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

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Keywords: Traditional Chinese Medicine, pilot trial, feasibility, guideline adherence

Posted Date: January 3rd, 2020

DOI: https://doi.org/10.21203/rs.2.19852/v1

Version of Record: A version of this preprint was published at Pilot and Feasibility Studies on April 22nd, 2020. See the published version at https://doi.org/10.1186/s40814-020-00602-4.

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 liteature survey.

Methods We systematically searched MEDLINE, EMBASE and CNKI to retreive 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 stuides 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 requried 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 aoviding 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 unkonwn 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 issuses 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 retreive 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 eligilibity.

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], seperated 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 adherene of the included pilot trials

published before and after 2016. When there was a cell with expected frequency < 5 in the contigency 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.

Table 1
Characteristics of the 50 included studies

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 Rrsearch	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 adherece 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 leves (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						
1a	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)
1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	37 (74.0)	9 (75.0)	28 (73.7)	27 (71.1)	10 (83.3)
Introduction						
2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomized pilot trial	11 (22.0)	3 (25.0)	8 (21.1)	8 (21.1)	3 (25.0)
2b	Specific objectives or research questions for pilot trial	9 (18.0)	3 (25.0)	6 (18.4)	8 (15.8)	1 (8.3)
Methods						
3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	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

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

Table 3
Unidentified issues related to TCM pilot trials from the guidelines

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 guieline 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 sruvey.

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 effciacy 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 requried even in those pilots trials with specified feasibility objective(s). Therefore all these findings suggested further dissemination of the guidline to help clarify the definition of feasibility and pilot trials [2] and to enhance the guildeline 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 pariticipants 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 comparions 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 Chinsese 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 requried 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

This study was supported by research grant from the Science Foundation of Guangdong Second Provincial General Hospital (YY2018-002) and the Project of State Key Laboratory of Dampness Syndrome of Chinese Medicine (No. 2019KT1209)

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

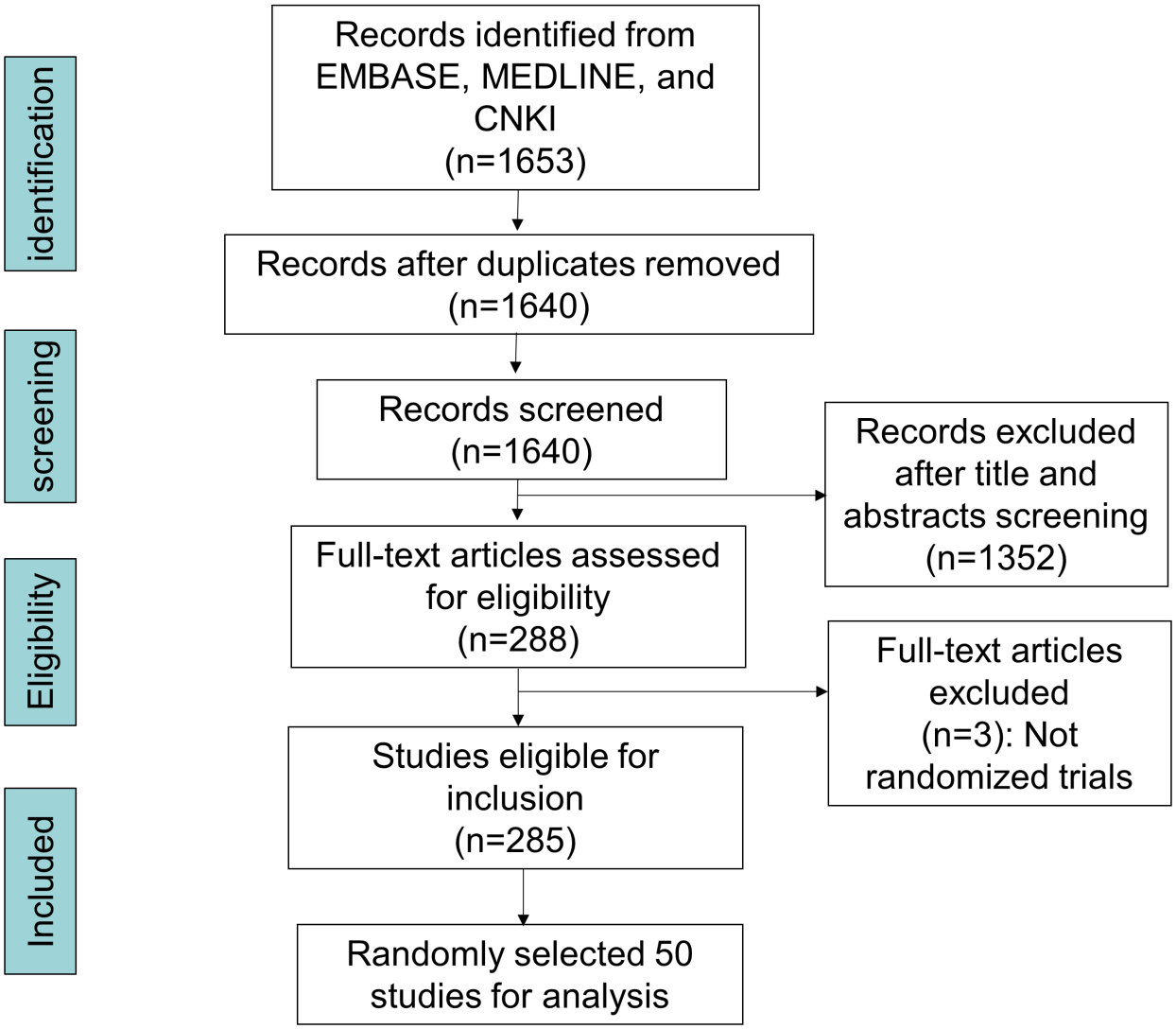

Figure 1

Flow diagram showing the process of eligible study identification

Supplementary Files

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