treatment, through the comparison with placebo or other treatment, in order to make sure what is the effective and efficiency of the new drug/treatment.'

Most of my interviewees gave similar responses; therefore I believe they have good understanding about the definition of an RCT.

'It is a scientific research method for new drug. Before the drug was accepted broadly, RCT is the necessary test for drugs. There are 4 stages of clinical trial, stage one is toxicity and pharmacology trials, which are concerned with drug safety. Stage two trials are conducted on patients only, without a control group. On Stage three, there are randomized controlled trials, with a control group and based on a large population; In China, stage two and stage three are usually combined, so there are no real stage two trials. Stage four is the post-market research about the drug.' (S21)[*]

'A group of patients were randomized and allocated to two or more research groups, with active drug or placebo, and do statistical comparison between groups about patients' disease progress, then draw a conclusion about whether the drug is efficient or not.'(S16)

Most of my interviewers could give a similar answer. I believe they had good understanding about the definition of RCTs.

[*] [*] This citation is from my interview record. S is abbreviative word of Senior, the number followed is my interview order. J is abbreviative word of Junior, P is abbreviative word of Patient.

When I carried out the focus group meeting in the Red Cross hospital, I asked about the definition of a randomized controlled trial. Responses (below) suggested they had received training about RCTs and understood it's purpose and usefulness.

'Clinical trial is defined as planned experiments involving patients, the purpose of which is to determine the most appropriate form of treatment for future patients, this includes 4 phases. Randomised controlled trial is the phase 3 trials, which involve a comparison group, receiving the new treatment with a control group, usually receiving a standard treatment or a placebo. This is the most rigorous and extensive type of scientific clinical investigation of a new treatment, which is considered the 'gold standard' in new medical research.' they told me that their department as clinical trial unit passed quality inspection just a few days ago, which was conducted by the relevant medical and health administrations. As a clinical trial base, it should be inspected at a municipal, provincial and national level frequently. As members of the clinical trial base, they are required to have adequate knowledge of randomized controlled trial. Therefore, they had collective training about the randomized controlled trial on its definition and methodology.

- **Randomization and the reason for using randomization**

Senior doctors all had good knowledge of randomization; they described randomization as *'a scientific method, statistical method. A statistician created a number sheet, which was created based on a certain statistical method' (S12)*

'Usually we got a computerized random number list, which was used to allocate RCT participants.'(S21)

An important issue in design is to ensure that the allocation of the treatment to patients is independent of the characteristics of the patients, so that when we come to compare groups, they will differ only in the treatment given. Randomization is the accepted method of eliminating allocation bias in clinical trials.

I believe that they are aware that randomization is important in patients' allocation; however, few of them could clearly state the reason for this. Clinicians' understandings of why randomization is used are poor.

'It was used for scientific reason;' (S8)

'It was used to allocate participators in different treatment group.' (S9)

'I was told have to do this in the RCT study; because it is a multi-centre study, we have to follow the same regulation as other centres…. Statisticians know the reason why we should do it' (S17)

Junior clinicians stated 'It is a word from statistics, which is to allocate patients into two or more trial arms.' 'It is a statistical method to put patients into two groups without particular order' 'statisticians do that, and that will help on their final data analysis.' 'Randomization is the way to avoid bias in experiment, which is a scientific method to allocate patients.'

They describe the meaning of using randomization is ‘to allocate patients, make two groups with similar patients’ ‘ make the trial group and placebo group the ‘same’ at the beginning.’(Of course they are not really same, but differ only on the basis of the play of chance.) ‘Usually they have a random number sheet, but as a researcher, I only have a patient’s number and their medicine code. I know randomization is quite important to this research.’

- **Blinding**

Senior clinicians appear to understand blinding quite well. ‘Blinding is quite important to randomized controlled trials, without blinding, the accuracy of randomized controlled trial would be low.’ ‘Blinding is not a difficult definition in randomized controlled trials, as a researcher we should put our personal preference aside from the real data, therefore I think blinding is a good way to help us record just true data.’

Senior clinicians know the principle of blinding, so they preferred to be blinded. I asked them whether they did guess the patients’ allocation, they told me: ‘yes, personally I did. But I haven’t communicated patients’ allocation with my colleague or patients.’ ‘I have some suspicion, but I think it is useless to talk about patients’ allocation. We were blinded. As a scientific worker, I should comply with research rules.’

Junior clinicians had a good understanding of blinding and its definition. *'Most research is double blind or single blind. Blinding is a method by which the participants, clinicians or patients are unaware of which treatment group they are in.'(J40) ' in some of the trials, we clinicians don't know which group these patients are in, that is the double blind trial, but in some trials, we clinicians could not be blinded, because of its specified treatment, that is a single blind trial'.(J41)*

'Blinding is the method which keeps clinicians and patients' personal psychological effects separate from the treatment result. Psychological effect would certainly influence treatment result.'(J45) 'I think blinding is quite important in randomised controlled trials, which bring placebos into play.'(J47)

All junior clinicians I spoke to had good understanding about the meaning of using blinding. At least they had understood the blinding principle, but found it hard to execute in practice.

I observed clinicians in their work; I found most clinicians can't blind their patients during the whole RCT process. When conducting a double blind trial, clinicians are often quite curious to know which patients are taking the real medicine. Also, some participating patients keep asking clinicians whether they are in a new drug group; if they found out that they were not they would withdraw from the trial. Some clinicians felt under pressure to guess whether the patient was in the drug group. Therefore, it appears that

blinding is easy to understand in methodology, but hard for Chinese clinicians to operate in practice.

- **Where did senior doctors learn about randomized controlled trials?**

Senior doctors are all over 40 years old. In my interviews, I found that almost every senior clinician had been trained, (within the last 6 months to 2 years). Although senior doctors had a good understanding about randomized controlled trial, that knowledge is more from their practical work but less from their education. I was told that

'When I was in medical school, I studied clinical knowledge and practice my work in hospital. I had no idea about what is randomized controlled trial.' (S1)
'In recent year, there was more and more RCT research conducted in hospital, but just a few years ago, I have no idea about what it is.'(S2)

'I learned RCT in my work;' (S3)

'When a new RCT project start, people from pharmaceutical company or from leading institution will come to our hospital; and they usually give a speech to explain their research method, where I learned many new skills from.' (S4)

'Our hospital have the qualification of play clinical trial, which is in order to get this qualification; we have to be trained and pass some exam. I learned a lot from these training.' (S6)

'Well, I can't remember whether I was trained clinical trial in school, you know, I am a clinical student, not good at statistics, which I only learned a little. Anyway that is not my main course.'(S10)

- **Lack of concern about methodology and statistic course**

The RCT as an experimental method is new to those clinicians who graduated from medical school more than 20 years ago. From their descriptions I found the discrimination in medical school that students and teachers are concerned with all clinical subjects, but not epidemiology or medical statistics, which is in line with the Chinese culture and Chinese social hierarchies. Surgeons are a group receive the most respect because they could perform operations, save patients lives, and in the war they could join the army immediately; followed by physicians, who are considered as skilled people who can help patients in daily life, old (that means experienced) physicians are also admired by patients; and then the third kind of people who worked in hospitals, but do not conduct clinical jobs, are epidemiologists or medical statisticians.

Another reason is the difference in financial income. Given the strong link between clinical work and financial income, Surgeons are an unbeatable group to receive more grey incomes, because they would be the direct person to make effect on patients' bodies, followed by physicians, but not epidemiologists or statisticians. Therefore, these people are not working in hospitals, and so could not help professional clinicians when conducting research work.

Those clinicians whom I interviewed in hospital are all good at clinical practice. They are concerned about clinical skills much more than research design. Especially those clinicians who graduated from medical school 20 years ago; there was no relative training course on research methodology available from medical school at that time. On the other hand, randomised controlled trials as a new method was introduced to medical research just about 30 years ago. Chinese senior clinicians may not take enough concern on RCT research methodology.

4.3 Discussion

This is the original research about Chinese clinicians' understanding and attitude toward RCTs. I found the use of focus group meeting is quite suited for my research, because without the group circumstance, junior clinicians would not like to talk more details of their RCT experiences. In my focus group meeting, clinicians are from different department, they are quite excited to hear from their colleague of different department

on conducting RCTs, some recruitment experience and reward information they would like to share with others.

When I asked junior doctors whether they would like to participate as a researcher in a randomized controlled trial, most junior clinicians responded that they would, for example, '*yes, I like to participate in randomized controlled trials, because this is a good opportunity to learn what is the most advanced technology or treatment of the disease area.' 'I could learn from the randomized controlled trial about their research design and some research methods.' 'Participating in randomized controlled trials would bring me more research experiences, and learn more advanced research methods.'* Therefore, from their opinions, I found that most junior clinicians mentioned that they could learn through the trial, about new techniques, advanced treatments and research strategies**.** Even some junior clinicians who would contribute their working time to complex and trivial tasks, but junior doctors are still consider this is a good opportunity to gain research experiences.

- **Good reputation and social status**

Doctors' good reputation is based upon their research and clinical achievements. In order to be promoted to a senior member in the hospital, publications in high quality medical journals are essential requirements. Although there are debates about this strict requirement, this has been a basic requirement for medical doctors, for at least the last 20 years and has had an impact on all Chinese doctors.

Their clinical experiences and skills are enhanced during their daily work. Based on the large population of China, the number of patients in this country is substantial as well. Chinese patients often prefer to go to famous hospitals in bigger cities. Therefore, the patients of Guangzhou hospitals include not only local citizens, but also patients from the surrounding rural areas and undeveloped provinces nearby, such as Guangxi and Guizhou.

Junior doctors commonly enjoy a high social status, often combined with expectations of a high and stable income and job security. Although they are not senior doctors in the hospital, they believe that through their hard work they will be promoted to senior status in the future. On the other hand, doctors as a professional group have always been considered as a high social class in Chinese history. Even through difficult times, for example, in 1950's most of the Chinese medical clinicians were 'barefoot' doctors, but they were considered experts with the most medical knowledge in their village, and they were considered to save peoples lives. They were farmers who received minimal basic medical and paramedical training and worked in rural villages in the People's Republic of China to bring primarily health care to rural areas where urban-trained doctors would not settle[84].They promoted basic hygiene, preventive health care, family planning and treated common illnesses[85]. (The name comes from southern farmers, who would often work barefoot in the rice paddies.)

- **participating research activity**

In my study, I interviewed senior doctors from Guangzhou. They had the choice of deciding whether to participate in a medical study or not. Those senior doctors all had experience of conducting medical research, but few had worked on randomized controlled trials. I think the main reason is that randomized controlled trials are complex experiments that involve teamwork, especially if they are multi-centre projects. In my research, I have found that most randomized controlled trials were organized by big institutions from Beijing and Shanghai, this may be because those institutions have larger research teams than in other cities.

In my study, my interviewee doctors had been involved in randomized controlled trials as partner leading researchers, who were in charge of recruiting patients and conducting trials in Guangzhou, but not involved in the trial design, quality control, data analysis and resulting report.

When the hospital was invited to take part in a randomized controlled trial, the host institution would set up a meeting to introduce their study proposal. Senior doctors would be invited to the meeting to discuss whether they would like to participate. Senior doctors would judge the feasibility of the study from their personal experience: the effectiveness of the drug / treatment, the acceptability of the patients and the impact on medical workers. In addition, the financial and academic reward is a consideration to senior doctors. Once the senior doctor decides to participate in the RCT, then their department would have another introduction meeting, but the main target of that meeting is to allocate research work to each clinician.

Junior clinicians are clinical and research team members in their department. Some of them will view outpatients in clinic, and also join their colleagues taking care of inpatients in the wards. They are the people doing a substantial amount of work and working inflexible hours. Although they are not the lead within the department, once the team leader decides to do some research, junior clinicians will deal with the detail of the research. In addition, senior doctors would carry out important operations or treatments for patients, but junior doctors carry out all routine works which are basic but substantial and important procedures to patients. Similarly to clinical practice, junior doctors are also doing substantial work in research as well, for example enrolling patients or recording data.

- **Clinicians' working profile**

The senior doctor is the core person in the department and leads the team. From my observations, I found that senior doctors are always followed by junior doctors because they are reporting update information on patients and looking for changes to prescribing. On encountering difficult cases, junior doctors are accustomed to consulting senior clinicians**.** Therefore, senior clinicians not only take care of their own patients, but also patients from junior clinicians. In addition, senior clinicians are invited as consultants by different departments and different hospitals. They are considered experts in their clinical area.

Senior doctors are not only the chief of clinical practice, but also the leaders of medical research. They take the lead role in medical research and hold academic titles as professor or assistant professor. In addition, they are required to produce a certain amount of publications each year. In order to get promoted to a senior and research position, doctors should have at least 2 publications in high impact factor medical journals. Once they are appointed to senior level they need to maintain their good reputation and seek further promotions, and high-quality publications are a substantial and necessary requirement in achieving this.

- **What are the factors that facilitate junior clinicians' participation in research work?**

From my research I found

1. Collective activity. Junior clinicians are in the department as a group member, he or she has the awareness of collectivity. As an individual, he or she should comply with the group rules (i.e. the rules of their department, hospital, profession, culture etc), which is a common psychological impact from being a member of a group or organization. Normally the leader of the department decides to participate in clinical research, however, the leading member is also the junior clinician's supervisor as well, therefore junior clinicians usually choose to comply with their leader's decision. Even if they can't get any direct benefit from the research they could be rewarded by the supervisor's good impression of them.

4 Financial reward. To be involved in some research, especially randomised controlled trials, junior clinicians could receive some financial rewards from the research organizer or pharmaceutical companies. This is a possible reason for participating in research, however from my study I found that clinicians are not generally satisfied with this research income.

5 'Collective reputation', almost every junior clinician I interviewed mentioned this. They believed that the good reputation of the department would be potential wealth for their department and individuals working within it. This indirect benefit from research was considered a very important issue by junior clinicians.

On the other hand, there are also some junior clinicians who do not like to participate in randomized controlled trials. As I mentioned before, to work in a Chinese hospital, the Chinese clinicians' workload of viewing outpatients is heavy. Clinicians, who work in clinics, have to view 20- 50 patients in every session (a morning or an afternoon, about 4 hours). Therefore, they are very busy in clinic and are also busy in wards. They need to take care of in-patients and monitor their disease progress each day. If they agree to participate in a randomized controlled trial that means they should spend more time on the concerns of those patients eligible for the research study, and recruiting them to take part. This can be quite time-consuming for clinicians because adhering to randomized controlled trial regulations means that they need to clearly explain the research proposal to patients. Some junior clinicians complained to me 'I prefer not to recruit patients compared to the limited financial reward' 'the financial reward is so little,

I prefer not to participate, because spending so much time on it isn't worth it. But that is my department research project, so I have to do it. From a financial perspective, it isn't worth it.'

Patient complaints could be another barrier preventing junior clinicians' involvement in clinical trials. Clinicians mentioned that their main aim in being a medical doctor is to treat patients. Without medical research, they believe they could best treat patients based upon their personal clinical experiences, or, for difficult cases, call for senior clinicians' opinion / consultation. Therefore, junior clinicians believe they did not get complaints as much as if the patients were involved in a trial, because they give their patients proven efficient treatments.

Clinicians are not only doing randomised controlled trial research; clinical reports, case reports, case control, cohort or cross sectional studies are also potential research methods they could manage. Even some clinical practice could be reported as case series which are quite good research methods as they are easy to handle and there is less use of statistics. Furthermore, randomised controlled trials require a large patient population and the trial quality requirement is strict, which makes it hard for an individual clinician to set up. On the other hand, the funding of randomised controlled trials is relatively large. Therefore, individual clinicians in Guangzhou are always involved in trials as patient recruitment leaders. This is another conflict, because the senior clinicians are used only as recruitment leaders in their local area, but not used in conducting the pivotal work in trials, so they are not first or second author of the

research publication. They would not care about a paper with his/her name as 5th or 6th author, which deters them from participating in RCTs. I quite understand that Guangzhou clinicians prefer to do other types of research more than randomised controlled trials.

In the recent year, press and media coverage is not supportive to Chinese clinical trials[86-88]. Improper research proposals and unfair issues in past medical research trials have harmed patients' rights. Educated patients do not like 'medical research', because they have heard so many bad stories about research. If they participated in a randomised controlled trial, they worry about their situation. They may link any discomfort or untoward event to a medical accident. Patients' complaints and special requirements increase junior clinicians' workload, which annoys clinicians. At least 10 junior clinicians complained to me about their patience of research. *'Sometimes I feel regret to involve some patients in a randomised controlled trial. If I know they were fussy guys, I prefer not to take the recruitment reward (financial reward) and not get them involved.'*

4.4 Conclusion

Chinese clinicians need more encouragement on conduct RCT research from Chinese medical system. Junior doctors require more practice in RCT work another than recruitment only. The work-load pressure and traditional Chinese culture made clinicians are in dilemma of being a medical doctor or a researcher. Chinese clinicians also need to improve their knowledge of RCTs.

Summary

In this chapter I made comparison between Chinese and Western clinicians on their answers of physicians orientation profile, detected what are the differences and then interviewed senior and junior doctors. I described clinicians'' routine work and research activities and examined the differences from Chinese culture and current Chinese medical system.

Chapter 5. Chinese Patients' experiences of randomized controlled trials

Outline

In this chapter, I present another study of experienced RCT participants, about their understanding and attitude towards RCTs, Because they would influence clinicians and then the RCT quality in an indirect way. This chapter and chapter 4 are both trying to explore the barriers of Chinese RCTs.

5.1 Method

Patient recruitment was discussed with individual clinicians during the clinician interviews or focus group meetings. After discussion, clinicians suggested they introduce me to their patients and explore whether they would be interested in answering my questions. All involved patients gave their consent and half of recruited patients had previous experience of participating in a randomised controlled trial.

Patients, as the main research subjects are important to the quality of randomised controlled trials. Their understanding and attitude would reflect the clinical trial in many ways. I conducted personal interviews with patients, whom I met in First Municipal People's hospital of Guangzhou, No. 12 hospital and Red Cross hospital; I contacted all my interviewed clinicians, and recruited patients with their help. I was introduced to patients by those clinicians and I interviewed eligible patients whilst they were waiting to see doctors.

The patient's experience of randomized controlled trial is my first concern. Therefore, I contacted those departments carrying out randomized controlled trials at that time, and tried to contact their recruited participants. Although most patients had no experience of RCT, they could be a potential RCT participant; therefore I conducted interviews with them as well, if they had heard of an RCT before.

5.2 Research question

I aimed to explore the patients' understandings and personal experiences of randomized controlled trials and to identify the barriers to participation in clinical trials. Therefore my research questions are;

1. What is a randomized controlled trial?
2. What is your personal experience of randomized controlled trials?
3. What are the reasons for patients preferring to participate in randomized controlled trials?

Patients interview questions

1. Can you describe what a randomized controlled trial is?
2. Can you describe what informed consent is?
3. Do you trust your doctor will give you the best treatment?
4. Do you prefer the doctor to make a decision for you or you and your doctor to make the decision together?
5. What is your personal experience of participating in a randomized controlled trial?

5.3 Results

132 experienced patients were contacted, 82 of them refused interview, 50 patients completed an interview. In 82 of refused cases, 23 of them said they were busy and short of time to participate; 25 of them said they did not participated in any RCT, just routine treatment; the rest 34 of them said their clinicians knew everything, I should ask their clinicians instead of themselves.

- **Age and sex**

Interviewed patients age ranged from 17 to 66, mean is 47.5, median is 52. There were more female (66%) interviewees than male (34%);

- **Understanding of randomised controlled trial**

I found compared to 'randomised controlled trial', 'medical research' is a more understandable and acceptable term for patients, whether they had experience of RCTs or not. When I mentioned 'randomised controlled trial', patients stumbled over their words. That maybe because clinicians use the term 'medical research' to discuss their RCT projects with patients.

I found that none of my interviewees could accurately describe randomised controlled trials to me. Most of my interviewees just shook their head and said 'no, I do not know.' A few of the interviewed patients said '*my clinician told me there is a new medicine which maybe fit for me, they invite me to the medical research , because I could have chance to use this new medicine free.'(P35) 'My clinician told me, they have a medical*

research which included 2 different medicines. If I participated in, I can use one of them free. However, my clinician does not know which medicine I am using, I just believe my clinician would not harm me, he would choose the best treatment for me' (P43)

- **Randomisation**

I think patients interviewed had a limited knowledge of randomization. Even patients who are involved in a trial could not describe randomization. These details were ignored by clinicians when they recruit patients into the study. Randomization is not considered an important factor to patient recruitment. Therefore, involved patients are not clear about this concept.

Most interviewed patients said 'I do not know'. One interviewee said *'clinician choose one group for me, I know maybe the decision is not from my clinician but from other clinicians in this hospital.'(P20) Another patient told me 'clinician said we were randomized to choose for different treatment groups, which was decided by the computer. I believe computer scientific arrangement. (P31)*

- **Blinding**

I think all my interviewed patients had a good understanding of blinding; From the patients point of view, they found it difficult to understand that the clinician was blinded in a randomised controlled trial. More than half of my interviewed patients told me that they do not believe that their clinician had no idea about allocation, even in trials which are multi-centre and double-blind. The reality is that clinicians do not know patient's

allocation, however patients consider blinding is a clinician's trick. For example, one patient commented,

'*My clinician told me he doesn't know which group I was in, but I do not think so. He told me only a small group of people know that, we need wait until they finish the trial. I think they are all in the same group.'(P2) 'My clinician told me he doesn't know, but how could it possible? Even my clinician does not know, but his supervisor would know. Therefore, my clinician would know which drug I am using.'(P6)*

- **Understanding of Research uncertainty and equipoise**

In randomized controlled trials, uncertainty is the main reason for setting up research and then which would cause varied result, although trial designer tried to give equipoise to all patients. I had discussed this question with patients: 'Do you believe there are some uncertainties in medical research?' they all replied to me that they understood that there are uncertainties in medical research, but they can't believe that uncertainty would impact upon them, especially comparing a new drug to placebo treatment; they can't understand the equipoise between groups. Although I explained the principle of randomised controlled trials, which is based on medical uncertainty, all of my interviewee patients refused to accept it, with explanations such as *'if the clinician is not sure about the effect of that drug, he would not use it on patients.'(P41) 'I believe, before the drug is used on patients, they must have very strict research. This new drug is safe.' (P42)'I can't believe the clinician would allow use of a placebo on me. Clinicians*

bear responsibility for my disease, I do think he will try his best to help me recover.' (P25)

I have no idea about how to make patients understand medical equipoise, which is not difficult to explain, but when patients talk about this on their personal medial condition, they tend to ignore and refuse to think about this question. The reason for this phenomenon could be linked to Chinese patient's unique trust in medical doctors, which I will discuss later.

- **Free drug attraction**

From my research, I found free drug treatment is available in all Chinese randomised controlled trials, which was supported by pharmaceutical companies. Usually pharmaceutical companies are the organizers and sponsors of randomised controlled trials; after all, most trials were conducted in order to apply for a drug licence? From my research, clinicians told me that 'free drugs' were attractive a couple of years before, but because people have heard increasing bad news about free drugs, that this no longer works. Patients are active in current clinical trials, although increasingly patients are seeking help from other resources rather than clinicians, for example, consulting experts or checking the internet. However, to those patients with poor economic conditions or from rural areas, free drugs are still attractive, although the number of poor patients has decreased.

Patients describe free drugs as *'if the drug is free, I will think about it more carefully. But if my clinician told me to take it, I would. But I do not think free drugs are attractive to me.' (P23) 'My clinician told me that this drug is free, I feel lucky, although I need to give 4 blood samples. But I think it is good for clinicians to understand my health condition.'(P31) 'My clinician suggested I take that drug, with his recommendation I would like to use it, and save quite a lot of money.'(P32) 'It doesn't matter whether the drug is free or not. We patients come to the hospital for the best treatment, no matter how much we should pay'(P34) 'there is no free lunch in the world, when I was introduced to using a new drug, I checked it through the internet and consulted other clinicians and later I accepted, because many doctors agreed to me using it.'(P48,P49,P50)*

Free drugs are welcomed when patients are experiencing difficult economic times. However, with the development of the Chinese economy, people are increasingly caring about their health rather than economic cost.

- **Patient-doctor relationship in patients description**

The patient-doctor relationship plays an important role in medical treatment[89]. A good relationship combined with trust and friendship has a more beneficial psychological effect than medical treatment alone[90]. the quality of the doctor-patient relationship can affect diagnosis, treatment and recovery and there is a correlation between effective doctor-patient relationships and improved health outcomes[91-93]. Chinese patients

appreciate their relationship with their clinicians, because they know that when they are facing clinicians, they are individuals but clinicians are more like a group. The cost of an accident for a clinician could be rigorous criticism, and even a revoked medical licence, however, for individual patients, that cost is their personal health or even their life, which is not affordable.

I asked patients 'how is your clinician? Did he/she treat you well?' all nodded with a serious face and 100% of patients answered 'yes'. I asked why they said yes and they described *'my clinician treats me very well. I am very appreciative of his medical treatment. On the other hand, he inspects wards everyday. I could find him every time I want. I can crack a joke with him, and he will play back as well. He is a nice man.'(P2,P3,P14,P15) 'My clinician treats me very well, he checks my body very carefully and answers my questions patiently.'(P20, P21)*

- **Chinese patients' Decision making**

Uncertainty is quite a difficult concept to Chinese patients; they find it difficult to believe that clinicians have uncertainty in routine medical treatment. Thus from patients view they have never thought about their personal decision making patterns before. I asked patients 'have you participated in decision making for your own treatment?' almost 100% of my interviewee patients said 'no'. Only one of my interviewees thought for a while and said '*a few years ago, when my wife was going to give birth, that clinician had asked us whether we prefer abdominal delivery or natural labour? That is the only one I*

could remember the clinician discussing medical issues with me. But I asked in reply to that clinician, and followed her advice to do natural labour.' (P13)

I asked them 'if you had the opportunity to make decisions for your own treatment, would you like to make decisions with your clinician or let your clinician make the decision for you?' To my surprise, 100% of my patients said 'I would prefer my clinician to make the decision for me'. The reasons given were;

'Clinicians are the professional people in this area'. (P12) 'Clinicians are certain to have more professional knowledge than me in this area'. (P18) 'They (clinicians) are all experts in this area. I come to hospital to seeking their help, or I will stay at home.'(P35)

- **Clinicians elicit high levels of trust**

AThrough my research, I found Chinese Patients are extremely trusting of their clinicians which is maybe unique around the world. 100% of my interviewed patients said they trust their clinician to provide the best treatment to them, even if they are in a randomised controlled trial. One of my interviewee patients said *'if I do not trust my clinician I would not come to hospital.'*(P5) Several patients echoed these words. I believe Chinese patients have a high level of trust for their clinicians. However, there has been no comparative research into patient trust in clinicians among countries conducted before.

5.4 Discussion

- **Conflict: Informed consent or extremely trust in clinicians**

Through my study, I found Chinese clinicians are not like their colleagues in Western countries, they did not get annoyed by getting patients' signature on informed consent. From Western literature, I found Western clinicians were bothered by the time-consuming nature and impact of doctor-patient relationships. However, Chinese clinicians do not worry about those issues at all.

Most of my interviewed patients said they joined the randomised controlled trial because they trust their clinician. I think the Chinese doctor-patient relationship is different to Western style and this is because of the history and cultural context in China. I tried to explain clinicians' uncertainty of their clinical practice to patients, but I found that patients did not understand or do not accept that clinicians have uncertainties in their clinical practice. When I asked patients whether they trust their doctors, they answered 'of course, if I don't trust these doctors, I would not come to hospital.' 'This is a big and famous hospital, I think all of here clinicians are very good at clinical practice, especially those senior doctors.' When I explained that clinicians may have some uncertainty about their clinical treatment, most of my interviewed patients said 'really? Oh maybe, but I still think clinicians would do their best and give me the best treatment.' 'I believed they are all expert in this area.' 'I think the doctor let me sign on the file (informed consent) because he thinks that would be good for me'

On the other hand, the population of Chinese patient is large, clinicians meet new patients everyday, only a very few of them would call back. Therefore, clinician are not concerned about the clinician- patients relationship of the future. This is maybe a difference compared with Western countries.

- **A typical case of informing patients and getting their signature**

I observed the whole course of DR. W and Patient Mr.J conversation, afterward I interviewed Mr. J. However, I found that Mr.J's understanding of informed consent was quite different from what he had been told. The Clinician introduced their randomised controlled trial project to the patient. This particular project was about a new drug compared with a placebo, in a double blind, randomised controlled trial. Therefore, neither clinician nor patients know the allocation. The clinician describes the randomization to patients as 'you may receive the new drug or you may receive the placebo, this is decided by the computer. We clinicians do not know which group you are in either. This new drug passed Phase 2 trials with very good results, but we are not sure whether it would be good for all common patients.' The patient had a quick look at the informed consent, and signed his name at the end of the sheet.

After the clinician left, I asked the patient 'what is the main reason for you taking part in this research?' he answered 'I believe the doctor would treat me the best way.' I reminded him that the clinician had said he put the patient in an uncertain group. But the patient replied 'I trust the doctor. He is very nice, since I was in the hospital he was quite careful and responsible to me, I am appreciative. I trust his decision'.

This special doctor-patient relationship is one of the potential reasons for the ease and large quantity of patient recruitment in Chinese RCTs. At the beginning, Chinese clinicians enjoyed the convenience of recruiting patients by using the special relationship; however, later they have suffered in this relationship as well, because patients expected a certain positive result but that can't be guaranteed in RCT. When adverse incidents happen, frontline clinicians are the people who have to face the consequences.

Informed consent is a legal condition whereby a patient can be said to have given consent based upon a clear appreciation and understanding of the facts, implications and future consequences of an action. Informed consent was accepted as not only a clear statement of the research, but also the memorandum for patients and clinician. It is showing the contemporary acknowledged medical relationship between clinicians and patients in research. However, this kind of statement was not recognized properly within Chinese patients, maybe that is also problematic with Western patients..

Normally, in an informed consent, it should present not only the research background, subject and method, but also the researchers', hospital's and the patients' responsibility. Furthermore, in case of accident, what and how they treat and who takes responsibility is also stated clearly. From my study, I found that clinicians welcome this detailed informed consent. Because there are some accidents that have happened before, and patients complained they were cheated by clinicians into participating in a clinical trial. A

signed informed consent is the only legal evidence for public judgement. Most clinicians told me they prefer a detailed informed consent, which could protect both patient and clinician's rights in research. Some patients suspect any uncomfortable reactions were caused by participating in the medical trial, rather than caused by their disease progression. A detailed informed consent would help frontline clinicians protect their interests in this case.

5.5 Conclusion

Traditional Chinese culture has had an effect on Chinese patients. Not only in RCT but in all medical activities, patients are passive objects. Chinese patients need to improve a lot on their self-determination, however, which would involve fundamental changes to Chinese society. Chinese patients are lack of the consciousness of self-determination in patient-doctor relationship. They used to rely on medical clinicians to make decision for them that is the traditional pattern of doctor-patient relationship, but not fit for current medical circumstance any more. In order to protect patients' benefit, healthy doctor-patient relationship and quality of RCT conduct, patients need to learn playing independent role in the relationship, not only in RCT research, but all medical activities.

Summary

In this chapter, I described the research of Chinese patients' knowledge and attitude to RCTs. The influence from patients is also important to the conduct of RCTs. With the result from chapter 4, I discuss several conflicts which are existing in current Chinese medial society, and which are the barriers of blocking RCT conduct.

Chapter 6. Discussion

I have conducted a substantial original study concerning quality of RCTs conducted in China, and the attitude of Chinese clinicians and patients toward RCTs. Although RCT have been conducted in China for around 20 years there has been no comparative research focussing systematically on Chinese RCT quality. The RCT as the 'gold standard' research method has become widely used in Chinese medical research, however, inadequate reported information and biased results limit Chinese RCT quality, and lead to rejection from the world medical society.

I have identified that reporting of RCTs in China requires substantial improvement to meet the criteria described in the CONSORT statement. The conduct of Chinese RCTs cannot be directly inferred from the standard of reporting; however without good reporting the methods of the trials cannot be clearly ascertained. Research bodies in China should ensure that the reporting of RCTs is improved to meet internationally agreed standards, thereby allowing the conduct of their studies to be monitored and encouraging high quality standards.

In addition, from my analysis comparing the results of Chinese RCTs with those from other counties, I found Chinese RCTs biased.

I have also conducted original research on Chinese clinicians and patients' attitudes toward the RCT. It seems likely that the understanding and attitude towards RCTs by those involved in their conduct as subjects or investigators may have a substantial impact upon the manner in which RCTs are conducted and reported. The RCT as a research method, developed in Western countries, and is historically located in the Western medical system and social background. Chinese medical professionals and Chinese medical culture are different to that in the West; therefore Chinese RCTs may have some specific characteristics. In order to improve the conduct and reporting of Chinese RCT we have to understand Chinese medical society and Chinese medical culture. Chinese clinicians' experiences are different to those of clinicians in the West; therefore, we should consider that they need specific strategies of encouragement to improve their RCT work. Western clinicians' experiences are helpful, but may not on their own be sufficient.

More training and education should help improve Chinese physicians and patients' understanding and conduct of RCTs. The stage of population development may also be another factor for the current state of RCT practice and reporting.

Frequent medical academic publications benefit to Chinese clinician's career much more than Western clinicians', which is a significant founding through questionnaires survey. This result is confirmed by my following quantitative research. Clinicians

complained participating in RCT was not benefit to their academic publication or any other reward other than financial income. The only standard of Chinese clinicians' research work is their publications; this evaluation standard is sole. These made clinicians (most of them are junior clinicians) feel they are wasting time when they participate in RCT, such as recruiting patients and explaining protocol to patients. Therefore, this made effect to Chinese clinicians on their attitude to participating RCTs.

In addition, Western clinicians may consider that patients' rights to select treatment options are more important than scientific knowledge advancement, but Chinese clinicians do not. In my subsequent qualitative research, I also found Chinese clinicians prefer to make decision for patients, and Chinese patients prefer this pattern of decision making rather than their autonomy, this is a Chinese specialized doctor-patient relationship. Cong's study also demonstrated the difference in doctor-relationship between China and Western countries[94]. The reasons for this kind of relationship are discussed below. However, in the context of the RCT, patients should be independent to their clinicians; therefore, a brand new doctor-patients relationship should be build on. This is not an easy and fast process, which is opposite to Chinese traditional doctor-patient relationship.

6.1 Inadequate report and publication bias

From my study I found that the standard of reporting of trials was generally poor, inadequate information of RCT were reported, for example nearly two-thirds failed to report any information on their methods of randomisation; none of the trials discussed allocation concealment. Those inadequate reports of such essential trial information demonstrated that the quality of Chinese RCT papers needs to improve. In addition, the failure to prespecify a primary outcome measure may lead to the inappropriate application of apparently positive results from trials when in fact chance alone may often provide an adequate explanation for the observed results.

Publication bias appears prevalent in Chinese RCT publications. From my research, I found Chinese RCTs reported fewer outcomes than Indian and Western papers, but with high rates of positive results reported. Those outcomes with non-significant results appear frequently to have been omitted in the final report. In addition, I found the outcomes described in the methods and results sections did not match in many Chinese RCT papers. All of this evidence strongly indicates publication bias in Chinese RCT papers.

6.2 Clinicians dilemma in conducting RCTs

Traditional culture makes Chinese clinicians more willing to be a medical doctor rather than a researcher, which has an effect not only on clincians but also on medical school

students. The basic statistical principles, which are important to RCTs, are largely ignored by Chinese clinicians.

The RCT as a research method was developed in Western countries, providing unbiased evaluation of medical interventions. However, when the RCT method was first introduced to China, the different culture and social background may have undermined the quality of the conduct of RCTs which I discussed in chapter 4. The unique doctor-patient relationship and high levels of patients' trust could prove damaging to both clinician and patients, because in context of randomized controlled trial and elsewhere, clinicians do have limitations of knowledge, attitudes and abilities, naïve patient trust has possible limitations and disadvantages for patients.

Chinese senior clinicians are the leading group in clinical practice and medical research. They have adequate knowledge about conducting a proper RCT, and participating in RCT research. However, senior clinicians are not the people who directly conduct RCTs in practice, which instead are undertaken by junior clinicians who are in charge of recruiting patients, getting their informed consent and taking care of patients during RCTs.

Financial rewards are another incentive to push clinicians to go further on their clinical practice but not medical research. The rationale for conducting medical research among junior clinicians is weak, which needs to be rectified.

From my research, I found junior doctor are in need of more encouragement for their research work, their motivation and their work quality appears highly correlated. Currently, they only receive limited financial reward as a result of conducting RCT, but that is not considered as important issue to junior clinicians. I hope Chinese medical professionals including medical editors will take on board the findings of this research and make some changes on their daily work that improve the quality of RCT conduct and publication accordingly. Below are listed some suggestions I summarised from my interviews:

1. Link conducting RCT research to junior doctors work performance and progression

2. Provide ongoing research methodology training in hospitals

3. Make research data available to junior doctors, and encourage them to write a research paper if they have good idea

4. Ensure editors in medical journals have received suitable training in research methodology

5. Make the CONSORT statement as the essential RCT report standard of medical journal national wide

6.3 Conflict: Clinical doctor and researcher

Compared to Western clinicians, Chinese clinicians are significantly more motivated to work as a medical doctor rather than an academic researcher, althrough Western clincians are also facing the same dilemma[78]. Chinese clinicians all have substantial experience of clinical practice; I believe that every senior clinician could be called an expert in their own area. Compared with conducting research, clinical practice brings clinicians more praise from patients and greater financial return, which are direct and visible benefits.

Research could help Chinese clinicians enhance their reputation in a certain medical area, but they still believe research is a supplement of their clinical work, not their main objective. Clinical work is their main target forever. The reasons given for this interest included: social responsibility; personal interest and as a requirement for promotion.

‘I am already a professor; I do not need to get any promotion. What I do will just help the development of medical science, not only for Chinese patients but also for all populations in the world. We are doing diabetes research, which is quite complicated; but any small progress would help human beings in preventing diabetes.’

‘I have been doing diabetes research for a long time. I worked in this department for 25 years, my PhD is about this topic as well, and any relative research about this topic I am still very interested in. yes, I love any research on diabetes.’

‘I am assistant professor at the moment; I need publications to obtain promotion. This research is about a new medicine, I discussed with the project manager about whether could I share their final data to write some papers, and they agreed. I asked on other research projects, not just randomised controlled trial research, but most of them said no. So I am quite pleased to do this project. Although I know it will be hard in data analysis later, but it is good to have final data.’

6.4 Conflict: traditional Chinese doctor’s role and modern clinician’s role

As a medical doctor, the traditional image is a knowledgeable and busy person working in clinic. Personal knowledge and experience are the most important issues of taking this role. At that time, people preferred to judge a clinician’s ability though their appearance: older doctors were considered experienced and knowledgeable, especially for doctors practising traditional Chinese medicine. Chinese medicine is much more reliant on experience rather than medical knowledge[94]. Nowadays, since the Internet is increasingly used in medical work, clinicians are involved in bigger teams, not only working with colleagues in their own hospital, but also with clinicians in their field around the world, including bio-scientists or pathologists. The internet has enabled individual clinicians to be linked around the world. Progress in each medical area can be reported rapidly. Easier communication means that co-operation across countries or a province is more feasible. Therefore the traditional clinicians working pattern was broken. Clinicians not only have to concentrate on their current patients, but also on updating

their medical information, including possible treatments and effects of other treatments. If clinicians are just working in clinic with their patients without checking recent medical information, this clinician cannot be considered to be a qualified clinician, because it is a present requirement that modern clinicians should keep up with scientific developments.

There are substantial training courses about IT skills, research methodology and statistics provided by Chinese medical schools currently. However, my interviewee senior doctors had graduated at least 20 years previously. At that time, they were only expected be good at clinical practice, but with social development, the requirements for clinicians have changed as well. Senior doctors did not receive enough training in research when they were in medical school; however many have caught up by themselves in their daily work and learnt to update information for themselves.

6.5 Traditional doctor-patient relationship needs to be changed

Although Chinese medical society accepted Western medicine and health service, however, the relationship between doctor and patients are still kept as traditionalised: patients rely on clinicians completely, patient and doctor are not equal in the relationship, doctors are demanders and patients are negative acceptors[94]. In this relationship, patients consider doctor as their representative, and doctors used to make decision for patients. However, RCT as a modern medical research method which based on Western medical circumstance, patients and doctors are equally and independently. This is the basic understanding of informed consent and patient allocation. In my focus group meeting and interview, I found clinicians are confused about this conflict. They

spend lot of time trying to explain the research protocol, and ask whether patients would like to participate in, but most patients said 'you make decision, I trust you'. When ask for their signature on informed consent, most patients fear to take responsibility by themselves, and withdraw at the beginning. If Chinese doctor-patients relationships could be adjusted, I believe the conduct of RCT would be improved in many ways: clinicians could save time on explain protocol and have written informed consent; eligible patient would be easier to recruitment than before.

From Cong's study, he remind in Chinese medical relationship, the Western Patient-doctor relationship was replaced to chinese patient-family- doctor relationship, which was the consequence of Chinese traditional culture[94]. Therefore, to explore a new patient-doctor relationship in Chinese society is in need.

6.6 Ethic issues

The reporting of ethical issues was inadequate in Chinese RCTs. Fewer than 11% of the trials reported having ethical committee approval, although the latter is a legal requirement in China[59]. Also, only a minority of the Chinese studies (17.4%) gave adequate details about the informed consent procedures; a few mentioned that participants attended of 'their own free will' but the remainder made no mention of consent. However, this level appears better than in a recent review of traditional Chinese medicine trials[57;59]. In my study, I found significant shortcoming in the

reporting of ethical issues in Chinese papers. Informed consent and ethical committee approval are widely accepted as fundamental requirements of conducting RCTs in China but not all hospitals involved in trials have institutional ethical committees[64] .

From my interviews, I found ethical issues were considered an important procedure in starting an RCT in China. The Helsinki Declaration is known by all qualified hospitals undertaking RCTs, whose researchers understand that having approval from an ethical committee is a necessary precursor to conducting RCT.

In the Chinese cultural context, it is not difficult for Chinese clinicians to get patients' signature on informed consent. Because of the unique Chinese doctor-patient relationship, patients place substantial trust in their doctor. However, increasingly, Chinese clinicians have found that this convenience is not so helpful, but instead may harm their reputation among their patients. The RCT is a research method based on uncertainty, which undermines the basic image of the traditional Chinese medical doctor. Therefore, it is important that Chinese clinicians and patients come to understand uncertainty and equipoise.

6.7 Patient autonomy, is it still far from Chinese patients?

In developed countries, patients are being expected to take a more active role in the management of their health. In recent years the UK government has introduced a range of health reforms, including recommendation for greater patient choice in healthcare options[95]. The Wanless report[96] called for a greater focus on effective health promotion

and active involvement of patients in their health care. In the Helsinki Declaration, the fundamental principle is respect for the individual, their right to self determination and the right to make informed decisions regarding participation in research, both initially and during the course of the research. However, patients' autonomy was not considered an important issue in Chinese society[97].

Extreme trust in Chinese clinicians may lower patients' incentives to participate in decision making. Although patients' passivity in decision making is now discouraged[98], patients who prefer passive roles generally have high, sometimes naïve, levels of trust[99]. Patients who totally depend on their clinicians to make medical decisions trust their clinicians significantly more than other patients do[100]. The belief 'doctor knows best' maybe due to the intense sense of vulnerability and anxiety that illness creates. Nevertheless, such unrealistic beliefs lower patients' incentives to participate in shared decision making[101].

I questioned interviewees whether 'for your treatment, would you like your clinician to make the decision for you, or for you two to discuss and make a decision together?' 100% of my interviewed patients answered 'I prefer the clinician to make the decision for me'. In Western countries, patients' autonomy is applauded by ethicists, which empowers patients to have more control over their medical treatment. The reality is that medical professionals would have some uncertainty about their clinical practice; patients should afford the final result then should be able to join clinicians to make decisions for

their own body. Sometimes patients may even have the opposite opinion to the clinician, and the clinician should follow the patient's decision.

Although patient's medical freedom and autonomy is becoming increasingly popular in Western countries, in China patients are still cautious of clinicians' opinion. It is likely that educated patients understand clinician's uncertainty, but most of them prefer to ignore it; they are still willing to let clinicians resolve all the uncertainty for them. Patients believe that 'clinicians are the professional persons in this area, but they are not. So their decision is certainly better than mine.' This is a big difference between Chinese and Western patients, which may be the reason for high levels of compliance and low drop-out rates in Chinese RCTs. Some research has found that increasing trust in a specific clinician is strongly associated with improved adherence to treatment regimens[102;103].

The limited number of Chinese medical doctors made patients is more willing to follow clinicians' suggestions. In China, the rate of medical doctor to total population is 150/100,000, which is considered an ideal rate. However, those patients from rural areas, spend considerable time and money to arrive in urban hospitals. They care about their relationship with doctors. If the clinician has an opinion, they would find it difficult to refuse, because that means they damage the relationship and lose their clinician's concern. And the result is may often be unaffordable' to change clinician within hospital is quite hard and to change hospital is quite expensive.

6.8 What we learn from the comparison of RCT quality evaluation between different time periods

I conducted updated Chinese RCT report quality evaluation of 2008-09, and made comparison with my previous study of 2004. I am glad to see the improvement on many clinical trial quality items, especially on those ethical issues; Chinese published RCTs had a rapid improvement. The improper procedure of having ethical approval and uninformed consent were always criticized by local and foreign media[104;105]. Therefore, the ethical regulation for medical research has been build as prior to other problems. It is certain that with the official regulation for medical research, more RCT papers declared they having ethical approval and participants' informed consent in text. I consider this is a significant improvement both in RCT reporting and practical conduct.

However, the quality of Chinese RCT report is a complex subject, which is relative to many items, such as medical authors' (clinicians) understanding of the principle of RCT, medical journals' publication requirement and the general accepted RCT standard in Chinese medical society, clinicians and participators' attitude also affect the trial conduct and the trials' result. Therefore, in order to improve the quality of RCT reporting across the spectrum of quality items requires systematic work across all Chinese medical society. In my research, I just detect what the problems are, but to solve all of them, it need a series of substantial reforms.

In recent years, more and more Chinese and foreign medical researchers are caring about Chinese published RCTs, a series of publications of quality evaluation have been published[106-109]. The common suggestion to Chinese publications is to accept CONSORT statement as the basic standard of RCT report. However, from my study, Chinese medical journals still haven't taken this advice so far, and the RCT publications are still in low quality. Only one leading Chinese medical journal recommends CONSORT to their authors in journal's 'instruction and guide'. I found just through researchers' publication to make a suggestion is not able to influence the whole medical society and make any reform. Further research need to be conduct to find what is the right way to make change.

6.9 Suggestions from this thesis

1. Chinese medical journal editors need to take training on the reporting of RCTs, and they need to set quality standards for their accepted Chinese RCT papers.

2. All medical professionals and medical journal editors need to correct their attitude to positive result of RCT research, which is not the only standard of good RCT.

3. Chinese general population needs to learn more about the RCT, public media should help lay public's to understand RCT. Chinese public media or the hospitals would have more introduction on the basic knowledge of RCT, such as the basic principals and the meaning of informed consent, through public service announcement or publicity brochure.

4. Chinese medical society needs to take more concern about medical doctor's research work; doctors need to have more opportunity to conduct medical research.

5. The requirement of medical doctor's research work should be various, publication as the only trace of doing research which need to be changed. For example, clinicians took time in patient recruitment of RCT, which could be record as their research work, and the amount of conducting research work could be accumulated as clinicians' promotion requirement.

Further research suggestions

1. I could continue to assess the quality of Chinese published RCT, compared with Western leading medical journals, in order to detect whether Chinese RCTs are minimising the quality gap with Western research, and making Chinese RCTs acceptable to world medical society in the near future.

2. The research on clinicians' attitudes could to be extended national wide, in order to gain more generalisable information from clinicians. To understand clinicians' attitude and barriers to the conduct of RCTs would be important to policy maker.

6.10 Limitations

I may have missed relevant studies not included in the database. The sample of Indian trials may not have been representative; my research would not have located all

published trials although my searches included Pubmed, ISI web of Science and the Journal Series of the Chinese Medical Association.

Considering the large and disparate Chinese medical doctor population, the qualitative aspects of this study only involved a small number of doctors within one city. Therefore, further research should be conducted in this area in order to explore Chinese clinicians' attitudes and in order to predict their behaviours in the future.

All my interviewed clinicians and patients are nominated by the hospital, and all of these involved hospitals were nominated by the Guangzhou Public health bureau. The sample is not randomly selected; therefore, it could be that some selection bias exists affecting the result. I believe the results from my research is biased towards a positive outcome because those participators with good understanding and attitude would be nominated.

Two hundred and fifty physicians were selected from 7378 doctors registered as fellows of the royal Australasian college of physicians (RACP) in May 2002. Fellows included clinicians, non-clinician, or retired doctors. They provide the data for the Western clinician's data which was compared with my Chinese clinicians. All my Chinese clinicians are clinical doctors, and thus differ from Western participants.

Western participants included retired doctors, but RCTs had been conducted since 1940's in Western countries, therefore, those retired clinicians are considered as experienced clinicians. Although the Chinese clinicians are younger than Australian

participants, but they are the first generation who had RCT experience; Chinese retired clinicians had no experiences of RCTs, because of the short history of Chinese RCT conduct. Non-clinicians are also including as Western participants , who had experience of management of support RCT conducts. However, in most Chinese hospitals, senior clinicians are taking management role in RCT conduct; there is limited staff taking support role in Chinese hospitals.

All my Chinese participants are clinical doctors, but not all the Western participants, which would make affect to the comparison result. Chinese clinicians would report more about their practical conduct problems, but Western clinicians would have more management problems. Western clinicians might have more experiences but Chinese clinicians'' expenses are limited. All Western clincians are random selected, but not my Chinese clinicans. Therefore, the attitude from Western clinicians may be more representative than the included Chinese clinicians.

China is a big country; the population of clinicians is also substantial. Although I conducted a survey in 3 large hospitals in Guangzhou, when compared to the clinician population of China, the findings are limited, which I have stated in the limitations section. However, my study was the original study in this area in China, and is the first to explore these issues among Chinese clinicians; having more accurate results of Chinese clinicians' attitudes need more evidence from future research.

6.11 Conclusions

The quality of Reporting of RCTs in China has improved between 2004 and 2008-09 period, but which still requires substantial improvement to meet the targets of the CONSORT statement. In my work I identified strong evidence that Chinese RCTs are biased. The difference in positive results reported between Chinese trials and Western or Indian trials cannot plausibly be explained by the play of chance or the *a priori* identified confounding factors. Clinicians need more systematic training and incentives from the Chinese medical system. The RCT is not accepted properly by Chinese society, there are many cultural items which block RCT conduct in practice. Patients are influenced by traditional Chinese culture. Patients' rights of selection and determination need to be strengthened in Chinese society.

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Appendixes

Physicians Orientation Profile

(Questions order is different from Chinese version)

Primary allegiance

Q1. Although many doctors are expected to perform both tasks, as a doctor my primary commitment is to:
Future generations of patients (society)
Present patients (individual)

Q2. If I had to choose, I would say my primary task is:
Caring for individual patients
Contributing to scientific knowledge

Q3. I would like to assess how successful I was as a physician by:
My research contribution
How I helped individual patients
Both

Q4. I would rather be somewhat:
Too involved with my patients
Too detached from my patients

Q5. If a patient refuses to participate in a randomised clinical trial, I would:
Treat the patient off the study
Refer the patient to another doctor

Q6. I would rather be known for:
My interpersonal skills with patients
My research accomplishments

Q7. Overall I feel the quality of patient care:
Increases when a patient is in a clinical trial
Decreases when a patient is in a clinical trial

Does not change when a patient is in a clinical trial

Q8. Randomised clinical trials restrict my ability to individualise patient care:
True
Makes no difference

Q9. I think the patient's right to select treatment options is always more important than the advancement of scientific knowledge:
True
False

Q10. ***Personal satisfaction is an important element of all professionals' work. I get more satisfaction from:***

The work itself
My patients/their family

Decision –making under conditions of uncertainty

Q11. When there is controversy in the literature as to which treatment is best:
I enter the patient in a clinical trial if one exists
I personally select the best treatment for the patient

Q12. When making critical and controversial decisions, I usually:
Seek major input from my patients
Do not seek major input from my patients

Q13. When published data and my clinical judgement conflict, I am more likely to rely on:
My clinical experience
Published data

Q14. When a protocol includes a treatment that is more aggressive than I would usually give to similar non-trial patients:
I am often reluctant to participate
It makes no difference

Q15. When a protocol includes a treatment that is less aggressive than I would usually give to similar non-trial patients:
I am often reluctant to participate
It makes no difference

Q16. I am reluctant to participate in a trial that may randomise the patient to a "no treatment" group:
Yes
No

Q17. When I am personally uncertain as to which treatment is best, I am likely to:
Enter the patient in a randomised clinical trial if I am aware one exists
Personally select a treatment

Q18. When a potentially eligible patient chooses not to enroll on a trial that I have suggested:
I often feel disappointed
I seldom feel disappointed

Q19. As a physician, I am obliged to
Follow medical tradition
Question medical tradition

Professional activities

Q20. Ideally I would like to refer or enter the following proportion of my potentially eligible patients into randomised clinical trials:
None
Some
Half
Most

All

Q21. The time I devote to publications, lectures and research commitments, compared to clinical work, is relatively:

Totally clinical work

Mainly clinical work

Clinical and research equally

Mainly research

Totally research

Q22. Frequent publications are important to my career advancement:

Yes

No

Q23. I am more likely to attend a conference that focuses on:

Clinical issues

Research issues

Perceived rewards

Q24. In my hospital, doctors are given more reward for:

Clinical skills with patients

Contributing to scientific knowledge

Q25. If written informed consent was not required, I would approach more patients to enter clinical trials

True

Makes no difference

Q26. The need for detailed monitoring of my management of trial patients by trial staff deters me from participating in randomised clinical trials:

Yes

No

Q27. The increased paperwork involved in treating patients on trials deters me from participating in randomised clinical trials:

Yes

No

Q28. The thought of having to spell out all the details of a trial to eligible patients discourages me from approaching them to participate:
True
False

Q29. A major reason for my participation in randomised clinical trials is that it financially benefits my institution or department:
Agree
No

Q30. Overall, involvement in randomised clinical trials:
Enhances my reputation
Does not enhance my reputation

Q31. If research activities were to enhance my income, I would enter more patients in randomised clinical trials:
Agree
No

Q32. When I participate in a randomised clinical trial, it is more likely that:
I increase my patient population
I lose patients I might otherwise keep
It makes no difference to my patient population

Q33. My income is dependent on my research activities:
Yes
No

Peer-group influence

Q.34. If you were to poll my staff, they would probably say I was particularly 'good with patient'
Yes
No

Q35. In my hospital the pressure to participate in a randomised clinical trial is relatively:
Low
High

Q36. Of all eligible patients, I approach to participant in clinical trial, they agree:

Less than 50%

More than 50%