Pilot and feasibility trials in traditional Chinese medicine: a literature survey

Guowei Li (lig28@mcmaster.ca)
Guangdong Second Provincial General Hospital

Darong Wu
Guangdong Hospital of Traditional Chinese Medicine

Xuejiao Chen
Guangdong Second Provincial General Hospital

Jie Zeng
Guangdong Second Provincial General Hospital

Ziyi Li
Guangdong Second Provincial General Hospital

Lehana Thabane
McMaster University

Research

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Abstract

Background The guidelines for pilot and feasibility studies were published in 2016. Little is known about the guideline adherence of TCM (Traditional Chinese Medicine) pilot trials or whether the guidelines can significantly enhance the quality of implementation and reporting of TCM pilot trials. We aimed to investigate the guideline adherence, assess the impact of guidelines on TCM pilot trials, and discuss potentially undetected challenges for TCM pilot trials, by conducting a literature survey.

Methods We systematically searched MEDLINE, EMBASE and CNKI to retrieve TCM pilot trials. We randomly chose 50 pilot trials from the eligible studies for analyses. The CONSORT extension to pilot and feasibility studies was used as a framework to assess the methodology and reporting quality of the studies.

Results The included studies had a guideline adherence level ranging from 4% to 96%, where the lowest adherence was found in the item 6c (prespecified criteria used to judge progression to future definitive trial). The guidance published in 2016 seemed to exert minimal effect on guideline adherence in TCM pilot trials. The unidentified issues related to TCM pilot trials from the guidelines included blinding, lack of standard formula of interventions, difficulty in comparison for effect assessment of interventions, and difficulty in bias control.

Conclusions The current practice in TCM pilot trials required substantial improvement in the literature. Further endeavors are needed for training and dissemination of guideline adherence, and development of more detailed methodology in the field of TCM pilot trials.

Introduction

Pilot and feasibility trials have been published with a growing number. Pilot trials are significantly important for the design of a future main trial (or definitive trial) by providing evidence of feasibility issues and avoiding wasted recourses [1]. In 2016, Eldridge et al published two critical publications aiming to reduce the misunderstanding and improve the reporting quality of pilot trials: the first providing a conceptual framework to define a pilot trial [2], and the second developing a CONSORT (Consolidated Standards of Reporting Trials) extension for pilot trials with a 26-item checklist included [3]. While the two publications may help with the design, implementation, reporting and dissemination of pilot trials, it remained largely unknown about their impact on the pilot trials published in the literature. Confusions remained in the pilot trials including their definitions and terms, purpose, sample size determination, and criteria for progression or cessation, to mention a few [4–6].

Traditional Chinese medicine (TCM) is a hot topic in the health research community, especially given its alternative and integrated effect as a palliative treatment option [7]. Notably, some uncertainties and challenges existed in clinical trials for TCM that mainly included the difficulty in standardized procedures, potential heterogeneity in interventions and operators, control selection and outcome assessment. Pilot trials for TCM offered a platform to identify and address these issues before a main trial. However current evidence about the conduct and reporting of pilot trials for TCM is limited and sparse. Furthermore, little is known about whether the CONSORT extension for pilot trials can significantly enhance the quality of
implementation and reporting of TCM pilot trials. Likewise, further evidence is needed to reveal the unidentified issues specific to TCM pilot trials from the guidelines [3]. Therefore in this study, we conducted a literature survey to investigate the guideline adherence of pilot trials for TCM, aiming to appraise the issues related to methodology and reporting. We also aimed to assess the impact of CONSORT extension for pilot trials, and discuss any potentially undetected challenges for TCM pilot trials.

**Methods**

**Search strategy and study selection**

We systematically searched MEDLINE, EMBASE and CNKI to retrieve TCM pilot trials. Descriptors including synonyms for traditional Chinese medicine or herbal medicine or folk medicine, and pilot trials or feasibility studies, were used in combination for the literature search (Supplemental Table 1 presents the search terms used). Studies were eligible for inclusion if they explicitly identified their TCM research as a randomized pilot or feasibility trial in the titles, abstracts or introductions. Studies were excluded if they did not specify as a randomized pilot or feasibility trial, or they were not related to TCM, or they did not have information for methodological and reporting appraisal. Two reviewers (GL and XC) independently screened the records and determined study eligibility.

**Data extraction**

Data extraction was completed by two independent reviewers (GL and XC). We categorized the included TCM pilot trials into two groups: 1) pilot trials that had at least one objective or assessment of feasibility and were conducted in preparation for a future definitive trial (FDT), and 2) trials that did not have feasibility objectives or assessment, termed as non-feasibility trials (NFT). This methodology was similar to Horne's approach [8].

We assessed the guideline adherence about Title and Abstract (1a and 1b listed in the checklist), Introduction (2a and 2b), Methods (3a, 4c, 6a, 6c, 7a and 12a), Results (13a) and Discussion (20, 21, and 22a) [3], separated by the two groups (FDT and NFT).

To document the unidentified issues specific to TCM pilot trials, we also extracted the relevant data throughout the text from the included studies, especially in their Discussion sections.

**Statistical analyses**

We expected that the proportion of FDT in our included studies would be approximately 15%. Therefore we randomly chose 50 pilot trials from the 285 eligible studies for analyses (Supplemental Table 2 shows the reference details for the included studies and Fig. 1 shows the process of identifying eligible studies). To assess the impact of CONSORT extension for pilot trials on reporting, we selected the 50 studies that were published in either before or after the year 2016; i.e., no studies published in 2016 were identified for our analyses.

Guideline adherence was presented using counts and percentages. We performed a Chi-square test to compare the guideline adherence levels between the two groups (FDT and NFT). To evaluate the impact of the CONSORT extension for pilot trials, we compared the guideline adherence of the included pilot trials...
published before and after 2016. When there was a cell with expected frequency < 5 in the contingency table, we used Fisher's exact test to compare the guideline adherence levels between the groups. All analyses were conducted using the STATA Version 13 (Stata Corp., College Station, TX, USA).

Results

As shown in Fig. 1, we identified 285 eligible TCM pilot trials, among which 50 were randomly selected for analyses. The selected 50 trials were published between year 1998 and 2019, and had a sample size ranging from 7 to 160 (Table 1). The TCM assessed in the trials included herbs, acupuncture, Chinese patent medicine, Qigong, massage, and others. There were 12 trials categorized as FDT (24%) and 38 as NFT (76%). Thirty-eight trials (76%) were published before year 2016, and 12 trials (24%) after 2016.
| Study author | Publication year | Journal                                  | Country | Type of TCM | Number of participants randomized | Type of pilot trial |
|--------------|-----------------|------------------------------------------|---------|-------------|-----------------------------------|---------------------|
| Agarwal      | 2014            | Asian Journal of Pharmaceutical and Clinical Research | India   | Herb        | 62                                | NFT                 |
| Ahn          | 2007            | Acupuncture in Medicine                  | USA     | Acupuncture | 32                                | FDT                 |
| Avis         | 2008            | The Journal of The North American Menopause Society | USA     | Acupuncture | 104                               | NFT                 |
| Chen         | 2003            | Maturitas                                | China   | Herb        | 44                                | FDT                 |
| Choi         | 2012            | The Journal of Alternative and Complementary Medicine | Korea   | Herb        | 40                                | NFT                 |
| Chung        | 2012            | Journal of Affective Disorders           | China   | Acupuncture | 50                                | FDT                 |
| Gong         | 2019            | Evidence-Based Complementary and Alternative Medicine | China   | Herb        | 63                                | NFT                 |
| Hsu          | 2008            | Advance Access Publication               | China   | Herb        | 24                                | NFT                 |
| Huang        | 2019            | Plos One                                 | China   | Herb        | 60                                | FDT                 |
| Iwasaki      | 2007            | Journal of the American Geriatrics Society | Japan   | Herb        | 48                                | NFT                 |
| Jones        | 2001            | BMC Complementary and Alternative Medicine | China   | Qigong      | 117                               | NFT                 |
| Kainuma      | 2004            | Human Psychopharmacology                 | Japan   | Herb        | 33                                | NFT                 |
| Kalman       | 2007            | Nutrition Journal                        | USA     | Chinese patent medicine | 60 | NFT |
| Kampman      | 2003            | Addictive Behaviors                      | USA     | Herb        | 14                                | NFT                 |

FDT: trials in preparation for a future definitive trial
NFT: non-feasibility trials
| Study author | Publication year | Journal | Country | Type of TCM | Number of participants randomized | Type of pilot trial |
|--------------|------------------|---------|---------|-------------|-----------------------------------|---------------------|
| Kang         | 1999             | Hong Kong Medical Journal | China  | Chinese patent medicine | 120                 | NFT                 |
| Kong         | 2009             | Cerebrovasc Diseases | Singapore | Herb | 60                  | FDT                 |
| Kuo          | 2012             | Evidence-Based Complementary and Alternative Medicine | China | Herb | 28                  | NFT                 |
| Kuratsune    | 2010             | Phytomedicine | Japan | Herb | 12                  | NFT                 |
| Ladas        | 2010             | Cancer | USA | Herb | 106                 | FDT                 |
| Lee          | 2010             | Complementary Therapies in Medicine | China | Herb | 28                  | NFT                 |
| Lee          | 2011             | Planta Medica | Korea | Chinese patent medicine | 40                  | NFT                 |
| Li           | 2009             | Complementary Therapies in Medicine | China | Herb | 24                  | NFT                 |
| Li           | 2015             | HIV Clinical Trials | China | Herb | 140                 | NFT                 |
| Liew         | 2015             | Asia Pacific allergy | Singapore | Chinese patent medicine | 44                  | FDT                 |
| Liu          | 2018             | Evidence-Based Complementary and Alternative Medicine | China | Chinese patent medicine | 20                  | NFT                 |
| Luo          | 2018             | European Journal of Integrative Medicine | China | Acupuncture | 20                  | FDT                 |
| Noorbala     | 2005             | Journal of Ethnopharmacology | Iran | Herb | 88                  | NFT                 |
| Otto         | 1998             | American Academy of Addiction Psychiatry | USA | Acupuncture | 19                  | NFT                 |
| Pan          | 2018             | Chinese Journal of Integrative Medicine | China | Other | 60                  | NFT                 |

FDT: trials in preparation for a future definitive trial
NFT: non-feasibility trials
| Study author | Publication year | Journal | Country          | Type of TCM                  | Number of participants randomized | Type of pilot trial |
|--------------|------------------|---------|------------------|------------------------------|----------------------------------|---------------------|
| Reshef       | 2013             | Sleep Disorders | Israel          | Acupuncture                  | 27                               | NFT                 |
| Ritenbaugh   | 2008             | The Journal of Alternative and Complementary Medicine | USA              | Other                        | 18                               | FDT                 |
| Scheid       | 2015             | Maturitas | United Kingdom   | Herb and/or acupuncture      | 42                               | FDT                 |
| Shelmadine   | 2017             | The Journal of Alternative and Complementary Medicine | USA              | Chinese patent medicine      | 56                               | NFT                 |
| Singh        | 2010             | Indian Journal of Medical Sciences | India          | Herb                         | 7                                | NFT                 |
| Sitzia       | 2019             | Clinical Trial | Italy           | Other                        | 56                               | NFT                 |
| Sordi        | 2019             | Journal of Natural Remedies | Brazil          | Herb                         | 70                               | NFT                 |
| Spasov       | 2000             | Phytomedicine | Russia          | Herb                         | 128                              | NFT                 |
| Stockert     | 2007             | Pediatr Allergy Immunol | Austria        | Acupuncture                  | 12                               | NFT                 |
| Tao          | 2013             | Evidence-Based Complementary and Alternative Medicine | France         | Other                        | 40                               | NFT                 |
| Tsai         | 2018             | Complementary Therapies in Medicine | China          | Herb                         | 160                              | NFT                 |
| Wang         | 2014             | Prev Chronic Dis | USA           | Herb and/or acupuncture      | 70                               | FDT                 |
| Wei          | 2015             | International Journal of Clinical and Experimental Medicine | China          | Chinese patent medicine      | 18                               | NFT                 |
| Wong         | 2006             | Journal of Child Neurology | China          | Acupuncture                  | 120                              | NFT                 |

FDT: trials in preparation for a future definitive trial
NFT: non-feasibility trials
| Study author | Publication year | Journal                                      | Country | Type of TCM                  | Number of participants randomized | Type of pilot trial |
|--------------|------------------|----------------------------------------------|---------|------------------------------|----------------------------------|---------------------|
| Wu           | 2014             | Journal of Clinical Medical                  | China   | Acupuncture and massage     | 36                               | NFT                 |
| Wu           | 2015             | Neuropsychiatric Disease and Treatment       | China   | Herb                         | 46                               | NFT                 |
| Xu           | 2009             | Phytotherapy Research                        | China   | Chinese patent medicine      | 30                               | NFT                 |
| Yu           | 2018             | Journal of Acupuncture and Meridian Studies  | Canada  | Acupuncture                  | 60                               | NFT                 |
| Zhang        | 2015             | Journal of Alzheimer's Disease              | China   | Chinese patent medicine      | 12                               | NFT                 |
| Zou          | 2017             | Journal of Nutrition Health & Aging         | Canada  | Other                        | 21                               | FDT                 |
| Zou          | 2017             | Inquiry                                      | Canada  | Other                        | 36                               | NFT                 |

FDT: trials in preparation for a future definitive trial  
NFT: non-feasibility trials

Table 2 presents the detailed guideline adherence levels of the selected trials. The adherence ranged from 4–96%, with the lowest adherence found in 6c (prespecified criteria used to judge progression to future definitive trial) and highest in 12a (qualitative or quantitative methods used to address objectives). The checklist items 2b (specific objectives or research questions), 7a (rationale for sample size) and 21 (generalizability of methods and findings) also had low guideline adherence levels (18%, 8% and 18% respectively). Table 2 also shows comparisons between FDT and NFT, and between studies published before and after year 2016. Compared with the NFT, the FDT had a significantly higher guideline adherence in the item 7a (rationale for sample size; 25% vs 3%) and 20 (discussion of study limitation, bias and uncertainty; 58% vs 34%). Guideline adherence level was only found significantly higher in the item 12a (qualitative or quantitative methods used to address objectives) in trials published after year 2016, when compared with studies published before 2016 (100% vs 55%).
Table 2
Details for guideline adherence of the included studies

| Number of item | Checklist item | Guideline adherence | Subgroups | By type of pilot trial | By year of publication |
|----------------|----------------|---------------------|-----------|------------------------|------------------------|
|                |                | Overall studies (n = 50) | FDT (n = 12) | NFT (n = 38) | Studies published before 2016 (n = 38) | Studies published after 2016 (n = 12) |
| Title and abstract | Identification as a pilot or feasibility randomized trial in the title | 47 (94.0) | 11 (91.7) | 36 (94.7) | 36 (94.7) | 11 (91.7) |
| 1a              |                  | 37 (74.0) | 9 (75.0) | 28 (73.7) | 27 (71.1) | 10 (83.3) |
| Introduction    |                  | 11 (22.0) | 3 (25.0) | 8 (21.1) | 8 (21.1) | 3 (25.0) |
| 2a              | Scientific background and explanation of rationale for future definitive trial, and reasons for randomized pilot trial | 9 (18.0) | 3 (25.0) | 6 (18.4) | 8 (15.8) | 1 (8.3) |
| Methods         | Description of pilot trial design (such as parallel, factorial) including allocation ratio | 39 (78.0) | 9 (75.0) | 30 (79.0) | 29 (76.3) | 10 (83.3) |
| 3a              |                  | 35 (70.0) | 8 (66.7) | 27 (71.1) | 26 (68.4) | 9 (75.0) |
| 4c              | How participants were identified and consented | 39 (78.0) | 9 (75.0) | 30 (79.0) | 29 (76.3) | 10 (83.3) |

*p-value < 0.05 for difference test*
The interventions for each group with sufficient details to allow replication, including how and when they were actually administered

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 44 (88.0) | 10 (83.3) | 34 (89.5) | 34 (89.5) | 10 (83.3) |

Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 6a | Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed | 44 (88.0) | 10 (83.3) | 34 (89.5) | 34 (89.5) | 10 (83.3) |

If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 6c | If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial | 2 (4.0) | 1 (8.3) | 1 (2.6) | 1 (2.6) | 1 (8.3) |

Rationale for numbers in the pilot trial

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 7a | Rationale for numbers in the pilot trial | 4 (8.0) | 3 (25.0)* | 1 (2.6)* | 3 (7.9) | 1 (8.3) |

Methods used to address each pilot trial objective whether qualitative or quantitative

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 12a | Methods used to address each pilot trial objective whether qualitative or quantitative | 48 (96.0) | 11 (91.7) | 37 (97.3) | 21 (55.3)* | 12 (100.0)* |

Results

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 13a | For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective | 34 (68.0) | 10 (83.3) | 24 (63.2) | 26 (68.4) | 8 (66.7) |

Discussion

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 20 | Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility | 33 (66.0) | 7 (58.3)* | 13 (34.2)* | 27 (71.1) | 6 (50.0) |

Generalizability (applicability) of pilot trial methods and findings to future definitive trial and other studies

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 21 | Generalizability (applicability) of pilot trial methods and findings to future definitive trial and other studies | 9 (18.0) | 3 (25.0) | 6 (15.8) | 7 (18.4) | 2 (16.7) |

Implications for progression from pilot to future definitive trial, including any proposed amendments

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 22a | Implications for progression from pilot to future definitive trial, including any proposed amendments | 31 (62.0) | 6 (50.0) | 25 (65.8) | 24 (63.2) | 7 (58.3) |

*p-value < 0.05 for difference test
The unidentified issues related to TCM pilot trials from the guidelines were shown in Table 3. There were 3 trials raising the issue of blinding in TCM pilot trials, mainly due to the acupoints, administration forms, smells, and other reasons [9–11]. Other issues included lack of standard formula of interventions, difficulty in comparison for effect assessment of interventions, and difficulty in bias control [9, 10, 12, 13] (Table 3).

| Unidentified issues related to TCM pilot trials | Authors’ statements | Reference |
|-------------------------------------------------|---------------------|-----------|
| Blinding; Intervention                          | Chen, 2003 (9)      |           |
| Randomization and blinding; Intervention         | Lee, 2010 (10)      |           |
| Comparison and effect estimate                   | Choi, 2012 (13)     |           |
| Blinding                                        | “although the shape and color of the placebo were similar to Yueju, the smells of Yueju and placebo were not exactly identical, which may lead to the plausible incomplete blind treatment to patients.” Wu, 2015 (11) |
| Intervention and bias control                   | Tsai, 2018 (12)     |           |

**Discussion**

In this study, we performed a survey to assess the guideline adherence of TCM pilot trials. The guideline adherence varied acrossing the checklist items, where some items required significant improvement. The guidance papers published in 2016 seemed to exert minimal effect on guideline adherence in TCM pilot trials. We also identified several issues specific to TCM pilot trials in this survey.

Interestingly, there were only 24% TCM pilot trials that had an objective of feasibility and were performed in preparation for future definitive trials (FDT). This indicated the inappropriate use of the term pilot in many small trials that aimed to test the hypotheses of efficacy or safety with an insufficient sample size albeit being underpowered to do so [8, 14, 15]. It also corresponded to the item 2b (specific objectives or research questions), where surprisingly only 3 (25%) FDT clearly stated their objectives related to feasibility.

Furthermore, there were only two items (7a and 20) found with significant improved guideline adherence in FDT compared with NFT, implying that more endeavours were required even in those pilots trials with specified feasibility objective(s). Therefore all these findings suggested further dissemination of the guideline to help clarify the definition of feasibility and pilot trials [2] and to enhance the guideline adherence [3].
Likewise, our study indicated that the impact of CONSORT extension for pilot trials warranted more efforts in TCM pilot trials, because the improvement was only found in one item (12a) after the guidelines were published (Table 2). The minimal effect of the guidance papers may be because either that the guidelines did not reach the relevant research parties, or that the guidelines were largely ignored by the research parties [8]. In any case, our survey reveals the urgent need for both training and dissemination of research methodology and guideline adherence in TCM pilot trials.

Besides the common practice of the inappropriate hypothesis testing and insufficient power for conclusion in pilot trials [14, 16], our study also identified some issues specific to TCM pilot trials including blinding, standards for intervention and comparisons, and bias reduction (Table 3). This entails more guidance on methodology and reporting specific to TCM pilot trials, because the existing guidelines including CONSORT extensions to acupuncture [17], herbal interventions [18], and PAFS [3] could not fully cover these issues in TCM pilot trials. The progression criteria (guideline adherence level: 4%), sample size rationale (18%) and generalizability of methods and findings (18%) were also notable issues found in the TCM pilot trials (Table 2). This may be, at least in part, due to the insufficient details on explanation and elaboration from the guideline. For example, even though the CONSORT extension recommended that authors should justify the number of participants in pilot trials [3], no sufficient details on how to exactly provide sample size rationale could be found in the guideline. Likewise, how to specify the progression criteria to determine whether the pilot trial can progress to future main trial, and whether the methods and findings can be generalizable to main trial and other pilot studies, required further detailed investigation and guidance in TCM pilot trials. The TCM field is substantially different from modern medicine, especially in their intervention, control and outcome assessment. Thus, our findings call for the need for further methodology and guidance in the research area of pilot and feasibility studies to address the unidentified issues and the other notable issues related to TCM pilot trials.

Our study was the first to explore the current practice of methodology and reporting in TCM pilot trials. We completed the data acquisition and analyses by two reviewers independently, thereby enhancing the accuracy of study findings [19]. There are also some limitations to our study. Due to the small numbers of the included FDT (n = 12) and studies published after year 2016 (n = 12), we only performed raw comparisons without adjustments, which may yield biased findings in univariate analyses. We could not further extract potential solutions from the included TCM studies, indicating the important gap in methodological guidance in TCM pilot trials. Furthermore, only studies in Chinese and English were screened and selected, which may therefore introduce selection bias due to lack of studies in other languages such as Japanese and Korean. Moreover, the impact of time lag between the publication of a new guideline and the adoption and implementation of it could not be fully assessed, which may therefore weaken the findings of our study.

To conclude, the current practice in TCM pilot trials required substantial improvement in the literature. The guideline seemed to have only minimal effect on the methodology and reporting in TCM pilot trials, and some issues related to TCM pilot studies still warranted further methodology and guidance. Further endeavors are needed for training and dissemination of guideline adherence, and development of more detailed methodology in the field of TCM pilot trials.
Declarations

Funding

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Availability of data and materials

All the data are already publicly available in the literature.

Acknowledgement

None

Authors’ contributions

GL, DW and XC contributed to study conception and design. GL, DW and XC contributed to searching, screening, data collection and analyses. GL was responsible for drafting the manuscript. JZ, ZL and LT provided comments and made several revisions of the manuscript. All authors read and approved the final version.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.
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Figures
Figure 1
Flow diagram showing the process of eligible study identification

Supplementary Files

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