THE PROCESS EVALUATION OF CLINICAL TRIALS

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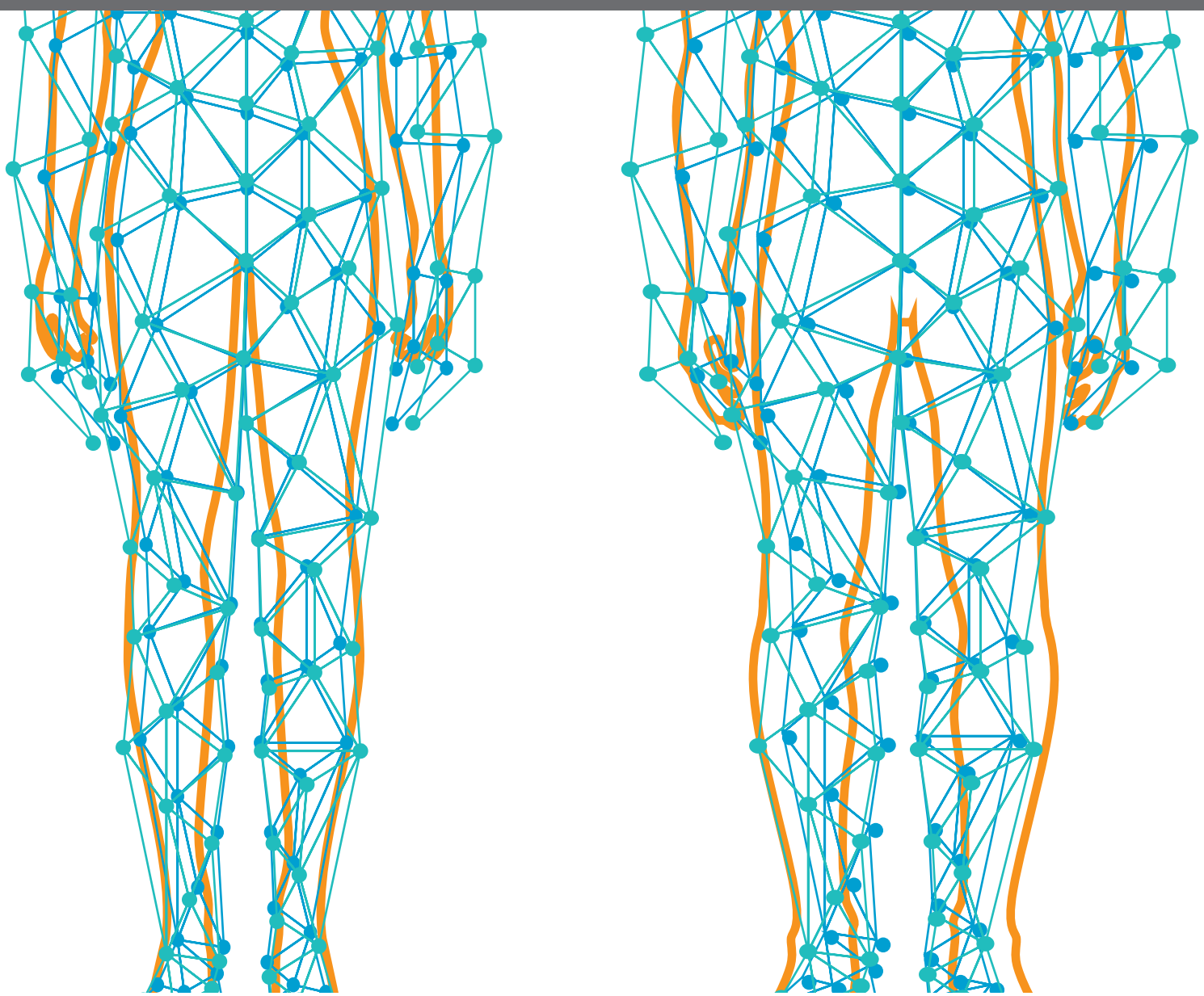

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THE PROCESS EVALUATION OF CLINICAL TRIALS

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EDITORIAL
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Editorial: The Process Evaluation of Clinical Trials

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Editorial on the Research Topic

The Process Evaluation of Clinical Trials

BACKGROUND: HISTORY OF PROCESS EVALUATIONS

The history of clinical trials goes back a long way to 500 BC, though some credits French surgeon Ambrose pare for the first documented clinical trial involving treatment of wounds during sixteenth century (1). Since then, clinical trials have evolved tremendously and have now become the foundation of modern medical and healthcare practice, focusing on clinical outcomes. However, over the past decades there has been increasing interest in performing "process evaluations" of clinical trials of complex interventions (2). While the outcome evaluation focuses on whether a new intervention works, a process evaluation supplements our knowledge by providing an understanding of the causal mechanisms of the intervention, contextual factors, and implementation factors impacting on the outcomes (3).

Process evaluation methodology has evolved through the years (2). Previously, they were used to assess implementation through the analysis of quantitative process indicators. Subsequently, there was increasing recognition and the need for qualitative research alongside trials to provide a deeper understanding of the disease condition, acceptability of an intervention and implementation issues (4). Process evaluations were deemed particularly relevant during a negative trial result, as to whether there was either implementation or intervention failure, or both. However, there is also a growing recognition that using qualitative and quantitative data, and theoretical frameworks within process evaluations will help facilitate evidence to practice (5–7). Process evaluations can help address stakeholders' question of "Is this intervention acceptable, effective, affordable and feasible (for me or) for this population?" (7).

Key domains are summarized in UK Medical Research Council (MRC) process evaluation guidance (context, quality of implementation and mechanisms of the intervention), and also include concepts from established evaluation frameworks that have been used widely including: Reach, Effectiveness, Adoption, Implementation and Maintenance framework (RE-AIM) (8) and Linnan and Steckler (9). Although each is unique, there is some overlap, in their emphasis to enable research translation. The key concepts include: (i) reach and recruitment (i.e., investigating the extent to which the intervention as received by the targeted group), (ii) adoption (i.e., related to the delivery of the intervention, (iii) acceptability (i.e., extent to which participants find the intervention acceptable), (iv) implementation fidelity (i.e., extent to which intervention is delivered

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as planned), (v) maintenance (i.e., extent to which the intervention can be sustained over time after the clinical trial is over).

SPECIAL ISSUE: PROCESS EVALUATIONS OF CLINICAL TRIALS

This special issue builds on the emerging value and methodology of process evaluations. It includes nine manuscripts focusing on a range of interventions. Therefore, highlighting the transferability and value of process evaluations across types of interventions, and also in unpacking context from lower-middle income countries to high income countries with established health systems. Chu et al. presented the mixed-methods process evaluation of community-based dietary sodium reduction in Rural China. In another study, expectations regarding pragmatic trial design of integrative medicine for diabetes and kidney diseases among patients and physicians was evaluated and reported (Chan et al.). Four studies focused on process evaluation of telehealth interventions. Meijerink et al. presented process evaluation of online support program for hearing aid users. Beukes et al. and Biliunaite et al. provided process evaluation results of internet-based cognitive behavioral therapy for tinnitus and informal caregivers, respectively. Indraratna et al. presented the process evaluation of TeleClinical care for acute coronary syndrome and heart failure. Two studies also included implementation science approach. Riddell et al. evaluated the implementation and scalability of the Accredited Social Health Activists (ASHAs) led community-based support groups for hypertension in Rural India. In another study, Ouyang et al. provided the process evaluation of implementation trial on intracerebral hemorrhage. Finally, Wu et al. presented the comprehensive process evaluation of the pediatric drug clinical trials through a literature review.

The process evaluations in this collection are also conducted across different phases of the research cycle, from study design (Chu et al.), pilot/feasibility phase (Biliunaite et al.; Indraratna et al.), evaluation of the clinical trial (Chu et al.; Meijerink et al.; Beukes et al.; Riddell et al.; Ouyang et al.) including long term sustainability (Riddell et al.; Wu et al.). Therefore, highlighting the value of process evaluation findings to inform intervention design and optimize implementation. Moreover, while the use of theoretical frameworks is helpful in eliciting contextual determinants across individual, organizational and system, and policy levels, often the breadth and scope of them in literature can be daunting (3). Careful consideration of what theories are relevant would be helpful (10). For instance, in this special issue, for interventions that are related to individual behavioral change, health belief model used by Chu et al. or others such as behavior change wheel, or cognitive theories may be helpful. Normalization process theory that has a strong focus on understanding organizational behavior, was also used by Ouyang et al. the implementation study in stroke units for intracerebral hemorrhage.

WHERE TO FROM HERE?

Indeed, as we reflect on the emerging value and methodology of process evaluations, it is worth noting its contributions to implementation science, as researchers endeavor to meet end-users' needs, understand what happened on the ground, and how to overcome implementation barriers. As we continue to invest in clinical trials to inform evidence-based medicine and policy, we recommend that we embed process evaluations throughout the research cycle, to examine for whom, how and why the clinical trial had its outcomes. This will require building capacity in mixed-methods, implementation science, stakeholder engagement/co-design of implementation strategies, which will require allocation of sufficient resourcing, budgeting, time and most importantly training those who are involved in performing clinical trials on process evaluation and implementation science elements. And in doing so, regardless of a positive or negative trial result, we will learn to improve our research and intervention design to meet local context and enable long term sustainability and scale up of effective interventions.

AUTHOR CONTRIBUTIONS

HL drafted the initial manuscript, with significant input from VM. All authors have reviewed the manuscript versions and approved its submission.

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REFERENCES

1. Bhatt A. Evolution of clinical research: a history before and beyond James Lind. *Perspect Clin Res.* (2010) 1:6–10.
2. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ*. (2015) 350:h1258. doi: 10.1136/bmj.h1258
3. Liu H, Mohammed A, Shanthosh J, News M, Laba TL, Hackett ML, et al. Process evaluations of primary care interventions addressing chronic disease: a systematic review. *BMJ Open.* (2019) 9:e025127. doi: 10.1136/bmjopen-2018-025127
4. Lewin S, Glenton C, Oxman AD. Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions:

methodological study. *BMJ*. (2009) 339:b3496. doi: 10.1136/bmj.b3496
5. Curry LA, Nembhard IM, Bradley EH. Qualitative and mixed methods provide unique contributions to outcomes research. *Circulation*. (2009) 119:1442–52. doi: 10.1161/CIRCULATIONAHA.107.742775
6. McIlvennan CK, Morris MA, Guetterman TC, Matlock DD, Curry L. Qualitative methodology in cardiovascular outcomes research: a contemporary look. *Circ Cardiovasc Qual Outcomes*. (2019) 12:e005828. doi: 10.1161/CIRCOUTCOMES.119.005828
7. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ*. (2021) 374:n2061. doi: 10.1136/bmj.n2061
8. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health*. (1999) 89:1322–7. doi: 10.2105/AJPH.89.9.1322
9. Linnan L, Steckler A. *Process Evaluation for Public Health Interventions and Research*. San Francisco, CA: Jossey-Bass (2002).
10. Nilsen P. Making sense of implementation theories, models and frameworks. *Implement Sci*. (2015) 10:53. doi: 10.1186/s13012-015-0242-0

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ORIGINAL RESEARCH
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A Mixed Methods Process Evaluation of a Clustered-Randomized Controlled Trial to Determine the Effects of Community-Based Dietary Sodium Reduction in Rural China

Hongling Chu[1], Jing Zhang[2], Michael D. Fetters[3], Wenyi Niu[4], Huijuan Li[5], Nicole Li[6], Lijing L. Yan[2,7], Yanfang Wang[5] and Yangfeng Wu[2,5]**

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Purpose: A clustered-randomized controlled trial was conducted to determine the effects of a sodium reduction program in 120 rural villages in Northern China. This mixed-methods process evaluation was used to investigate the implementation and to evaluate the feasibility of the complex intervention to translate the findings from clinical study to the real world.

Methods: A convergent mixed-methods process evaluation design was used in this study. Quantitative data were collected from activity logs and routine study records. Qualitative data were collected from 53 project stakeholders and 45 villagers from 10 intervention villages. Thematic analysis of qualitative interviews facilitated integration with the descriptive quantitative data analysis based on theory-informed domains of fidelity, delivery, reach, receipt, and contextual factors of intervention from a process evaluation framework.

Results: The intervention was implemented with high fidelity, delivery, reach, and receipt. A total of 5,450 sheets of posters, 31,400 calendars, and 78,000 sheets of stickers were delivered as planned, and 11 promotion activities were conducted in each village. Contextual factors hindering full uptake of the intervention included preference for salty taste, higher cost of low-sodium salt, and low education levels of villagers. Other contextual factors, positive policy support, administrative support, and staff enthusiasm were the facilitators for implementation.

Conclusions: This multifaceted intervention was implemented well and effectively in rural China. This process evaluation has indicated that conducting health education

interventions in rural areas requires policy and administrative support, enthusiastic staff, easy-to-understand health education materials and activities, and key persons, but tempered expectations as behavior change requires time. This project demonstrates the feasibility and benefits of using mixed-methods process evaluation in large-scale studies.

Keywords: hypertension, clustered-randomized trial, salt reduction, complex intervention, process evaluation, mixed methods

INTRODUCTION

Stroke is the leading cause of death in China, responsible for about 1.7 million deaths each year (1, 2). Excess sodium intake is a key determinant of high blood pressure (3), the leading cause of stroke (4). The magnitude of the effect of sodium on blood pressure is such that each 75-mmol difference in daily salt intake translates into an ∼5.4 mm Hg difference in systolic blood pressure among individuals with hypertension, and 2.4 mm Hg among individuals without hypertension (3). Chinese people, especially those living in northern rural areas, have the highest sodium intake levels in the world, where hypertension and the incidence of stroke are also all very high (5). In Western populations, most dietary sodium derives from processed and restaurant foods, but in rural China the major source comes from salt and condiments added in home cooking (6).

Given this hypertensive crisis in rural China, a clinical trial was conducted to identify a novel, low-cost, scalable, and sustainable, community-based strategy for the prevention of blood pressure-related diseases in rural China (7). The trial was registered with clinicaltrial.gov in December 2010, registration number NCT01259700.

The main study was published (8). The overall intervention was designed on the basis of the health belief model (HBM). The HBM is a theoretical model that has been constructed from six domains, which are perceived susceptibility, severity, barriers, benefit, cues to action, and self-efficacy. According to the framework of the HBM and proved cost-effective strategy for sodium reduction (9), the complex intervention contained three parts, health education materials with key message about salt reduction (posters, calendars, and stickers were pasted, respectively, on the wall outside, indoors, and in salt containers), health education activities (launch events, activities organized in consideration of local context, activities for individuals at elevated risk of cardiovascular disease, and student-to-parent education activities), and low-sodium salt substitute supply (**Table 1**). The intervention is further depicted in the tables in the appendix (**Supplementary Material** in Appendix 1).

After complex intervention being conducted for 18 months, 1,903 people had valid 24-h urine collections. The mean urinary sodium excretion in intervention compared with control villages was reduced by 5.5% (−14 mmol/day, 95% confidence interval −26 to −1; $p = 0.03$). In the intervention group, potassium excretion was increased by 16% (+7 mmol/ day, +4 to +10; $p < 0.001$), and the sodium to potassium ratio declined by 15% (−0.9, −1.2 to −0.5; $p < 0.001$). Between the intervention and control groups, the mean blood pressure differences were −1.1 mm Hg systolic (−3.3 to +1.1; $p = 0.33$) and −0.7 mm Hg diastolic (−2.2 to +0.8, $p = 0.35$). The difference in the proportion with hypertension was −1.3% (−5.1 to 2.5, $p = 0.56$) (8). The absence of effects on blood pressure reflects the moderate changes in sodium and potassium intake achieved (**Supplementary Material** in Appendix 1).

However, alongside intervention efficacy, some questions are still unclear, these are as follows: how are the components of the complex intervention implemented; what are the barriers or facilitators within its context; and how can implementation be optimized in future practice. Therefore, the mixed-methods approach was used to integrate qualitative and quantitative aspects of this study, to investigate the fidelity, delivery, reach, receipt, and context of intervention. The current study could provide us a comprehensive view of implementation and effectiveness and promoted evidence-based practice for village doctors who provide the basic medical service as a family doctor to prevent and control chronic disease in local village in rural China.

METHODS

Theoretical Framework of Process Evaluation

"How-to Guide" (10) and REAIM frameworks (11) were used for the process evaluation to examine the level of implementation comprehensively. This involves understanding the implementation of intervention in terms of (1) fidelity, defined as to what extent the intervention was implemented consistently with the underlying theory as planned; (2) delivery, defined as to what extent all of the intended activities, training, and materials were provided to program participants; (3) reach, defined as the absolute number, proportion, and representativeness of individuals who are willing to participate in a given initiative, intervention, or program; (4) receipt, defined as to how participants reacted to specific aspects of the intervention; and (5) context, defined as what contextual factors influence implementation or the intervention outcome.

Design

A convergent mixed-methods design (12) was used in the current study that was guided by the process evaluation theoretical framework. While data were collected prospectively, the analysis of the data occurred at the same time after the intervention. The impetus for the mixed-data evaluation was to provide a comprehensive view of the extent the intervention worked, and to understand why the interventions conducted in this study were effective (**Figure 1**).

TABLE 1 | The health belief model and derived intervention used in this project.

Domains of HBM	Features of the intervention in this project according to the HBM	Intervention
1. Perceived susceptibility, severity	**Improving the awareness of:** a. How much salt is consumed b. High salt intake worsens health and diseases caused by high salt intake	**a. Health education materials** - Posters - Calendars - Stickers for placing on salt containers
2. Perceived benefit, barriers, cues to action	**Providing the information and cues about:** a. The benefits of consuming less salt b. The effects of low-sodium salt c. Removing concerns that low salt intake would result in no energy to work. d. To create a salt-reduction atmosphere and tell them how to reduce salt intake (knowledge and behaviors)	**b. Health education activities** - Program launch events - Activities organized in consideration of local context - Activities for individuals at elevated risk of cardiovascular disease - Student-to-parent education activities
3. Perceived self-efficacy	**Organizing activities to help them improve their self efficacy:** a. To carry out activities to encourage their beliefs and behaviors for salt reduction	**c. Low-sodium salt substitute supply**

Study Settings and Participants

The main trial was conducted in five Northern Provinces of China, including Hebei, Liaoning, Ningxia, Shanxi, and Shaanxi (7). Two counties from each province were selected for participation; twelve townships of each county were engaged with total 120 to wnships. A typical township in the study comprised ∼17 villages with a total population of 25,000. There was one village doctor in each village who provides basic health services there. The average population of included villages was 1,867 with 512 households. The annual per capita income was $884, and 91.5% participants have < 9 years of education. The village doctors, who conducted intervention in this study, have played a significant role in providing basic health services to villagers when the area had great shortage of health resources.

Data Collection

The health education activities and process evaluation were launched in May 2011, and health education activities ended on September 2012, while the process evaluation continued throughout the project and afterward until March 2013. The study data sources are represented in **Supplementary Material** in Appendix 1.

Quantitative Data

Data about delivery of the materials were collected from 150 activity logs and 91 routine records recorded prospectively by the county project officers and project assistants.

Qualitative Data

The strategy of purposeful sampling was used to select participants. Using a semi-structured, face-to-face depth interview (interview guides are shown in Appendix 2 in **Supplementary Material**), the qualitative evaluation was conducted in 10 intervention villages from five provinces (two villages intentionally sampled in each county, one county from each province). Interviews were conducted among 48 key stakeholders including five provincial project investigators, five province project coordinators, five county project officers, five county project governors, five county health educators, eight town health educators, 15 village doctors; and 45 villagers from intervention villages including 19 housewives, 13 general villagers, and 13 villagers with a high risk of cardiovascular disease (**Supplementary Material** in Appendix 1).

Data Analysis

Intramethod Data Analysis

The number and percentage of the education materials distributed and health education events held were calculated for each component on three dimensions including fidelity, delivery, and dose reached to villagers. SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp)software was used to analyze the quantitative data. An immersion/crystallization approach was used to analyze the qualitative data based on the dimension of receipt and contextual factors (13). The transcribed data were analyzed using Nvivo 11 (QRS, Australia) software of Chinese version. Three researchers (CH, LH, and GW) coded and analyzed the transcripts by making sense of the transcribed data, developing codes, categorizing the data, and abstracting. We discussed every discrepancy regarding the finding interpretation until reaching consensus. The analysts calibrated the coding process after reviewing one independently coded interview. Models were constructed through the analysis and then confirmed by reviewing the interview transcripts. The final agreement was achieved through the review of entire research team.

Mixed Data Analysis

The mixed data were analyzed based on the study process evaluation framework using the process of joint display analysis (14). This iterative process of juxtaposing links quantitative and qualitative data together, examining the implications of each other and looking for new facilitates drawing conclusions in light of both types of findings.

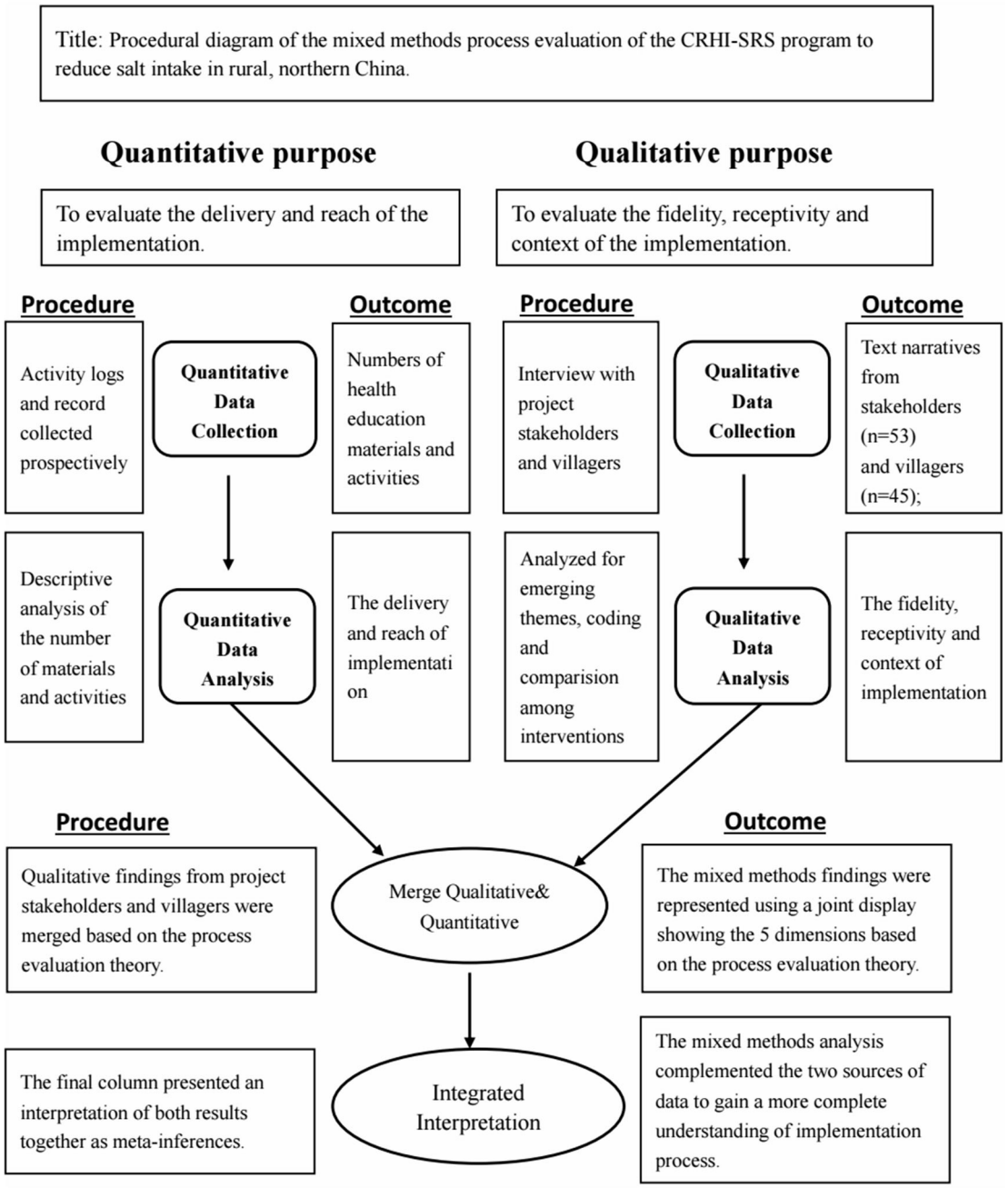

FIGURE 1 | Diagram of convergent mixed-methods process evaluation.

RESULTS

Interviews were completed among 93 stakeholders, and 150 records were collected prospectively. We present the quantitative findings for the three dimensions of process evaluation of fidelity to protocol, delivery and reach, and qualitative findings for two dimensions of receipt and contextual factors. The interview responses have been summarized in the results and specific quotations can be found in the related sections.

Fidelity/Delivery

Fidelity was determined by comparing the activities outlined in the strategic action plan with delivered activities. This comparison showed that all health education materials and activities were implemented as planned, with high fidelity (**Supplementary Material** in Appendix 1). A total of 5,450 sheets with five different types of posters, 62,800 sheets of yearly calendars, and 78,000 pieces of special designed stickers were delivered to intervention villages. Seven hundred and twenty

TABLE 2 | Joint display of fidelity, delivered, reach, receipt, and meta inferences by each component of intervention.

Dimension	Posters	Calendars	Stickers for placing on salt containers	Program launch events	Activities organized in consideration of local context	Activities for individuals at elevated risk of cardiovascular disease	Student-to-parent education activities	Low-sodium salt substitute supply
Fidelity (to protocol)	High	High	High	High	High	High	Moderate	High
Delivery (planned/ delivered)	5,450/ 5,450 units	31,400/ 31,400 units	78,000/ 78,000 units	60/60 events	300/300 events	240/228 events	60/120 events	NA/115, 228 bags
Reach	40/45 interviewees	40/45 interviewees	39/45 interviewees	43/45 interviewees	22/32 interviewees	12/13 interviewees	1,595 children's worksheets	37/45 interviewees
Receipt	Being popular, easy-to-understand, and simple	Deemed practical	Served to remind when using salt	Created a specific and suitable atmosphere for salt reduction	Some villagers felt the content became repetitive and wanted more variety of information	Some elders or people with CVD could not participate	Primary school students were interested in these activities	Some felt the taste was less salty than regular salt, and it was more expensive
Meta inferences	Recommended and accepted by villagers.	Recommended	Recommended	Strongly recommended	Strongly recommended	Moderately recommended	Strongly recommended	Recommended

health education events were held in total, and 115, 228 packs of salt substitute were delivered to the village stores.

In terms of student-to-parent education activities, the numbers of planned and delivered were 60 and 120, respectively (**Table 2**). The reason for this was when we completed the first round of student education activities (60 events), we found that the students were willing to participate in activities and the effect of health education was relatively good. Therefore, the second round of activities (60 events) was conducted. From qualitative interviews, some interviewees mentioned that children and primary school kids paid more attention to salt reduction, "I found that children were interested in those pictures, stories on the calendar, as well as the activities." (Villager).

Reach

The data was transformed from the interviews. It showed that the proportion of attended health education activities was low (61.5%) in general villagers, while the number was relatively high (92.3%) for people with high risk of cardiovascular diseases (**Table 3**). From the qualitative interviews, we found that a dearth of young adults participated in activities due to out-migration to cities. *"There are many middle-aged and young people moved into the urban cities or temporarily work there, who were unable to participate." (VHE).* In addition, some villagers felt that the content later during implementation became repetitive. *"There was no new ideas added with passing of time." (CHE).* These two reasons might explain a low reach of the health education activities in the general villagers.

Receptivity of Intervention

Generally, the salt reduction project was accepted and the local people were satisfied. The health education materials, including posters, calendars, and stickers, were accepted by the local people because they were popular, simple, easy-to-understand, and practical. However, posters placed outdoors were easily lost and less effective than posters placed indoors. Some interviewees suggested writing slogans on walls.

The health education activities created a specific and suitable atmosphere important during program launch and provided the detailed information and cues necessary to reduce salt intake. Some interviewees mentioned that children and primary students paid more attention to salt reduction. However, some villagers felt that the content later during implementation became repetitive and wanted a greater variety of information. Interviewees had many valuable suggestions, such as leading the salt reduction activities by enthusiastic volunteers who are the elders or children, and that activities should avoid busy farming times.

In terms of low-sodium salt substitute supply, most interviewees deemed that low-sodium salt substitute is acceptable because the village doctor told them that it is healthier than regular salt, even though some felt that the taste was less salty than regular salt and that it was more expensive. **Supplementary Material** in Appendix 3 provides typical interview quotes regarding receipt of the intervention.

TABLE 3 | Reach of each component that interviewees exposed to the intervention.

Interview groups and number interviewed	General villagers *N* = 13	Housewife *N* = 19	Villagers at elevated risk of CVD *N* = 13	Total *N* = 45
	n (%)	n (%)	n (%)	n (%)
Heard of this project	12 (92.3)	19 (100)	12 (92.3)	43 (95.6)
Saw posters	11 (84.6)	18 (94.7)	11 (84.6)	40 (88.9)
Received calendars	10 (76.9)	17 (89.4)	13 (100)	40 (88.9)
Received stickers	11 (84.6)	17 (89.4)	11 (84.6)	39 (86.7)
Attended health education activities	8 (61.5)	14 (73.7)	12 (92.3)	43 (95.6)
Used a low-sodium salt substitute	10 (76.9)	15 (68.4)	12 (92.3)	37 (82.2)

Contextual Factors

Contextual factors influencing implementation included policy support, administrative support, staff enthusiasm, and out-migration of young adults to cities. At present, some national chronic disease policies have been implemented in certain areas and incorporated into public health service projects. From the interviews, we serendipitously found that some areas with policy support for a chronic disease project improved the conduct of this project due to interactive and mutual support of both projects. Administrative support, in general, can improve the quality of project implementation. However, in some cases, there are some staff who conducted project work only because of administrative pressures—this has potentially negative implications for the quality of the project. Health educators paid time and effort on the project varying from 10 to 70%. In most counties, the health educators had more than one job. Thus, in addition to the program work, they already had a very heavy workload. This led to time conflicts and hampered the quality of the program's implementation. Still, some health educators prepared for this project in the evening or on weekends. This included drafting reports and other administrative activities. Some experienced health educators conducted a variety of health education activities. There was a dearth of young adults participating in activities due to out-migration to cities.

Contextual factors influencing the intervention's effect included the following: adding too much salt when cooking and eating pickled foods as long-standing behaviors, change is a long-term process that requires gradual adaptation; and as the education level of villagers is generally low, it takes a long time to change and maintain healthy behaviors. The **Supplementary Material** in Appendix 4 provides quotes of contextual factors from the study interviews.

To integrate the quantitative and qualitative results, we created **Table 2** based on the process evaluation framework and the structure of a joint display.

DISCUSSION

The clustered-randomized controlled trial was a rigorously conducted trial. The process evaluation found that the fidelity, delivery, reach, and receipt of the intervention were high. Posters were recommended for the value of creating a positive atmosphere; calendars were practical as they could be posted on the wall of the house for a long time and provide reminder information. Stickers for placing on salt containers were recommended as they prompted caution when using salt during cooking. This is especially important, since sodium intake primarily comes from added salt during cooking in the study population (6).

A program launch event is strongly recommended as it captured the attention of most villagers and implementers and created an atmosphere conducive to salt reduction among the whole village. Activities organized in consideration of the local context are also strongly recommended as they maximized the involvement of villagers in the sodium reduction intervention by holding a variety of activities based on local culture. Activities for high-risk individuals were only moderately recommended as they are very time consuming and covered only fewer topics about health, while the targeted people felt less benefit. The principle of "simple and repetitive" in health education in this case was not found suitable for activities (15). Villagers need more health-related knowledge, not simply a repetition of the same information. Interestingly, the student-to-parent education activities are strongly recommended because students played an influential role in families and they readily adapted the healthy behavior. From the interview, we also find that schoolchildren could take a leadership role in the sodium reduction intervention because of their key role in the family. This finding is seen also in a sequential school-based education program to reduce salt intake in children and their families (16, 17).

Notably, there were contextual factors influencing implementation and/or intervention effectiveness. Policy support, administrative support, and staff enthusiasm were all found to be facilitators, as they enhanced implementing this complex intervention in rural China. In contrast, lack of an effective governance mechanism to implement in low- and middle-income countries (LMICs) has been identified as an ongoing challenge in previous research (18, 19). The current project involves village doctors who conduct implement intervention as they easily gain trust from local villagers.

Moreover, there were three main barriers found from process evaluation. The first one is that general villagers were involved in the survey at the end of the intervention, although general

villagers had a low reach in health education activities during intervention. This might make the evaluated effect lower than the actual effect. Secondly are adding too much salt when cooking, and eating pickled foods, which were long-standing dietary habits. It is well-known that behavior change is a long-term process requiring gradual adaptation. Many studies have identified that the strong cultural importance of feasting and people's perception of salty food taste were barriers of sodium intake reduction (20). Third, because of the low educational level of villagers, it might take a longer time to change and maintain healthy behavior (21). This also explains the secondary outcome that over 18 months' intervention, blood pressure did not differ significantly between the intervention and control groups (8).

Limitations and Strengths

As for limitations, a. the evaluation would have been further strengthened if some process measurements could have been collected after completion of investigation, e.g., reach for each component of the intervention; b. data were not intentionally collected to show why differences in the extent of implementation had varied outcomes among different villages, because the process evaluation was conducted before the study outcomes were analyzed; and c. the insights about receptivity of intervention and context of this study from different populations including health educators, villagers, and implementers will be further analyzed for future research. As for strengths, the mixed-data evaluation provided a comprehensive understanding of the extent of the implementation and mechanism of effectiveness. It also promoted evidence-based practices in primary healthcare systems in rural China.

CONCLUSION

When conducting health education interventions for salt reduction in rural China, the design of easy-to-understand educational materials including posters, calendars, and stickers proved to be effectively implemented ways to attract the attention of villagers. The findings suggest that interventions deeply involving primary school students or enthusiastic volunteers can promote the implementation of health education activities. Stocking salt substitutes in stores appears to provide convenient access for villagers. Meanwhile, policy and administrative support and staff with enthusiasm were important for the success of the intervention. These recommendations may be relevant in other low-middle-income countries. This project also demonstrates the feasibility and benefits of using a mixed-methods process evaluation in large-scale clinical trials and promotes evidence-based practices for village doctors who provide the basic medicine care and promote behavior change as a family doctor to prevent and manage chronic disease in rural China. This successful example may also help in the adoption of mixed-methods health service research in China.

PRIOR PRESENTATION

1. The 18th National Annual Conference of Clinical Epidemiology and Evidence-based Medicine, Aug. 24, 2019, Dalian, China.
2. MMIRA Asia Regional Conference, Sept. 15, 2019, Hamamatsu, Japan.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Peking University Health Science Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YWu, MF, and YWa: conceptualization. NL, LY, YWu, HL, WN, MF, and JZ: writing—review and editing. HC, JZ, MF, and YWa: writing—original draft. HC: software. HC, JZ, and HL: project administration and formal analysis. YWa, WN, YWu, LY, NL, HC, and HL: methodology. YWu, LY, NL, WN, and JZ: investigation. YWu: funding acquisition. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. *Lancet.* (2012) 380:2095–128. doi: 10.1016/S0140-6736(12)61728-0
2. China HM. *China Annual Health Statistics Yearbook*. Beijing: Peking Union Medical College Press (2011).
3. He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: cochrane systematic review and meta-analysis of randomised trials. *BMJ.* (2013) 346:f1325. doi: 10.1136/bmj.f1325
4. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet.* (2006) 367:1747–57. doi: 10.1016/S0140-6736(06)68770-9
5. Tan M, He FJ, Wang C, MacGregor GA. Twenty-four-hour urinary sodium and potassium excretion in China: a systematic review and meta-analysis. *J Am Heart Assoc.* (2019) 8:e12923. doi: 10.1161/JAHA.119.012923
6. Anderson CA, Appel LJ, Okuda N, Brown IJ, Chan Q, Zhao L, et al. Dietary sources of sodium in China, Japan, the United Kingdom, and the United States, women and men aged 40 to 59 years: the INTERMAP study. *J Am Diet Assoc.* (2010) 110:736–45. doi: 10.1016/j.jada.2010.02.007
7. Li N, Yan LL, Niu W, Labarthe D, Feng X, Shi J, et al. A large-scale cluster randomized trial to determine the effects of community-based dietary sodium reduction–the China rural health initiative sodium reduction study. *Am Heart J.* (2013) 166:815–22. doi: 10.1016/j.ahj.2013.07.009
8. Li N, Yan LL, Niu W, Yao C, Feng X, Zhang J, et al. The effects of a community-based sodium reduction program in rural China - a cluster-randomized trial. *PLoS ONE.* (2016) 11:e166620. doi: 10.1371/journal.pone.0166620
9. Ya-Jing F, Wen-Hua Z. The experiences indications of successful national salt reduction strategy in U.K. and Finland. *Chin J Health Policy.* (2010) 3:52–6. doi: 10.3969/j.issn.1674-2982.2010.05.013
10. Saunders RP, Evans MH, Joshi P. Developing a process-evaluation plan for assessing health promotion program implementation: a how-to guide. *Health Promot Pract.* (2005) 6:134–47. doi: 10.1177/1524839904273387
11. Glasgow RE, Harden SM, Gaglio B, Rabin B, Smith ML, Porter GC, et al. RE-AIM planning and evaluation framework: adapting to new science and practice with a 20-year review. *Front Public Health.* (2019) 7:64. doi: 10.3389/fpubh.2019.00064
12. Creswell JW. *A Concise Introduction to Mixed Methods Research*. Thousand Oaks, CA: SAGE pulications, Inc (2014).
13. Borkan J. Immersion/Crystallization. In: Crabtree B, Miller W, editors. *Doing Qualitative Research. 2nd ed.* Thousand Oaks, CA: Sage Publications (1999). p. 179–94.
14. Fetters MD. *The Mixed Methods Research Workbook: Activities for Designing, Implementing, and Publishing Projects*. Thousand Oaks, CA: SAGE Publications (2020).
15. Ettema JS, Brown JW, Luepker RV. Knowledge gap effects in a health information campaign. *Public Opin Q.* (1983) 47:516–27. doi: 10.1086/268809
16. He FJ, Wu Y, Ma J, Feng X, Wang H, Zhang J, et al. A school-based education programme to reduce salt intake in children and their families (School-EduSalt): protocol of a cluster randomised controlled trial. *BMJ Open.* (2013) 3:e003388. doi: 10.1136/bmjopen-2013-003388
17. He FJ, Wu Y, Feng XX, Ma J, Ma Y, Wang H, et al. School based education programme to reduce salt intake in children and their families (School-EduSalt): cluster randomised controlled trial. *BMJ.* (2015) 350:h770. doi: 10.1136/bmj.h770
18. Webster J, Pillay A, Suku A, Gohil P, Santos JA, Schultz J, et al. Process evaluation and costing of a multifaceted population-wide intervention to reduce salt consumption in Fiji. *Nutrients.* (2018) 10:155. doi: 10.3390/nu10020155
19. Wolfenden L, Wyse R, Nichols M, Allender S, Millar L, McElduff P. A systematic review and meta-analysis of whole of community interventions to prevent excessive population weight gain. *Prev Med.* (2014) 62:193–200. doi: 10.1016/j.ypmed.2014.01.031
20. Ghimire S, Shrestha N, Callahan K. Barriers to dietary salt reduction among hypertensive patients. *J Nepal Health Res Counc.* (2018) 16:124–130. doi: 10.3126/jnhrc.v16i2.20296
21. Davies NM, Dickson M, Davey SG, van den Berg GJ, Windmeijer F. The causal effects of education on health outcomes in the UK biobank. *Nat Hum Behav.* (2018) 2:117–25. doi: 10.1038/s41562-017-0279-y

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PRAgmatic Clinical Trial Design of Integrative MediCinE (PRACTICE): A Focus Group Series and Systematic Review on Trials of Diabetes and Kidney Disease

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Background: Pragmatic trials inform clinical decision with better generalizability and can bridge different streams of medicine. This study collated the expectations regarding pragmatic trial design of integrative medicine (IM) for diabetes and kidney diseases among patients and physicians. Dissonance between users' perspective and existing pragmatic trial design was identified. The association between risk of bias and pragmatism of study design was assessed.

Method: A 10-group semi-structured focus group interview series [21 patients, 14 conventional medicine (ConM) and 15 Chinese medicine (CM) physicians] were purposively sampled from private and public clinics in Hong Kong. Perspectives were qualitatively analyzed by constant comparative method. A systematic search of four databases was performed to identify existing IM pragmatic clinical trials in diabetes or kidney disease. Primary outcomes were the pragmatism, risk of bias, and rationale of the study design. Risk of bias and pragmatism were assessed based on Cochrane risk-of-bias tool and PRECIS-2, respectively. The correlation between risk of bias and pragmatism was assessed by regression models with sensitivity analyses.

Results: The subtheme on the motivation to seek IM service was analyzed, covering the perceived limitation of ConM effect, perceived benefits of IM service, and assessment of IM effectiveness. Patients expected IM service to retard disease progression, stabilize concomitant drug dosage, and reduce potential side effects associated with ConM. In the systematic review, 25 studies from six countries were included covering CM, Korean medicine, Ayurvedic medicine, and western herbal medicine. Existing study designs did not include a detailed assessment of concomitant drug change and adverse events. Majority of studies either recruited a non-representative proportion of patients as traditional, complementary, and integrative medicine (TCIM) diagnosis was used as inclusion criteria, or not reflecting the real-world practice of TCIM by completely dropping TCIM diagnosis in the trial design. Consultation

follow-up frequency is the least pragmatic domain. Increase in pragmatism did not associate with a higher risk of bias.

Conclusion: Existing IM pragmatic trial design does not match the patients' expectation in the analysis of incident concomitant drug change and adverse events. A two-layer design incorporating TCIM diagnosis as a stratification factor maximizes the generalizability of evidence and real-world translation of both ConM and TCIM.

Keywords: integrative medicine, method, qualitative, pragmatic, clinical trial, systematic review, diabetes, kidney

EXISTING EVIDENCE

Pragmatic trials better reflect real-world effectiveness of interventions. Integrative medicine (IM) amalgamates multiple streams of medicine with different disease classifications and treatment strategies which require pragmatic assessment. However, existing pragmatic trial design seldom considers users' perspective and there are concerns on whether flexibilities in pragmatic trial design would compromise internal validity.

KEY CONTRIBUTIONS TO THE LITERATURE

1. This is the first focus group series to explore the expected outcomes of patients and physicians regarding pragmatic trial design of IM for diabetes and renal service, involving patients and family medicine, internal medicine, and Chinese medicine (CM) physicians. Unmatched expectation in existing studies was identified through systematic review.
2. Patients expected integrative Chinese-western medicine service to retard disease progression, stabilize concomitant drug dosage, and reduce potential side effects associated with conventional treatment.
3. Existing IM pragmatic trial designs did not include detailed assessment of concomitant drug change and adverse events. Consultation follow-up frequency is the least pragmatic domain in existing IM pragmatic trials.
4. Majority of studies either recruited a non-representative proportion of patients by using traditional, complementary, and integrative medicine (TCIM) diagnosis as inclusion criteria, or not reflecting the real-world practice of TCIM by completely dropping TCIM diagnosis.
5. Increase in pragmatism in study design did not associate with a higher risk of bias from existing evidence.

IMPLICATIONS

Existing IM pragmatic trial design does not match users' expectation in the analysis of incident concomitant drug changes and adverse events. A two-layer design incorporating TCIM diagnosis as a stratification factor maximizes the generalizability of evidence and real-world translation for both conventional medicine and TCIM.

Abbreviations: TCIM, traditional, complementary and integrative medicine; CKD, chronic kidney disease; CM, Chinese medicine; DKD, diabetic kidney disease; GFR, glomerular filtration rate; IM, integrative medicine; ConM, conventional medicine.

INTRODUCTION

Pragmatic trials evaluate the effectiveness of interventions in the real-world setting aiming to inform clinical decision and implementation with better generalizability (1, 2). Compared to conventional phase III randomized controlled trials, pragmatic trials often are open-label, have less stringent inclusion/exclusion criteria, involve complex/flexible interventions, compare to usual care, and measure outcomes that are patient-centered (1, 2). Integrative medicine (IM) amalgamates conventional medicine (ConM) and other streams of medicine from a patient-centered and effectiveness-driven approach (3–5).

Traditional, complementary, and integrative medicine (TCIM), including Chinese medicine (CM), naturopathic medicine, mind–body therapies, and other streams of medicine, are often personalized as their theories were developed predominantly from expert consensus and case series (6). Differences in epistemology (for instance, disease classification and treatment strategy) between ConM and TCIM led to controversies in the evaluation of TCIM's effectiveness (7–10). Most clinical trials and meta-analyses were designed to estimate the adjusted or averaged effectiveness of a regimen from a population of patients. However, the likelihood of being responsive toward a regimen of each individual patient with distinctive demographics and phenotypes is often more needed by a physician in the clinical situation (11–13). There are continuous concerns on the conventional evidence-based paradigm building on meta-analyses and randomized controlled trials with limited personalized design (e.g., prespecified subgroup analysis, responder analysis), such as being over-concentrated in population-based assessment (14, 15), over-standardized treatment (15, 16), and lacking personalization (17). This affected the clinical utility of the evidence (18) and was contradicted with many core principles of TCIM. The efficacy-driven approach, which focuses on comparative effectiveness, has been proposed to bridge ConM and TCIM (8, 19–22).

Stakeholder (e.g., patients and physicians) engagement is the foundation of designing pragmatic studies (2, 23). Stakeholder involvement in the study design stage, from the selection of disease condition, drug formulation, and outcome measurement, is increasingly emphasized to enhance the clinical utility

and translation of evidence (18, 24). Nevertheless, there are controversies over the pragmatic features (e.g., unblinding of subjects, no placebo control, intervention adjustment) as these flexibilities may enhance generalizability at the expense of internal validity of the evidence (25, 26). The correlation between risk of bias and pragmatism remains unclear.

Diabetes presented in 9.5% of adult population and accounted for 9.9% of all-cause mortality globally (27, 28). The healthcare expenditure on diabetes mounted to US $850 billion worldwide in 2017, representing 11.6% of the total health expenditure (27, 28). Both diabetes and kidney dysfunction are the top 10 conditions attributed to disability-adjusted life-years among population aged over 25 globally (29). In the past decade, CM formulations have been reported to protect against diabetes and chronic kidney disease (CKD) *via* orchestrated mechanisms (30–35). However, less than 2% of diabetic patients have ever used CM for diabetes or CKD in Hong Kong which was substantially lower than the utilization in other disciplines (e.g., 50% for cancer patients) (36). Lack of high-quality and communicable evidence has been suggested as one of the key obstacles in implementing IM (6).

This study aimed to collate and explore the expectations regarding the pragmatic trial design of IM for diabetes among patients and physicians. Subsequently, the existing trial design was systematically assessed to identify the dissonance with users' perspective.

METHODS

Study Design

A 10-group semi-structured focus group interview series was conducted among patients and physicians with constant comparative method to explore their expectation regarding the IM management of diabetes in general (37). Seven high-level themes were previously identified from the interview series. Two themes regarding the barriers to access and the preferred delivery mode of health services were reported (6). In this study, we report another major theme related to pragmatic trial design. A systematic review was conducted subsequently to contrast existing IM pragmatic trials to the users' perspectives identified from the focus group interviews.

Focus Group Interview

The focus group interview series was designed to explore the expectations and concerns of the patients and physicians regarding the IM service access and further research. Detail of the interview methods was previously described (6). Briefly, 50 subjects (21 diabetes patients, 14 ConM physicians, and 15 CM physicians) with diverse demographics and experience were purposely sampled from public clinics, private clinics and teaching hospitals in Hong Kong. A series of face-to-face group interviews with three groups of 6–8 patients, three groups of 3–6 ConM physicians, and four groups of 3–4 CM physicians were conducted. Each interview lasted 60–120 min allowing at least 20 min per participant for adequate interaction. CM physicians were sampled to represent TCIM in Hong Kong as CM is the mainstream of TCIM, and integrative Chinese-western medicine is the major form of IM globally including Hong Kong (38).

The interviews were facilitated by a moderator (P.W.L) with relevant experience and conducted in Cantonese (native language of participants). The identity of interviewees and the moderator was blinded before the interview took place. The interviews were built around participants' consultation experience, concerns and expectations based on a semi-structured interview guide (6). The process of recruitment, interview and analysis were iterative until data saturation during the last round of interview (patient and ConM: third round, CM: fourth round). Interview content was analyzed by constant comparative method (37). Maximum codes on main themes and subthemes were first generated independently by two bilingual investigators (K.W.C., P.W.L.) for initial open coding with revisit to check for emerging ideas. The concepts and theories were refined, and the association of the coding was explored to form axial coding. Final core coding was formed after data saturation and was applied to index the whole dataset. Charted result was translated by a bilingual investigator (K.W.C.) when used as illustrative quotations. Data were processed with the support of simple software (Microsoft Word and Excel) for convenient access.

Systematic Review

Search

We sought to assess the pragmatism, risk of bias, and rationale of study design of the existing pragmatic trials of diabetes and kidney disease using IM as intervention. The search strategy (**Supplementary File 1**) was formulated to include all IM pragmatic clinical trials and trial protocols that recruit patients with diabetes or kidney diseases published until 24 August 2020. IM included any intervention that is not conventionally used in clinical practice, for instance, herbal medicine, acupuncture, and massage. Four databases were searched including Cochrane, Medline, Embase and PubMed. Reference lists were also searched. A clinical epidemiologist (K.W.C.) led the search and data processing. Endnote X9 was used to aid the review process. Protocol registration: CRD4D2021231288.

Screening

After removing duplicated studies, screening started with title and abstract followed by full text before data extraction. All articles were dually screened, assessed, and extracted (Y.K.L, L.G.) independently with a standardized form. All disagreements were resolved by discussion and determined by K.W.C. if consensus could not be reached. There was no language restriction. All observational and qualitative studies were excluded. Studies that used health services or supplements as intervention were excluded.

Quality Assessment and Data Extraction

The co-primary outcomes were the pragmatism, risk of bias, and rationale of the study design. Pragmatism of the trials was assessed based on the PRECIS-2 tool (39) on study population, recruitment setting, intervention delivery, and outcome assessment. Risk of bias in randomization, allocation concealment, blinding, incomplete outcome data,

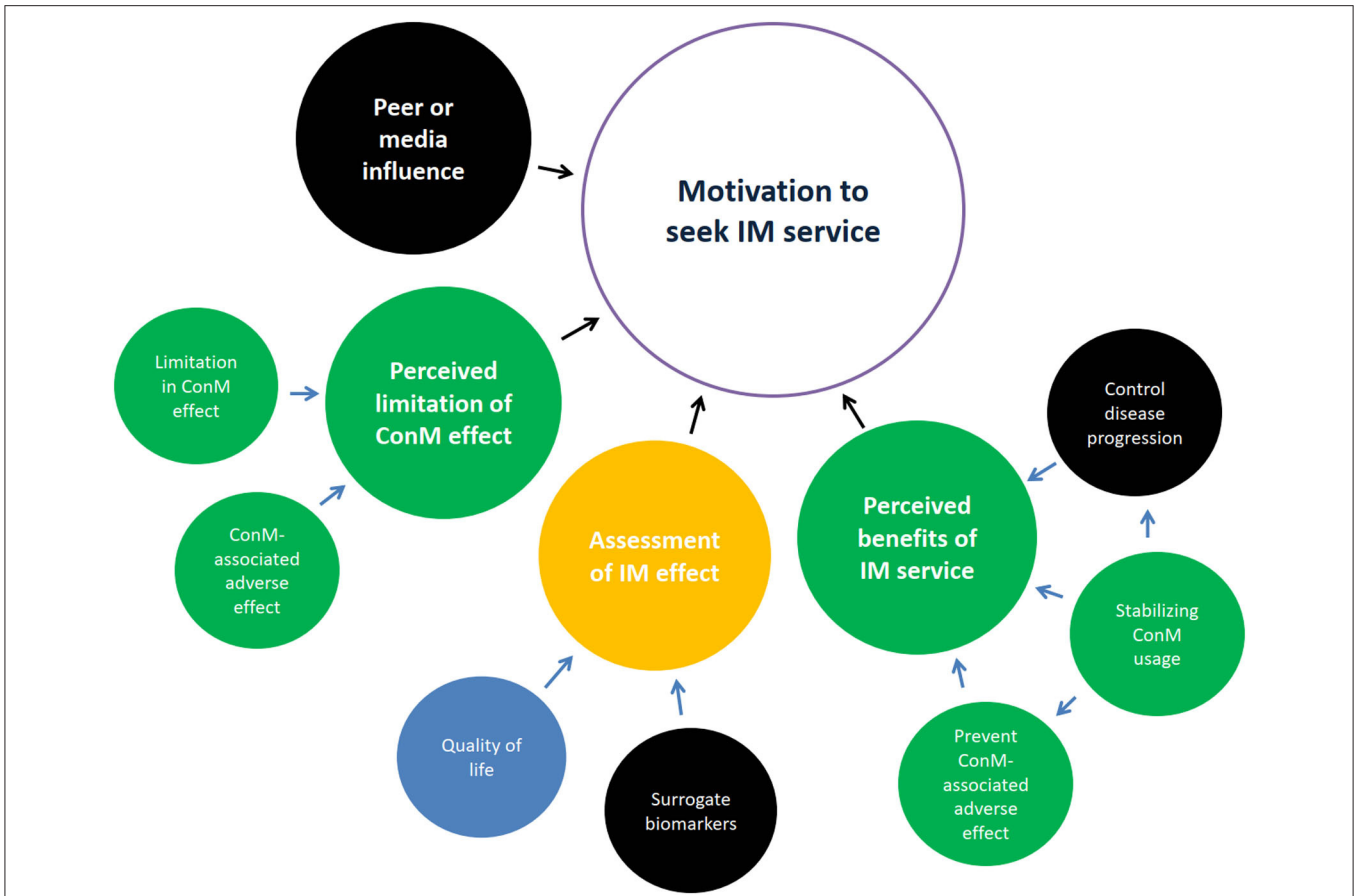


FIGURE 1 | Motivation to seek integrative medicine (IM) service. Themes generally agreed upon by patients in yellow, by Chinese medicine (CM) physicians in blue, by conventional medicine (ConM) physicians in red, by both patient and CM physicians in green, by both patient and ConM clinician in orange, by all parties in black. Control of disease progression was the common perceived benefit of IM. Stabilizing ConM usage was emphasized by patients and acknowledged by CM physicians. Surrogate biomarkers were mutually accepted among patients and physicians. Importance on quality of life divided between patients and CM physicians.

and selective reporting was assessed based on the Cochrane risk-of-bias tool (40). The rationale of study design in target population, intervention, comparator, and outcome assessment were identified from the study.

Statistical Analysis

The correlation between risk of bias and pragmatism was assessed by univariable and backward multivariable regression analysis adjusting publication year and sample size. For the quantified assessment of the overall risk of bias of each study, the scores of low, unknown, and high risk were given 0, 1, and 2 points. Lower total score represents low risk of bias in the reported study design. For pragmatism, each domain scored 1 for being least pragmatic and 5 for being most pragmatic, respectively, according to the guideline from the PRECIS-2 tool. For domains that were not assessable, the score was replaced by 3 (midpoint). As there is no consensus on the statistical handling of undetermined domains, sensitivity analysis was conducted to replace undetermined domains by 1 and 5 to test the robustness of results. STATA 15.1 was used for analysis.

RESULTS

Focus Group Interviews

Majority of patients had poor glycemic control (71.4%), with stage 2–4 CKD (95.2%) and albuminuria (90.5%); 4.8% of patients reached end-stage kidney failure, 57.1% (n = 8/14) of ConM physicians specialized in internal medicine, 42.9% (n = 6/14) of ConM physicians specialized in family medicine or practiced as general practitioners, 42.9% (n = 6/14) of ConM physicians received CM education, and all (n = 15) CM physicians received substantial credit bearing ConM education from their undergraduate study. Seven high-level themes, namely, barriers toward IM service, motivation to seek CM service, background knowledge on diabetes, experience of CM service, preferred model of integrative service delivery, and evidence of IM and CM hospital, were previously identified leading to 25 subthemes (6). Data on a high-level theme: motivation to seek IM service is related to the clinical trial design and reported in this study (**Figure 1**). Quotes are summarized in **Table 1**.

TABLE 1 | Subthemes and illustrative quotations of focus group interview.

Motivation to seek integrative medicine service	Source	Illustrative quotations
Subtheme: perceived limitation of ConM effect		
Limitation in ConM efficacy	Patient	"I have never got better with ConM. My kidney function is falling down…They always say that I am not going to recover. I can only wait for dialysis or transplantation." (Patient 21)
	ConM physician	"If I have done whatever I could do and the kidney function is still deteriorating, and there is a (CM) formulation that the patient may try, then the patient may want to try…that is if I can do nothing, you may try, but do no harm." (ConM physician 8)
ConM-associated adverse effect	Patient	"ConM cannot control my blood glucose. It fluctuated a lot. I tried to have CM for 1 year and the blood glucose was stabilized." (Patient 6)
	Patient	"They said there is a drug (ACEI/ARB) which can help my kidney but I could not take it as my (serum) potassium elevated. High (serum) potassium is even worse as it affects the heart." (Patient 18)
	CM physician	"Some patients were having poor liver function or hypersensitivity toward ConM and they came…they thought CM is natural and have a lower risk." (of toxicity)." (CM physician 1)
Subtheme: perceived benefits of IM service		
Better control of disease progression	Patient	"Kidney is the most important. We need dialysis once it deteriorated." (Patient 8)
	ConM physician	"It would be the best if CM can control diabetes and slower the progression of DKD as there is a group of patients deteriorated quite fast. Retarding the renal progression would be an important achievement." (WM physician 13)
	CM physician	"Patients that are highly educated and younger focused more on (laboratory) investigations. Older patients focused more on quality of life and wished CM can help." (CM physician 4)
Stabilizing ConM usage, preventing the associated adverse effects	Patient	"(I would like to have) less ConM intake and consultation." (Patient 4, 5, 7)
	CM physician	"Majority of patients were reluctant to take ConM as they believed they could not stop (taking ConM) once started. They were willing to try alternatives including CM." (CM physician 2)
Subtheme: assessment of IM effectiveness		
Surrogate biomarkers	Patient	"Data (investigation) is more objective as it can be measured." (Patient 2) "Kidney index (serum creatinine), urine protein." (Patient 17)
	ConM physician	"GFR, creatinine, urine protein, those routine measures." (ConM physician 6) "The kidney function may get worse even you treat the 'blood and qi'. There are some mismatch on the outcomes… you (CM) have to match ours (outcome measures) …There can be many outcomes but we have to be in the same direction… Those investigations (GFR, UACR, LFT) are a must for us, ConM clinicians. It would be hard for us to accept that we have to depend on other outcome measures just because we work with a CM physician." (ConM physician 9)
	CM physician	"DKD is (a condition) defined by ConM. We have to refer to ConM (investigations) for treatment. If the disease is classified by CM, then it should be referring to CM (outcome measures)." (CM physician 2)

(Continued)

TABLE 1 | Continued

Subtheme: perceived limitation of ConM effect		
Quality of life	ConM physician	"I always think that CM is totally different (when compared to ConM) from principles to treatment strategy. I do not understand what they measure and how they formulate treatment. They may work and I am not sure if (lab) investigation is a must for them." (ConM physician 13) "I am not sure if CM can go further into molecular level…if you can explain the pharmacology of every drug based on statistics, it would be a huge advancement." (ConM physician 2)
	CM physician	"I had a patient with long diabetes history and had good control on investigation markers. However, he has got symptoms of *spleen and kidney deficiency*. I believe his life expectancy and quality of life will get better with CM. It cannot be shown without CM assessment." (CM physician 11) "For elderly, the markers are not important except being rapidly deteriorating. Younger patients are more concerned about markers…that is, it (the outcome measurement) has to be personalized." (CM physician 15)

Perspectives of patients, conventional medicine (ConM) physicians and Chinese medicine (CM) physicians were compared.
Themes generally agreed upon by patients in yellow, by Chinese medicine (CM) physicians in blue, and by conventional medicine (ConM) physicians in red.

Main Theme: Motivation to Seek IM Service

Four subthemes related to the motivation of seeking IM service were identified, namely, (1) perceived limitation of ConM effect, (2) peer or media influence, (3) perceived benefits of IM service, and (4) assessment of IM effectiveness. Subthemes 1, 3, and 4 are relevant to study design and summarized below.

Subtheme: Perceived Limitation of ConM Effect

Majority of patients considered IM as they believed the effect of ConM was limited and was concerned about the adverse effects after receiving ConM.

Limitation in ConM Efficacy

Most patients believed that diabetes and diabetic kidney disease (DKD) are irreversible, which was reflected by the limitation of the current regimens (41–44). This prompted patients to explore alternatives for more options to control disease progression. Physicians from both ConM and CM acknowledged that patients generally prefer IM treatment. Majority of patients approached IM when they experienced disease progression, for example, poor blood glucose control, or developed complications including DKD.

ConM-Associated Adverse Effect

Patients mentioned their experience in developing adverse effects that perceived to be ConM-associated. These included hypoglycemia, hyperkalemia, diarrhea, fluctuating blood glucose, and fatigue. Majority of patients believed that CM has less adverse effects when compared to ConM. A similar observation was suggested by CM physicians.

Subtheme: Perceived Benefits of IM Service

There are several benefits that patients believed IM can offer, including better control of disease progression, prevention of ConM-associated side effect, and stabilizing ConM usage.

Better Control of Disease Progression

Patients sought to have better control of disease progression, for instance, reducing the risk of complications and increasing life expectancy when they consider IM. DKD was highlighted as a major concern as patients were reluctant to receive dialysis. Some CM physicians suggested that patients of different age groups had different treatment targets. Elder patients emphasized more on symptomatic improvement and quality of life, while younger patients focused on laboratory investigations. A few CM physicians suggested that CM emphasizes holistic improvement including both quality of life and biomarkers.

Although patients expressed subjective unwell feeling after receiving ConM, symptomatic improvement did not emerged as a major expectation from patients. CM physicians, however, believed that improving quality of life would be a major concern among patients and an advantage of CM. ConM physicians suggested control of renal function deterioration as an important milestone of complication management; however, they emphasized that more evidence is needed to demonstrate such effect of CM.

Stabilizing ConM Usage and Preventing the Associated Adverse Effects

Reducing ConM dependence was one of the common expectations of patients. Some CM physicians reported similar requests encountered in their clinical practice. This is likely because patients linked the use of ConM with disease progression

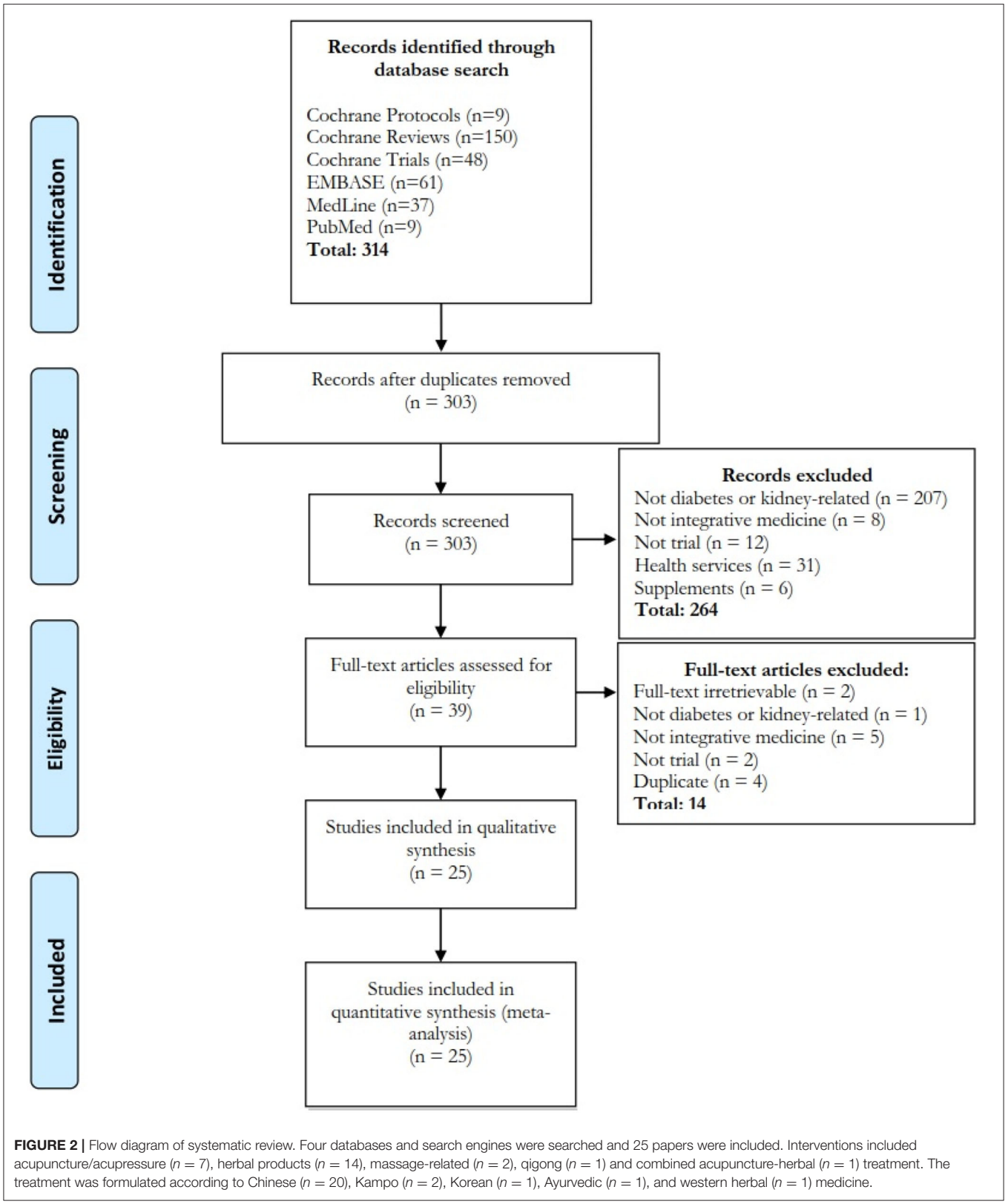


FIGURE 2 | Flow diagram of systematic review. Four databases and search engines were searched and 25 papers were included. Interventions included acupuncture/acupressure ($n = 7$), herbal products ($n = 14$), massage-related ($n = 2$), qigong ($n = 1$) and combined acupuncture-herbal ($n = 1$) treatment. The treatment was formulated according to Chinese ($n = 20$), Kampo ($n = 2$), Korean ($n = 1$), Ayurvedic ($n = 1$), and western herbal ($n = 1$) medicine.

and adverse effects. Minority of patients expect CM to reduce the adverse effects of ConM. Some CM physicians suggested that they have managed ConM-associated adverse events.

Subtheme: Assessment of IM Effectiveness

Patients generally focused on objective conventional biomarkers measured by laboratory investigations for the monitoring of treatment effect, which was supported by the ConM clinicians. Some CM physicians also believed that objective markers were important for their self-evaluation of treatment effect, as DKD is a ConM-defined condition. They also expected the patients would evaluate their treatment based on laboratory investigation results.

Substantially diverted opinion was noted among CM physicians, suggesting current biomarkers should not be the only outcome assessment. They believe CM manages patients' general condition simultaneously while treating DKD. DKD-related biomarkers were limited to only reflect a certain aspect of patients' overall condition. They suggest the concurrent use of CM-related outcome measures, which is phenome-based (e.g., change in symptoms, tongue color and pulse form).

Some ConM physicians acknowledged the difference in the epistemology between CM and ConM and suggested that CM may require different outcome measures. Nevertheless, ConM physicians generally believed that it would be an advantage if the effect of CM can be demonstrated with study designs conventionally used in ConM. There was also a suggestion to personalize the assessment of effect based on the patients' preference which is related to their demographics.

Systematic Review

Our search identified 303 studies from four databases after removing duplicated studies (**Figure 2**; 264 studies were excluded by title and abstract screening and 14 studies were excluded (**Supplementary File 2S**) after full-text screening. A total of 25 trials were included for analysis.

Characteristics of Included Trials

Geographically, 18 (72%), 2 (8%), 2 (8%), 1 (4%), 1 (4%), and 1 (4%) studies were conducted in China, Japan, United Kingdom, United States, Korea, and Sweden, respectively (**Table 2**). Target population included prediabetic ($n = 2$), diabetic ($n = 15$), glomerulonephritis ($n = 1$), chronic kidney disease ($n = 2$) and hemodialysis ($n = 5$) patients. Complication of diabetes included kidney ($n = 4$), neuropathy ($n = 4$) and arterial disease ($n = 1$). Fifteen were completed trials and 10 were trial protocols.

The IM interventions involved included acupuncture/acupressure ($n = 7$), herbal products ($n = 14$), massage-related ($n = 2$), qigong ($n = 1$), and combined acupuncture-herbal ($n = 1$) treatment. The treatment was formulated according to Chinese ($n = 20$), Kampo ($n = 2$), Korean ($n = 1$), Ayurvedic ($n = 1$), and western herbal ($n = 1$) medicine. The median sample size was 113 (IQR: 72–266), and the median treatment duration was 24 weeks (IQR: 10–26). The frequency of treatment ranged from once to three times daily for oral medication and once to three times weekly for acupuncture, respectively. Majority of studies required monthly consultation follow-up for oral medication and three times weekly for acupuncture. Twenty-four studies (96%) either recruited a proportion of patients according to TCIM-specific diagnosis or completely dropped TCIM diagnosis in study design. Five studies included TCIM-specific symptom-based diagnostic criteria in the inclusion/exclusion criteria of study population.

All DKD- related studies used urine albumin/protein and/or estimated glomerular filtration rate (GFR) as primary outcomes. All CKD-related studies assessed estimated GFR as the primary outcome. For hemodialysis-related studies, majority (4/5) assessed quality of life or symptom as primary outcomes. All studies described adverse events narratively. No studies measured the change of concurrent medication as primary or secondary outcomes. Nine, 12, two and two studies used standard care, placebo or sham acupuncture, both standard care and placebo, and other active intervention (e.g., other TCIM medication, active exercise) as comparators, respectively.

Risk of Bias, Pragmatism and the Association

Majority (22/25) of studies reported unclearly in at least one domain of potential bias (**Figure 3**). Twelve studies had unclear description on handling of attrition that led to undetermined bias on completeness of outcome measurement. Four studies were with high risk of bias in at least one domain. The main source of high-risk bias was from the blinding of outcome assessment ($n = 3$) and allocation concealment ($n = 2$).

In terms of pragmatism, the eligibility and outcome measurement of most trials were close to the target population with limited exclusion criteria (**Figure 3**). The outcome measurement was mostly relevant to the target population with clinical significance, for instance, the measurement of estimated GFR among DKD and quality of life among dialysis patients. The setting of trials was less pragmatic as most trials require additional expertise to execute on top of existing infrastructure. The follow-up duration was also less practical as the interventions require substantially more frequent service attendance. The reporting on recruitment strategy and adherence control was not clear to assess the degree of pragmatism. There is no observed positive correlation between the risk of bias and pragmatism of the included studies ($R^2 = 0.0215$, $\beta = -0.116$, $p = 0.484$) (**Figure 4**). Result was comparable in sensitivity analysis with imputation on undetermined domains in pragmatism (**Supplementary File 3S**). Replacing undetermined domains in the assessment of pragmatism with lowest value resulted in a negative correlation ($R^2 = 0.176$, $\beta = -0.277$, $p = 0.037$). Replacement with highest value did not result in significant correlation ($R^2 = 0.035$, $\beta = 0.129$, $p = 0.374$). The rationale of study design parameters was uncommonly reported. One study used estimated GFR as primary outcome based on conventional practice of other studies. No study included/referred to stakeholder analysis in justifying the study design.

DISCUSSION

Patients expected IM service to retard disease progression, stabilize concomitant drug (referring to any medications given to the patients except the investigational article) dosage and reduce

TABLE 2 | Characteristics of included studies.

First Author	Country/year	Title	Key inclusion/exclusion criteria	Size	Setting	Intervention	Frequency	Attrition	Period	Control	Primary outcomes
S. Ono	Japan/2015	Efficacy and Cost effectiveness of the acupuncture treatment using a new skin stimulus tool called m-test which is a measure based on symptoms accompanied with body movements: a pragmatic RCT targeting hemodialysis patients	Hemodialysis patients	47	Outpatient hemo-dialysis facilities	**Acupuncture**	Once weekly. Unknown follow-up frequency	8/47 (17.0%)	8 weeks	Standard care control	20 symptoms evaluated by visual analog scale, quality of life (EQ-5D), cost-effectiveness (ICER)
K. Watanabe	Japan/2016	Long-term effects of goshajinkigan in prevention of diabetic complications: a randomized open-labeled clinical trial	T2DM patients aged 40–75 years with HbA1c over 6.5%	149	Nine clinical centers	**Oral Kampo medicine** (Goshajinkigan extract) preprandially (Rehmanniae radix, Achyranthis radix, Corni fructus, Dioscoreae rhizoma, Hoelen, Plantaginis semen, Alismatis rhizoma, Moutan cortex, Cinnamomi cortex and Aconiti radix)	Three times daily. Unknown follow-up frequency	33/149 (22.1%)	28 months	Standard care control	Incident nonfatal myocardial infarction or nonfatal stroke or stage progression of diabetic nephropathy/retinopathy

(Continued)

TABLE 2 | Continued

First Author	Country/year	Title	Key inclusion/exclusion criteria	Size	Setting	Intervention	Frequency	Attrition	Period	Control	Primary outcomes
C. Elder	USA/2006	Randomized trial of a whole-system ayurvedic protocol for type 2 diabetes	Newly diagnosed T2DM patients aged 21–80 years	60	Kaiser Permanente Center for Health Research Clinic	**(1) Oral Ayurveda herbs**: Phylanthus niruri, Arjuna myrobalan, Eniconstema littlorale, Aegle marmelos, Azadirachta indica, Momordica charantia, blackberry; (2) **transcendental meditation; diet** (fresh cooked vegetables, small legumes, dry light whole grains, and lunch as the main meal); (3) **daily routine and exercise**	Daily. Unknown follow-up frequency	6/60 (10%)	6 months	Standard care control	Glycemic control (HbA1c and fasting glucose levels)
J. Gan	China/2019	Yinang formulation vs. placebo granules as a treatment for chronic kidney disease stages III-IV in patients with autosomal dominant polycystic kidney disease: Study protocol for a double-blind placebo-controlled randomized clinical trial	ADPKD patients aged 18–75 years with Chinese medicine diagnosis of the *spleen, kidney deficiency, and blood stasis* syndrome	72	Outpatient clinics of three university affiliated hospitals	**Oral Chinese medicine** formulation (*Yinang* formulation composed of 17 herbs) twice daily, 1h after breakfast and dinner	Twice daily. Monthly follow-up	N/A	24 weeks	Placebo	Estimated glomerular filtration rate

(Continued)

TABLE 2 | Continued

First Author	Country/year	Title	Key inclusion/exclusion criteria	Size	Setting	Intervention	Frequency	Attrition	Period	Control	Primary outcomes
J. Huo	China/2018	Stationary Treatment Compared with Individualized Chinese Medicine for Type 2 Diabetes Patients with Microvascular Complications: Study Protocol for a Randomized Controlled Trial	T2DM patients aged 18–75 years with Chiense medicine diagnosis of *qi-yin* deficiency and *blood stasis* syndrome and diabetic retinopathy, diabetic kidney disease or diabetic neuropathy	432	Inpatient treatment in 8 Hospitals	Protocoled individualized **Chinese medicine**	3 times daily. Unknown follow-up frequency	N/A	24 weeks	Chinese medicine pill (Qiming granule)	Diabetic retinopathy: changes in retina hemorrhage, retinal exudate, macular thickness, BCVA; diabetic kidney disease: changes in albumin-to-creatinine ratio, serum creatinine and estimated glomerular filtration rate; diabetic peripheral neuropathy: changes in electromyography, TCSS, VAS
D. Jin	China/2019	Chinese herbal medicine Tangshen Formula treatment for type 2 diabetic kidney disease in the early stage: Study protocol for a randomized controlled trial	T2DM patients with microalbuminuria	632	13 Hospitals	**Chinese medicine** formulation (Tangshen Formula)	Twice daily. Monthly follow-up	N/A	24 weeks	Placebo	Urinary albumin-to-creatinine ratio
D. Jin	China/2017	Chinese herbal medicine TangBi Formula treatment of patients with type 2 diabetic distal symmetric polyneuropathy disease: Study protocol for a randomized controlled trial	T2DM patients with polyneuropathy aged 30–70 years	188	Six Hospital clinical centers	**Chinese medicine** formulation (TangBi Formula) two times per day	Twice daily. Monthly follow-up	N/A	24 weeks	Placebo	Changes in clinical signs and symptoms. Changes in Michigan Diabetic Neuropathy Score
Z. Qi	China/2018	Acupuncture combined with hydrotherapy in diabetes patients with mild lower-extremity arterial disease: A prospective, randomized, nonblinded clinical study	Diabetes patients with lower-extremity artery disease	126	Hebei Chronic Disease Rehabilitation Center	**Acupuncture** and low-radon hot spring **thermal hydrotherapy**.	Once every 2 days. Monthly follow-up	5/126 (4.0%)	15 weeks	Standard care control	(1) symptomatic lower-extremity arterial disease assessment, (2) laboratory physical status, and (3) self-report quality of life measures
A. F. Walker	UK/2006	Hypotensive effects of hawthorn for patients with diabetes taking prescription drugs: A randomized controlled trial	T2DM patients with hypertension	79	Outpatient clinics at The University of Reading	Hawthorn (**French herb**) extract 1,200 mg	Twice daily. Monthly follow-up	14/79 (17.7%)	16 weeks	Placebo	Diastolic blood pressure

(Continued)

TABLE 2 | Continued

First Author	Country/year	Title	Key inclusion/exclusion criteria	Size	Setting	Intervention	Frequency	Attrition	Period	Control	Primary outcomes
M. Wang	China/2018	Effects of traditional Chinese herbal medicine in patients with diabetic kidney disease: Study protocol for a randomized controlled trial	Diabetic patients aged 25–75 years with estimated glomerular filtration not <30 ml/min/1.73m2 and (1) albuminuria, (2) diabetic retinopathy, or (3) confirmed biopsy	266	6 Hospitals	**Chinese medicine** formulation according to Chronic kidney stage	Twice daily. Follow-up at baseline, 4, 12, 24 weeks	N/A	24 weeks	Standard care control	Urinary excretion rate, 24-h urine protein and estimated glomerular filtration rate
X. Xie	China/2019	Effect of Gua Sha therapy on patients with diabetic peripheral neuropathy: A randomized controlled trial	Diabetic patients with clinical diagnosis of diabetic peripheral neuropathy aged 18-80 years	113	Not available	Gua Sha (**Chinese medicine physiotherapy**)	Once weekly. Weekly follow-up	6/119 (5.0%)	12 weeks	Standard care control	Validated scale and physical measurement for clinical neuropathy (TCSS, VPT, ABI) and fasting blood glucose
K. W. Chan	China/2016	Semi-individualized Chinese medicine treatment as an adjuvant management for diabetic nephropathy: a pilot add-on, randomized, controlled, multicenter, open-label pragmatic clinical trial	Diabetic kidney disease patients with chronic kidney disease stage 2–3 and macroalbuminuria aged 35 to 80 years	148	8 outpatient clinics	**Chinese medicine** formulations according to symptom-based diagnosis of Chinese medicine practice	Twice daily. Monthly follow-up	N/A	48 weeks	Standard care control	Estimated glomerular filtration rate and urine albumin-to-creatinine ratio
Y. Gao	China/2013	Clinical research of traditional Chinese medical intervention on impaired glucose tolerance	Impaired glucose tolerance patients aged 25–75 years	510	12 clinical centers	**Chinese medicine** formulation (Tangzhiping granules)	Twice daily. Unknown follow-up frequency	52/510 (10.2%)	3 years	Standard care control	Annual conversion rate to T2DM
A. P. Garrow	UK/2014	Role of acupuncture in the management of diabetic painful neuropathy (DPN): a pilot RCT	Diabetic patients with pain neuropathy aged 18–80 years	59	One local district general hospital	**Acupuncture** with five standard acupoints	Once weekly. Weekly follow-up	14/59 (23.7%)	10 weeks	Sham acupuncture	Neuropathic pain by Leeds Assessment of Neuropathic Symptoms and Signs
J. Kou	China/2014	Efficacy and safety of Shenyankangfu tablets for primary glomerulonephritis: study protocol for a randomized controlled trial	(1) diagnosis of primary glomerulonephritis, (2) aged 18–70 years, (3) estimated glomerular filtration rate over 45 mL/min/1.73 m2, (4) 24-h proteinuria level of 0.5–3.0 g, (5) traditional Chinese medicine syndrome conforming to Qi-Yin deficiency	720	Renal outpatient and inpatient departments of a hospital	**Chinese medicine** formulation (Shenyankangfu)	3 days daily. Unknown follow-up frequency	N/A	48 weeks	Placebo and losartan matching shape, size, taste, weight, and color	24-h proteinuria level

(Continued)

TABLE 2 | Continued

First Author	Country/year	Title	Key inclusion/exclusion criteria	Size	Setting	Intervention	Frequency	Attrition	Period	Control	Primary outcomes
S. Lee	Korea/2013	Electroacupuncture to treat painful diabetic neuropathy: study protocol for a three-armed, randomized, controlled pilot trial	Diabetic patients aged 18–75 with painful diabetic neuropathy	45	Outpatient clinic of a university hospital	**Acupuncture** with 12 standard points	Twice weekly. Follow-up twice per week	N/A	8 weeks	Sham acupuncture and usual care group	11-point pain intensity numerical rating scale
W. Mao	China/2015	Rationale and design of the Helping Ease Renal failure with Bupi Yishen compared with the Angiotensin II Antagonist Losartan (HERBAAL) trial: a randomized controlled trial in non-diabetes stage 4 chronic kidney disease	Stage 4 non-diabetic chronic kidney disease patients aged 18–80 years with Chinese medicine diagnosis of *spleen and kidney qi deficiency*	554	16 hospital centers	**Chinese medicine** formulation (Bupiyishen formula)	Three times daily. Unknown follow-up frequency	N/A	12 months	Losartan (standard care)	Estimated glomerular filtration rate
X. Sun	China/2015	The cost-effectiveness analysis of JinQi Jiangtang tablets for the treatment on prediabetes: a randomized, double-blind, placebo-controlled, multicenter design	Prediabetic patients aged 30–70	362	Five hospitals	**Chinese medicine** formulation (JinQi Jiang Tang)	Twice daily. Monthly follow-up	Unknown	12 months	Placebo	Incidence of T2DM
P. A. E. Wandell	Sweden/2013	Effects of tactile massage on metabolic biomarkers in patients with type 2 diabetes	Swedish T2DM patients aged 35–75 years	79	Four primary healthcare centers	**Tactile massage**	Unknown	26/79 (32.9%)	10 weeks	Relaxation exercise	Blood glucose related biomarkers
H. Wang	China/2013	The key role of Shenyan Kangfu tablets, a Chinese patent medicine for diabetic nephropathy: study protocol for a randomized, double-blind and placebo-controlled clinical trial	Diabetic kidney disease patients with diabetic nephropathy stage 3–4 diagnosed with *qi-yin deficiency*	80	Five hospitals	**Chinese medicine** formulation (Shenyan Kangfu tablets)	3 times daily. Follow-up at baseline, 2, 4, 8, 12, 16 weeks	N/A	16 weeks	Placebo	Composite of 24-h urinary protein levels and urinary albumin excretion rate

(Continued)

TABLE 2 | Continued

First Author	Country/year	Title	Key inclusion/exclusion criteria	Size	Setting	Intervention	Frequency	Attrition	Period	Control	Primary outcomes
C. F. Liu	China/2008	Effect of auricular pellet acupressure on antioxidative systems in high-risk diabetes mellitus	High risk diabetes patients	69	Unknown	**Auricular acupressure** (3 points)	Three times daily. Unknown follow-up frequency	Unknown	20 days	Standard care control	Serum superoxide dismutase level
M. Y. Tsai	China/2018	Treatment of intradialytic hypotension with an herbal acupoint therapy in hemodialysis patients: A randomized pilot study	Symptomatic hemodialysis patients aged 20–75 years	32	One academic dialysis center	**Herbal stimulation on acupoint**	Three times weekly. Follow-up three times weekly	5/32 (15.6%)	4 weeks	Placebo	Blood pressure, symptoms, dialysis target
S. L. Tsay	China/2004	Acupressure and fatigue in patients with end-stage renal disease-a randomized controlled trial	Hemodialysis patients aged 18 or above presented with fatigue	106	Four Dialysis centers in major hospitals in Taipei	**Acupressure** (4 points)	3 times weekly. Follow-up 3 times weekly	Unknown	4 weeks	Sham acupuncture	Piper Fatigue Scale, visual analog scale for fatigue, Pittsburgh Sleep Quality Index, Beck Depression Inventory
S. L. Tsay	China/2003	Acupressure and quality of sleep in patients with end-stage renal disease–a randomized controlled trial	Hemodialysis patients with sleep complain aged 18–65 years	98	4 Dialysis centers in major hospitals in Taipei	**Acupressure** (3 points)	3 times weekly. Follow-up 3 times weekly	Unknown	4 weeks	Sham acupuncture on non-acupoints 1 cm away from meridian	Quality of sleep measured by Pittsburgh sleep quality index (PSQI) and sleep log
C. Y. Wu	China/2014	Effect of qigong training on fatigue in haemodialysis patients: A non-randomized controlled trial	Hemodialysis patients aged 18 or above	172	Outpatient dialysis units of a medical center	**Qigong**	Daily. Follow-up three times weekly	6/172 (3.5%)	24 weeks	Standard care control	Fatigue measured by validated Haemodialysis Patients Fatigue Scale

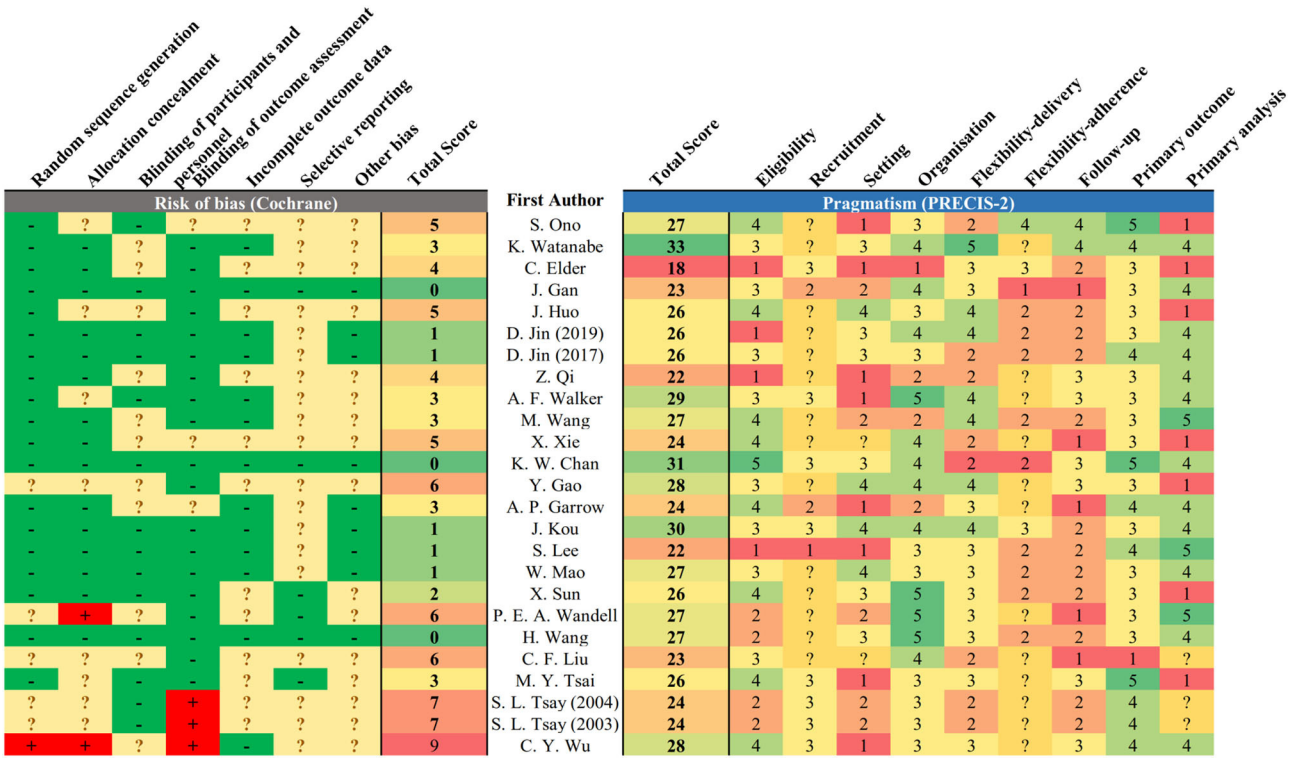


FIGURE 3 | Risk of bias and pragmatism of included studies. The risk of bias was assessed based on the Cochrane risk-of-bias tool, and pragmatism was assessed based on PRECIS-2. Lower total score represents low risk of bias in reported study design. A domain scored 1 or 5 for being least or most pragmatic, respectively, according to the PRECIS-2 tool. Undetermined domain was replaced by 3 (midpoint).

potential side-effect associated with conventional treatment where existing study designs did not include detailed assessment. Consultation follow-up frequency is the least pragmatic domain in existing studies. Increase in pragmatism in study design did not associate with higher risk of bias.

Outcome Measures on the Change of Concomitant Drug and Adverse Events

From the focus group interviews, patients expected IM service could retard disease progression, stabilize the use of concomitant drugs, and lower the risk of having adverse events associated with conventional treatment. Surrogate biomarkers were mutually accepted among patients and physicians. Most reviewed pragmatic DKD studies used GFR and urine albumin/protein to measure the change of renal function which addressed both patients' and physicians' preference (6).

Nevertheless, no study in the review reported the change of concomitant regimen as primary or secondary outcomes. Pragmatic trials often involve open-label design to better replicate real-world application. The potential bias in delivering intervention due to unblinding could be adjusted or assessed by mediation analysis on the dynamic change of concomitant regimens. Besides, as clinicians often adjust concomitant drugs to achieve or maintain targets of disease control (e.g., lowering hemoglobin A1c to below 7.0% or lowering systolic blood pressure to below 130 mmHg) in chronic conditions, the change in concomitant drugs could better reflect the disease progression than that of biochemical parameters, which is well-noted by patients in the focus group interviews. While most existing studies included analysis of adverse events, the data collection and assessment methods were unclear, and the reporting was often limited to narrative analyses. Further pragmatic studies should include the change of concomitant regimen as outcome measures and consider performing more systematic and in-depth quantitative analyses (e.g., survival analysis) on the incidence of adverse events.

Better Adherence by Reducing Intervention and Consultation Follow-Up Frequency

Among the existing studies, the frequency of add-on oral TCIM medication intake was often three times daily. Since the TCIM-ConM drug interaction is a common concern among ConM physicians, add-on oral TCIM medication is commonly taken separately with ConM (6). Therefore, existing IM study protocols require patients to take medication five to six times per day. Besides, most existing IM acupuncture programs require three times of consultation follow-up per week. We previously demonstrated that convenience of access is a key barrier of IM service implementation (6). Strategies to reduce the frequency of oral TCIM medication intake and integrate TCIM service

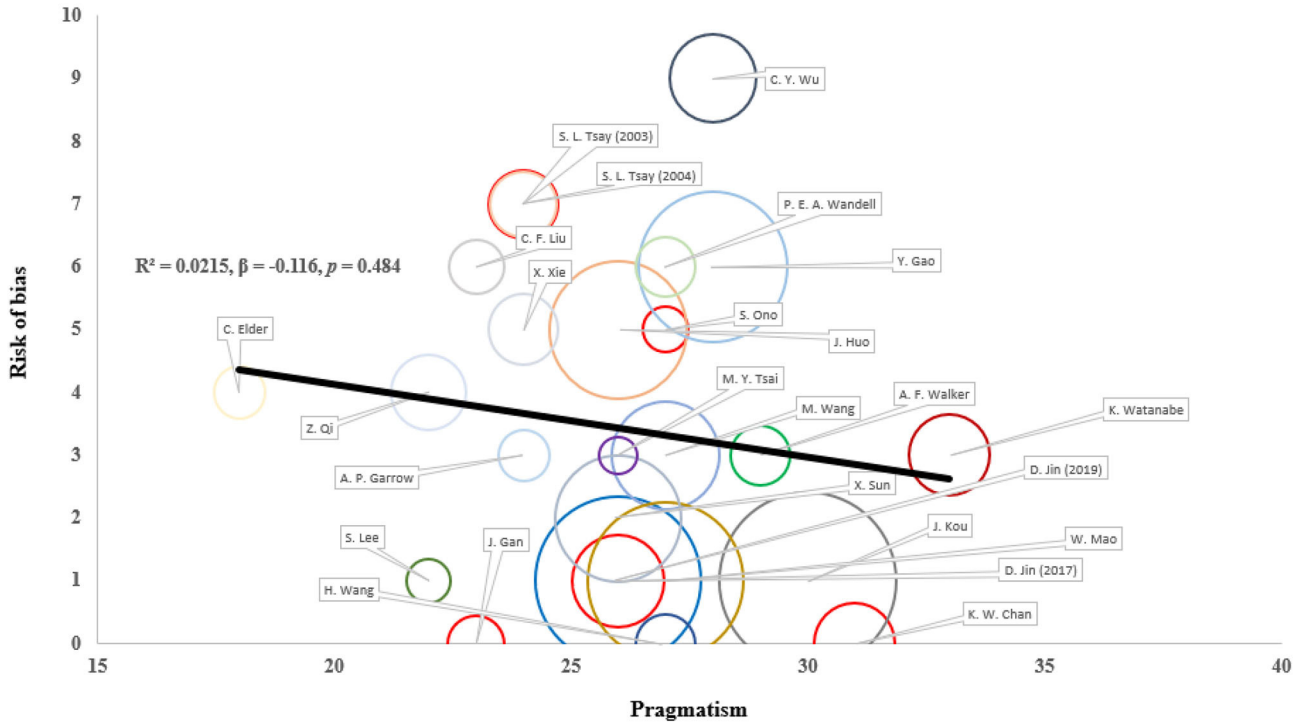


FIGURE 4 | Correlation between risk of bias and pragmatism in existing study designs. The risk of bias and pragmatism was assessed according to the Cochrane risk-of-bias tool and PRECIS-2 tool. Higher score corresponds to higher risk of bias and more pragmatism. Sample size is presented as the size of circle. There is no statistically significant correlation between risk of bias and pragmatism in both unadjusted and adjusted (publication year and sample size) models. Result is robust in sensitivity analyses replacing undetermined domains with extreme values.

delivery into the workflow of ConM would be important to enhance the service utilization and compliance.

Using Add-On Design With Standard Care Comparator to Inform Integrative Practice

Most existing studies used standard care or placebo/sham acupuncture as comparator. While placebo minimizes various kinds of bias, it is not an ideal control in pragmatic trial design as patients are neither blinded nor receiving placebo in real-world practice (1). Furthermore, our focus group series shows that both patients and clinicians focus on the add-on effect of TCIM. The add-on effect would be difficult to assess if other active interventions are used as comparator.

N-of-1 design is advocated in pragmatic trial to evaluate programs with individualized intervention (45). TCIM, including CM, strongly emphasizes personalization with tailor-made treatment and each patient would be an ideal self-control (6). However, the assumption underpinning N-of-1 design is that the intervention would not have a long-term effect after cessation. This assumption is contradictory to the theory of many streams of TCIM which consider that TCIM can restore the balance of human constitution and therefore offers a long-term healing effect (6, 46). As the latent effect of TCIM is often a subject of interest, the wash-out period of N-of-1 trial needs to be long enough and should be justified by pilot studies.

Implementation Challenges on Using TCIM Diagnosis as Inclusion Criteria

Five studies from our systematic review included TCIM-specific symptom-based diagnosis in the inclusion/exclusion criteria. Some streams of TCIM, for instance, CM, has a different epistemology compared to ConM, including disease stratification (6). CM defines disease predominantly according to phenotype. We previously demonstrated that add-on symptom-based diagnosis independently predicts renal progression among diabetic patients (47). Using standardized treatment across a study population with different CM-specific diagnosis is not personalized and contradictory to CM practice (6). As pragmatic trials are designed to reflect and inform real-world practice, CM-specific diagnosis is necessary in defining CM subgroups for intervention and assessment.

However, evidence generated from a specific subgroup of patients based on CM diagnosis may not be generalizable to the whole disease population (**Figure 5**) (48). For example, a formulation effective among diabetes patients that presented with *qi-yin deficiency* may not be effective among those without

qi-yin deficiency, and therefore, the evidence has limited external validity to the whole diabetes population. As majority of ConM physicians are not trained in CM, evidence from trials that only recruited a subset of patients defined by symptoms could not inform ConM physicians' decision in referring patients for IM service.

To facilitate the implementation of evidence to IM service, we propose not to include TCIM-specific diagnosis in the inclusion/exclusion criteria of IM pragmatic trials to maximize the representation of the study population of interest (49). TCIM-specific diagnosis can be included as a stratification factor in randomization instead to generate TCIM-specific subgroups for analysis (**Figure 5**). By combining all subgroups which represents a whole disease population, the primary analysis evaluates the overall effectiveness of a TCIM service program that is executed according to TCIM real-world practice (49). The main analysis informs ConM physicians on whether to make necessary referral to IM service. Subgroup analysis stratified according to TCIM theory evaluates the effectiveness of different treatments given to each TCIM-specific subgroup. The subgroup analyses inform TCIM physicians the choice of modalities from a personalized perspective. This two-layer design maximizes the generalizability of evidence and translation to real-world practice for both ConM and TCIM physicians.

Strategies to Maximize Reproducibility and Internal Validity in Pragmatic Trials

Although there are concerns over the trade-off between pragmatism and internal validity, our analysis showed that there is no positive correlation between risk of bias and pragmatism in existing study designs. Bias from randomization, allocation concealment, outcome assessment, and reporting in pragmatic trials can be controlled similarly to conventional trial designs (2). However, the intervention evaluated by pragmatic trials are often programs requiring flexibility, and the reproducibility is scrutinized (1). Although an unrestricted replicate of the real-world practice best produces evidence on effectiveness for implementation, the protocol may neither be applicable to nor reproducible in other clinical settings as high-quality standardized diagnostic instruments are lacking (50–52). For instance, the CM symptom-based diagnosis and personalized treatment in diabetes involves subjective professional judgment and likely differs between CM physicians. Although objective biomarkers may serve as alternative diagnostics, subjective symptom measures have been consistently demonstrated to correlate significantly with long-term clinical outcome independently (47, 53, 54) and has unique clinical value in patient-centered care (11).

To enhance the validity and reproducibility, symptom-based diagnosis and the corresponding variations in treatment should be pre-specified in a semi-individualized manner (49). Instead of diagnosing and treating patients purely by professional judgment that gives rise to unlimited combinations, patients can be divided by a predefined number of groups based on TCIM diagnosis with prespecified criteria. The treatment plan can be prespecified accordingly with clear instructions on adjustment. An alternative approach is to randomize or stratify the factor causing these variations, in most cases, the physician deciding the diagnosis and treatment. The potential confounding effect from different physicians can therefore be balanced between arms. However, a large cohort of subjects is needed for this method.

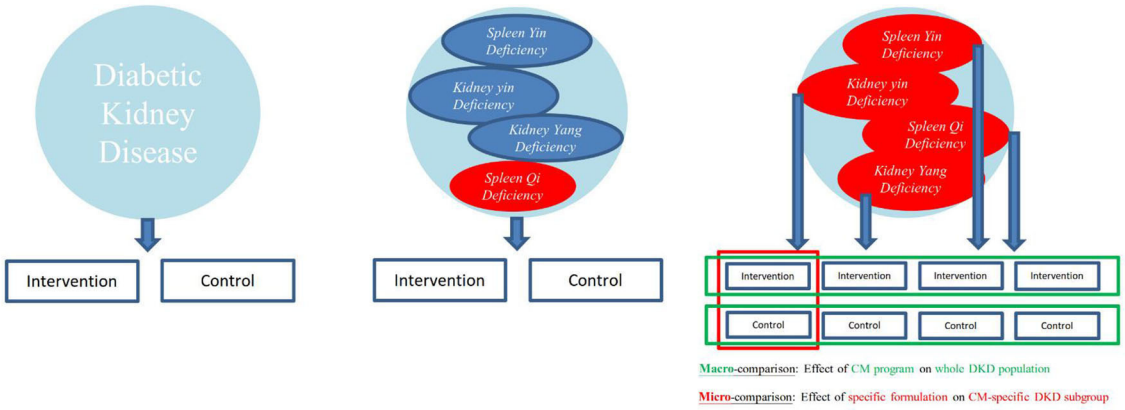
Non-uniform observation period is another commonly encountered challenge in pragmatic trial design. Most clinical trials would consider terminating subjects when serious adverse events develop due to clinical need and ethics concern, especially for patients under intervention in open-label design. As pragmatic trials often use standard care as control, subjects receiving standard care can be observed continuously without disturbing clinical management when serious adverse events develop. The imbalance in the length of observation between arms may confound outcome assessment especially for trials involving a long observation period and high incidence of serious adverse events, for instance, diabetes and CKD trials (55). A standardized termination criteria across arms upon developing serious adverse events can balance the observation length. Besides, using slope of change instead of absolute change in quantitative outcomes and incidence rate instead of incidence in count outcomes can also minimize the confounding from non-uniform follow-up.

Quality of Reporting

Overall, the quality of reporting of the included studies is suboptimal, often with limited information for assessing the completeness of outcome reporting. The prospective registration of a trial and/or protocol publication with clearly prespecified outcome measurements before completion of a study can increase the transparency of outcome reporting. Also, the handling of missing values in the statistical analysis was also unclear. The use of less biased statistical methods in handling attrition (e.g., mixed regression model) with sensitivity analyses could enhance the internal validity of the results. Several studies have high risk of bias in outcome assessment as assessors were not blinded. Although pragmatic trials are often open-label among subjects and investigators, the blinding of the outcome assessor (e.g., by independent laboratory/assessor) is critical to reduce the potential observer bias in outcome assessment.

Strengths and Limitations

This is the first focus group series to explore the specific expectation of the patients and physicians regarding IM diabetes and renal service, involving patients and family medicine, internal medicine, and CM physicians. A mixed-method approach was used in this study. The expectation of stakeholders was qualitatively explored to maximize the finding of mechanisms, and the *status quo* of clinical trial design was evaluated objectively and systematically with quantitative methods. This study has several limitations. As the focus group series focused on identifying detailed expectations on integrative Chinese-western medicine diabetes and CKD management,



Inclusion criteria	All diabetic kidney disease patients satisfying ConM criteria	Diabetic kidney disease patients satisfying both ConM criteria and belongs to a specific CM clinical subgroup	All diabetic kidney disease patients satisfying ConM diagnosis + randomization stratified by CM subgroups
Intervention	Universal (identical treatment for all patients)	Intervention targeted to the CM subgroup	Targeted intervention for each CM subgroup with matching control
Advantage	• Less restriction on study population • More representative sampling • Easily accepted by ConM reader	• More personalized with less heterogeneity from CM perspective • Smaller sample size is needed due to less off-target effect • Easily accepted by CM reader	• Less restriction on study population • Easily accepted by both CM & ConM reader • Less heterogeneity from CM perspective • Smaller sample size is needed due to less off-target effect
Limitation	• Impractical to use among CM physicians due to heterogeneity • Larger sample size is needed to compensate the off-target effect due to lack of personalization	• Incomprehensive and non-representative sampling from ConM perspective • Require *a priori* CM knowledge from ConM on reader • Prone to error in CM diagnosis (non-systematic)	• Prone to error in CM diagnosis (non-systematic) • Sample size may be underpowered for smaller CM subgroups

FIGURE 5 | Schematic integration of diagnostic criteria of Chinese medicine and conventional medicine for diabetic kidney disease. Proposed integration of diagnostic criteria of Chinese medicine (CM) and conventional medicine (ConM) is used as illustration for other traditional, complementary, and integrative medicine (TCIM). Recruiting all diabetic kidney disease (DKD) patients with subsequent randomization stratified by CM diagnosis provides good representation of DKD population, reflect real-world practice of CM, and can be easily interpreted by both ConM and CM physicians. Macro-comparison by combining all subgroups evaluates the effectiveness of CM program to inform ConM physicians on necessary referral. Micro-comparison by subgroup analyses evaluates the effectiveness of each CM regimen for the corresponding subgroup to inform CM physicians on the personalized effect.

findings could be context specific (6). Nevertheless, CM is the mainstream of TCIM and most of the papers identified from the systematic review used CM as the intervention. Also, focus group interviews only delineate possible mechanisms of behavior. Further quantitative studies including surveys are needed to quantify the magnitude of the concerns and test the generalizability in other diseases. The priority of recommendations on study design could be assessed by further consensus methods and surveys involving an extended scope of stakeholders (e.g., caregiver) (56, 57). In the systematic review, the lack of detailed reporting on methodology is partly attributed to journal word limit, which impeded the accuracy of assessment. The correlation analysis between risk of bias and pragmatism is likely underpowered, although all IM pragmatic trials were included. The best estimate of correlation only reflects the association from best available evidence currently. Lastly, the assessment in systematic review only evaluates the quality of trial design through reporting and may not reflect the true quality of trial execution, especially for study protocols.

CONCLUSION

Patients expected IM service to retard disease progression, stabilize concomitant drug dosage and reduce potential side-effects associated with conventional treatment, which were not reflected in existing study designs. Further pragmatic studies should consider more systematic and in-depth quantitative analyses of incident concomitant drug change and adverse events. Majority of studies either recruited a non-representative proportion of patients as TCIM diagnosis was used as inclusion criteria, or not reflecting the real-world practice of TCIM by completely dropping TCIM diagnosis. A two-layer design incorporating TCIM-specific symptom-based diagnosis as a stratification factor maximizes the generalizability of evidence

and translation to real-world practice for both ConM and TCIM physicians.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The University of Hong Kong/Hospital Authority Hong Kong West Cluster Institutional Review Board and Hong Kong East Cluster Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KC, ST, and TL conceived the study. KC and PL collected the interview data and performed the script analysis. KC, CL, and GC coordinated the focus group interviews. KC extracted literature from electronic database. YL and LG screened and assessed the literature. KC and ST drafted the manuscript. All authors involved in the interpretation of data and manuscript revision.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.668913/full#supplementary-material

REFERENCES

1. Ford I, Norrie J. Pragmatic Trials. *N Engl J Med.* (2016) 375:454–63. doi: 10.1056/NEJMra1a510059
2. Zuidgeest MGP, Goetz I, Groenwold RHH, Irving E, van Thiel G, Grobbee DE. Series: Pragmatic trials and real world evidence: Paper 1. *Introduction J Clin Epidemiol.* (2017) 88:7–13. doi: 10.1016/j.jclinepi.2016.12.023
3. Bell IR, Caspi O, Schwartz GER, Grant KL, Gaudet TW, Rychener D, et al. Integrative medicine and systemic outcomes research: issues in the emergence of a new model for primary health care. *Arch Intern Med.* (2002) 162:133–40. doi: 10.1001/archinte.162.2.133
4. Rees L, Weil A. Integrated medicine. *BMJ.* (2001) 322:119. doi: 10.1136/bmj.322.7279.119
5. Astin JA, Marie A, Pelletier KR, Hansen E, Haskell WL, A. Review of the incorporation of complementary and alternative medicine by mainstream physicians. *Arch Intern Med.* (1998) 158:2303–10. doi: 10.1001/archinte.158.21.2303
6. Chan KW, Lee PW, Leung CPS, Chan GCW, Yiu WH, Cheung HM, et al. Patients' and clinicians' expectations on integrative medicine Services for Diabetes: a focus group study. *BMC Complement Med Ther.* (2020) 20:205. doi: 10.1186/s1s2906-020-029944-5
7. Fan R. Modern Western science as a standard for traditional Chinese medicine: a critical appraisal. *J Law Med Ethics.* (2003) 31:213–21. doi: 10.1111/j.17488-720X00XX.2003.tb0b0082.x
8. Chen X, Pei L, Lu J. Filling the gap between traditional Chinese medicine and modern medicine, are we heading to the right direction? *Complement Ther Med.* (2013) 21:272–5. doi: 10.1016/j.ctim.2013.01.001
9. Seshia SS, Makhinson M, Young GB. Evidence-informed person-centred health care (part II): are 'cognitive biases plus' underlying the EBM paradigm responsible for undermining the quality of evidence? *J Eval Clin Pract.* (2014) 20:748–58. doi: 10.1111/jep.12291
10. Marcus DM. Alternative therapies in academic medical centers compromise evidence-based patient care. *J Clin Invest.* (2020) 130:1549–51. doi: 10.1172/JCI1I37561
11. Hill AB. Reflections on controlled trial. *Ann Rheumat Dis.* (1966) 25:107–13. doi: 10.1136/ard.25.2.107
12. Rao BS. Generation of evidence should be tailored to individuals. *BMJ.* (2018) 363:k4k115. doi: 10.1136/bmj.k4k115
13. DeMerle K, Angus DC, Seymour CW. Precision medicine for COVID-19: phenotype anarchy or promise realized? *JAMA.* (2021) 325:2041–2. doi: 10.1001/jama.2021.5248
14. Accad M, Francis D. Does evidence based medicine adversely affect clinical judgment? *BMJ.* (2018) 362:k2k799. doi: 10.1136/bmj.k2k799
15. Feinstein AR, Horwitz RI. Problems in the "evidence" of "evidence-based medicine". *Am J Med.* (1997) 103:529–35. doi: 10.1016/S0S002-9343(97)002444-1
16. Eddy DM. Evidence-based medicine: a unified approach. *Health Aff.* (2005) 24:9–17. doi: 10.1377/hlthaff.24.1.9
17. Tonelli MR. The philosophical limits of evidence-based medicine. *Acad Med.* (1998) 73:1234–40. doi: 10.1097/000018888-1998120000-00011
18. Califf RM, Robb MA, Bindman AB, Briggs JP, Collins FS, Conway PH, et al. Transforming evidence generation to support health and health care decisions. *N Engl J Med.* (2016) 375:2395–400. doi: 10.1056/NEJMsb1b610128
19. Tang J-L. Research priorities in traditional Chinese medicine. *BMJ.* (2006) 333:391–4. doi: 10.1136/bmj.333.7564.391
20. Witt CM, Chesney M, Gliklich R, Green L, Lewith G, Luce B, et al. Building a strategic framework for comparative effectiveness research in complementary and integrative medicine. *Evid Based Complementd Alternat Med.* (2012) 2012:531096. doi: 10.1155/2012/531096
21. Fonnebo V, Grimsgaard S, Walach H, Ritenbaugh C, Norheim AJ, MacPherson H, et al. Researching complementary and alternative treatments–the gatekeepers are not at home. *BMC Med Res Methodol.* (2007) 7:7. doi: 10.1186/14711-22888-7-7
22. Di MY, Tang JL. Adaption and application of the four phase trials to traditional chinese medicines. *Evid Based Complementd Alternat Med.* (2013) 128030:20. doi: 10.1155/2013/128030
23. Tembo D, Hickey G, Montenegro C, Chandler D, Nelson E, Porter K, et al. Effective engagement and involvement with community

stakeholders in the co-production of global health research. *BMJ.* (2021) 372:n1n78. doi: 10.1136/bmj.n1n78
24. Oakley A, Strange V, Bonell C, Allen E, Stephenson J. Process evaluation in randomised controlled trials of complex interventions. *BMJ.* (2006) 332:413–6. doi: 10.1136/bmj.332.7538.413
25. Godwin M, Ruhland L, Casson I, MacDonald S, Delva D, Birtwhistle R, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. *BMC Med Res Method.* (2003) 3:28. doi: 10.1186/14711-22888-3-28
26. Thabane L, Kaczorowski J, Dolovich L, Chambers LW, Mbuagbaw L. on behalf of the Ci. Reducing the confusion and controversies around pragmatic trials: using the Cardiovascular Health Awareness Program (CHAP) trial as an illustrative example. *Trials.* (2015) 16:387. doi: 10.1186/s1s3063-015-09199-3
27. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract.* (2018) 138:271–81. doi: 10.1016/j.diabres.2018.02.023
28. Sinclair A, Saeedi P, Kaundal A, Karuranga S, Malanda B, Williams R. Diabetes and global ageing among 65-99-year-old adults: Findings from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract.* (2020) 162:108078. doi: 10.1016/j.diabres.2020.108078
29. Murray CJL, Aravkin AY, Zheng P, Abbafati C, Abbas KM, Abbasi-Kangevari M, et al. Global burden of 87 risk factors in 204 countries and territories, 1990,1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* (2020) 396:1223–49. doi: 10.1016/S0S140-6736(20)307522-2
30. Zhong Y, Deng Y, Chen Y, Chuang PY, Cijiang He J. Therapeutic use of traditional Chinese herbal medications for chronic kidney diseases. *Kidney Int.* (2013) 84:1108–18. doi: 10.1038/ki.2013.276
31. Lin MY, Chiu YW, Chang JS, Lin HL, Lee CT, Chiu GF, et al. Association of prescribed Chinese herbal medicine use with risk of end-stage renal disease in patients with chronic kidney disease. *Kidney Int.* (2015) 5:226. doi: 10.1038/ki.2015.226
32. Hsieh CF, Huang SL, Chen CL, Chen WT, Chang HC, Yang CC. Non-aristolochic acid prescribed Chinese herbal medicines and the risk of mortality in patients with chronic kidney disease: results from a population-based follow-up study. *BMJ Open.* (2014) 4:2013–004033. doi: 10.1136/bmjopen-20133-004033
33. Tong XL, Dong L, Chen L, Zhen Z. Treatment of diabetes using traditional Chinese medicine: past, present and future. *Am J Chin Med.* (2012) 40:877–86. doi: 10.1142/S0S192415X55X1X2500656
34. Sun GD Li CY, Cui WP, Guo QY, Dong CQ, Zou HB, et al. Review of Herbal traditional chinese medicine for the treatment of diabetic nephropathy. *J Diabetes Res.* (2016) 5749857:15. doi: 10.1155/2016/5749857
35. Zhang, Yang L, Shergis J, Zhang L, Zhang AL, Guo X, et al. Chinese herbal medicine for diabetic kidney disease: a systematic review and meta-analysis of randomised placebo-controlled trials. *BMJ Open.* (2019) 9:e0e25653. doi: 10.1136/bmjopen-20188-025653
36. Chan KW. Integrative management for diabetic kidney disease – Patients' and clinicians' perspectives, clinical effectiveness and possible mechanisms [PhD thesis]. *Hong Kong: The University of Hong Kong.* (2018).
37. Barney G. Glaser. The constant comparative method of qualitative analysis. *Social Problems.* (1965) 12:436–45. doi: 10.2307/798843
38. Chung VC, Ma PH, Lau CH, Griffiths SM. Developing policy for integrating biomedicine and traditional chinese medical practice using focus groups and the delphi technique. *Evid Based Complementd Alternat Med.* (2012) 149512:10. doi: 10.1155/2012/149512
39. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ.* (2015) 350:h2h147. doi: 10.1136/bmj.h2h147
40. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane Handbook for Systematic Reviews of Interventions Version 6 2019.* Available online at: https://training.cochrane.org/handbook/current
41. Nanthakumar CB, Hatley RJ, Lemma S, Gauldie J, Marshall RP, Macdonald SJ. Dissecting fibrosis: therapeutic insights from the small-molecule toolbox. *Nat Rev Drug Discov.* (2015) 14:693–720. doi: 10.1038/nrd4d592
42. Humphreys BD. Mechanisms of renal fibrosis. *Annu Rev Physiol.* (2018) 80:309–26. doi: 10.1146/annurev-physiol-0225166-034227
43. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA.* (2011) 305:2532–9. doi: 10.1001/jama.2011.861
44. Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane Database Syst Rev.* (2006) 18:CD0D06257. doi: 10.1002/14651858.CD0D06257
45. Duan N, Kravitz RL, Schmid CH. Single-patient (n-of-1) trials: a pragmatic clinical decision methodology for patient-centered comparative effectiveness research. *J Clin Epidemiol.* (2013) 66:S2S1–8. doi: 10.1016/j.jclinepi.2013.04.006
46. Lam TP. Strengths and weaknesses of traditional Chinese medicine and Western medicine in the eyes of some Hong Kong Chinese. *J Epi Community Health.* (2001) 55:762. doi: 10.1136/jech.55.10.762
47. Chan KW, Chow TY, Yu KY, Xu Y, Zhang NL, Wong VC, et al. SYmptom-based STratification of diabEtes Mellitus by renal function (SYSTEM): a retrospective cohort study and modelling assessment. *Front Med.* (2021) 8:682090. doi: 10.3389/fmed.2021.682090
48. Chung VCH, Ho RST, Wu X, Wu JCY. Incorporating traditional Chinese medicine syndrome differentiation in randomized trials: Methodological issues. *Eur J Integr Med.* (2016) 8:898–904. doi: 10.1016/j.eujim.2016.08.164
49. Chan KW, Ip TP, Kwong AS, Lui SL, Chan GC, Cowling BJ, et al. Semi-individualised Chinese medicine treatment as an adjuvant management for diabetic nephropathy: a pilot add-on, randomised, controlled, multicentre, open-label pragmatic clinical trial. *BMJ Open.* (2016) 6: e0e10741. doi: 10.1136/bmjopen-20155-010741
50. Shuldiner SR, Chung VCH, Wu X, Ching J, Ho RST, Cheong PK, et al. Methodological challenges in mapping chinese medicine syndrome with conventional diagnosis: Implications for multi-centre trials in integrative medicine. *Eur J Integr Med.* (2015) 7:358–64. doi: 10.1016/j.eujim.2015.07.027
51. Ho LTF, Chung VCH, Wong CHL, Wu IXY, Lan KC, Wu D, et al. Evaluating traditional Chinese medicine diagnostic instruments for functional dyspepsia: systematic review on measurement properties. *Integr Med Res.* (2021) 10:100713. doi: 10.1016/j.imr.2020.100713
52. Wang ZC, Zhang SP, Yuen PC, Chan KW, Chan YY, Cheung CH, et al. Intra-rater and inter-rater reliability of tongue coating diagnosis in traditional Chinese medicine using smartphones: quasi-Delphi study. *JMIR Mhealth Uhealth.* (2020) 8:e1e6018. doi: 10.2196/16018
53. Menni C, Valdes AM, Freidin MB, Sudre CH, Nguyen LH, Drew DA, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nat Med.* (2020). doi: 10.1038/s4s1591-020-09166-2
54. Ganna A, Ingelsson E. 5 year mortality predictors in 498,103 UK Biobank participants: a prospective population-based study. *Lancet.* (2015) 386:533–40. doi: 10.1016/S0S140-6736(15)601755-1
55. Haff N, Choudhry NK. The promise and pitfalls of pragmatic clinical trials for improving health care quality. *JAMA Netw Open.* (2018) 1:e1e83376. doi: 10.1001/jamanetworkopen.2018.3376

56. Wong CHL, Wu IXY, Balneaves LG, Lo RSK, Witt CM, Wu JCY, et al. Prioritizing Chinese medicine clinical research questions in cancer palliative care: international Delphi survey. *J Pain Symptom Manage*. (2019) 58:1002–14.e7ee7. doi: 10.1016/j.jpainsymman.2019.08.002
57. Wong CHL, Wong W, Lin WL, Au DKY, Wu JCY, Leung TH, et al. Prioritizing Chinese medicine clinical research questions in cancer palliative care from patient and caregiver perspectives. *Health Expect*. (2021) doi: 10.1111/hex.13289

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Pediatric Clinical Trials in Mainland China Over the Past Decade (From 2009 to 2020)

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In mainland China, there remains a shortage of pediatric drugs. The Chinese government has recently launched policies and incentives to encourage pediatric drug development and clinical trials. However, data on the characteristics or development trends of these trials are limited. In this review, we extracted source data from the Chinese Clinical Trials Registry and Information Transparency Platform and systematically reviewed the pediatric clinical trials conducted in mainland China from 2009 to 2020, a comprehensive process evaluation of the pediatric drug clinical trials development in the past decade, providing data support to policy makers and industry stakeholders. We included 487 pediatric clinical trials. Over the past decade, the number of pediatric trials has increased, especially since 2016. The most common therapeutic areas were infectious diseases ($n = 108$, 22.2%), agents for preventive purpose ($n = 99$, 20.3%), and neurological and psychiatric diseases ($n = 71$, 14.6%). The number of clinical trials involving epilepsy (39, 10.1%), asthma (33, 8.5%), and influenza (24, 6.2%) were the highest. The distribution of leading institutions is unbalanced in mainland China, with most units in East China (34.0%) and few in Southwest China (6.9%). China has made progress in improving the research and development environment of pediatric drugs and increasing pediatric trials. However, a wide gap in pediatric drug development and clinical trials quality exists between China and the developed countries. The pharmaceutical industry in China has faced grim setbacks, including study duplication, lack of innovation, poor research design, and unbalanced resource allocation. Thus, we suggest that the Chinese government should adjust their policies to improve innovation and clinical design capacity, and optimize resource allocation between regions.

Keywords: pediatric clinical trials, National Medical Products Administration, Chinese Clinical Trials Registry and Information Transparency Platform, pediatric population, drug research and development

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INTRODUCTION

According to the statistics of the UN Children's Fund, the pediatric population aged 0–17 in China was 217 million in 2015, accounting for 13.0% of the world total and ranking in second place. Promoting safe drug use and protecting children's health are long-term health goals in China. To protect children's health, it is necessary to first meet their medicinal needs. In China, however, the

shortage of pediatric drugs is severe. Data in the White Paper on the Investigation of Pediatric Drug Use Safety (1) released in 2016 show that, of the 176,652 drugs approved in China by June 2016, only 3,517 were pediatric drugs, accounting for <2.0%. Thus, it is crucial to deal with the issue at a policy level, encouraging the development of pediatric drugs and their relevant clinical trials, and promoting the approval and marketing of pediatric drugs.

Over the past decade, especially since 2014, the Chinese government has launched a package of policies to encourage the development of pediatric drugs. However, research focusing on the current situation, the characteristics of pediatric trials, and their development trends is relatively rare.

At present, all the studies on pediatric clinical trials in mainland China that we have retrieved are based on data registered in the Chinese Clinical Trial Registry (Chi CTR) (2–4).

The Chi CTR database is not compulsorily collected for drug approval and marketing and focuses on investigator-initiated clinical studies rather than new drug development, limiting its use in analyzing the current situation of pediatric drug development in China.

Therefore, this study used the Chinese Clinical Trials Registry and Information Transparency Platform (CCTR and ITP) for source data. This platform was established in 2013 by the former China Food and Drug Administration (CFDA) and requires all entities who have been granted clinical trial approval and plan to conduct trials in China to register and make the information regarding the clinical trials public. With an in-depth analysis into the data on the platform through longitudinal and horizontal comparison of quantitative and qualitative indicators in different dimensions and a comprehensive process evaluation of the pediatric drug clinical trials development in the past decade, we hope to shed light on the current situation and development trends of pediatric clinical trials and detect existing problems. The findings of this analysis will provide effective data support for policy makers and other stakeholders.

RETRIEVAL STRATEGY AND SELECTION STANDARD

In 2013, the former CFDA, in accordance with World Health Organization requirements and international conventions, established the CCTR and ITP and stipulated that all entities who have been granted clinical trial approval and plan to conduct the trials [including bioequivalence (BE) studies, pharmacokinetics tests, and Phase I, II, III, and IV trials] in China must register on the platform. To ensure data timeliness, the initial registration must be submitted at least 30 days before the first subject is enrolled. The CFDA cross-checks all submitted clinical reports and materials on a regular basis to ensure data validity and integrity. In addition, clinical trials started before 2013 that have not received sales and marketing approval are required to register retrospectively.

The information made public on the platform includes information on sponsors and investigators, the first registration date, basic information regarding the clinical trial (drug name, indication, trial purpose, and trial design), subject information (inclusion and exclusion criteria and the number of subjects), primary and secondary endpoint criteria, ethical review, trial development, and a summary of the results.

We conducted a systematic review of the clinical trial information submitted to the platform before April 30, 2020. After preliminary retrieval, 10,601 registered clinical trials were found (**Figure 1**). Our study involved all the pediatric clinical trials, and the retrieval and data-processing was conducted in three steps. The first step was to select clinical trials which involved pediatric indications and conducted by institutions specializing in pediatric drugs. We used the search terms *neonate, infant, young children, preschooler, children, adolescent,* and *juvenile.* After the first round of screening, 848 clinical trials were incorporated into the study (**Figure 1**).

In the second step, we used Excel to screen and delete 318 trials with repeated Clinical Trials Register Numbers and remove 16 trials with repeated unofficial titles. Next, two pediatricians were invited to independently review the selected clinical trials and, if there was any disagreement, a third pediatrician was asked to arbitrate until an agreement was reached. This step helped to exclude 46 non-pediatric trials. To ensure that no relevant trials were omitted, we employed simple random sampling and selected 10.0% of the trials from the excluded group ($n = 10{,}115$). The selected 10.0% of trials were then reviewed by the two pediatricians mentioned above, and no pediatric-relevant trials were found.

The year 2020 has witnessed the ending of the National Major Scientific and Technological Special Project for "Significant New Drugs Development." Launched in 2008, the project symbolized the start of a new era for drug development in China. We selected January 1, 2009, just 1 year after the launching of the project, as the time node, and excluded all trials which underwent initial ethical review before this date. Only one trial that received its ethical review in 2005 was excluded. Finally, 487 pediatric clinical trials were included in this study. The third step involved data preparation and statistics. We statistically classified and analyzed the selected clinical trials according to various dimensions, including basic information on trials, drugs, indications, trial design, sponsors, and institutions.

DATA ANALYSIS METHODS

We employed Excel and SPSS to process and analyze the data, adopting descriptive analyses and using percentages to indicate qualitative variables. All data were collected and analyzed according to the four dimensions: basic clinical trial information, drugs and indications, trial design, sponsor and institution. To evaluate the development process of pediatric drug clinical trials in the past decade, we further subdivided the statistical data as follows: the trend of the quantity was

Abbreviations: CCTR and ITP, Chinese Clinical Trials Registry and Information Transparency Platform; Chi CTR, Chinese Clinical Trial Registry; NMPA, National Medical Products Administration; UN, United Nations; CFDA, China Food and Drug Administration; BE, Bioequivalence; R&D, Research and Development; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

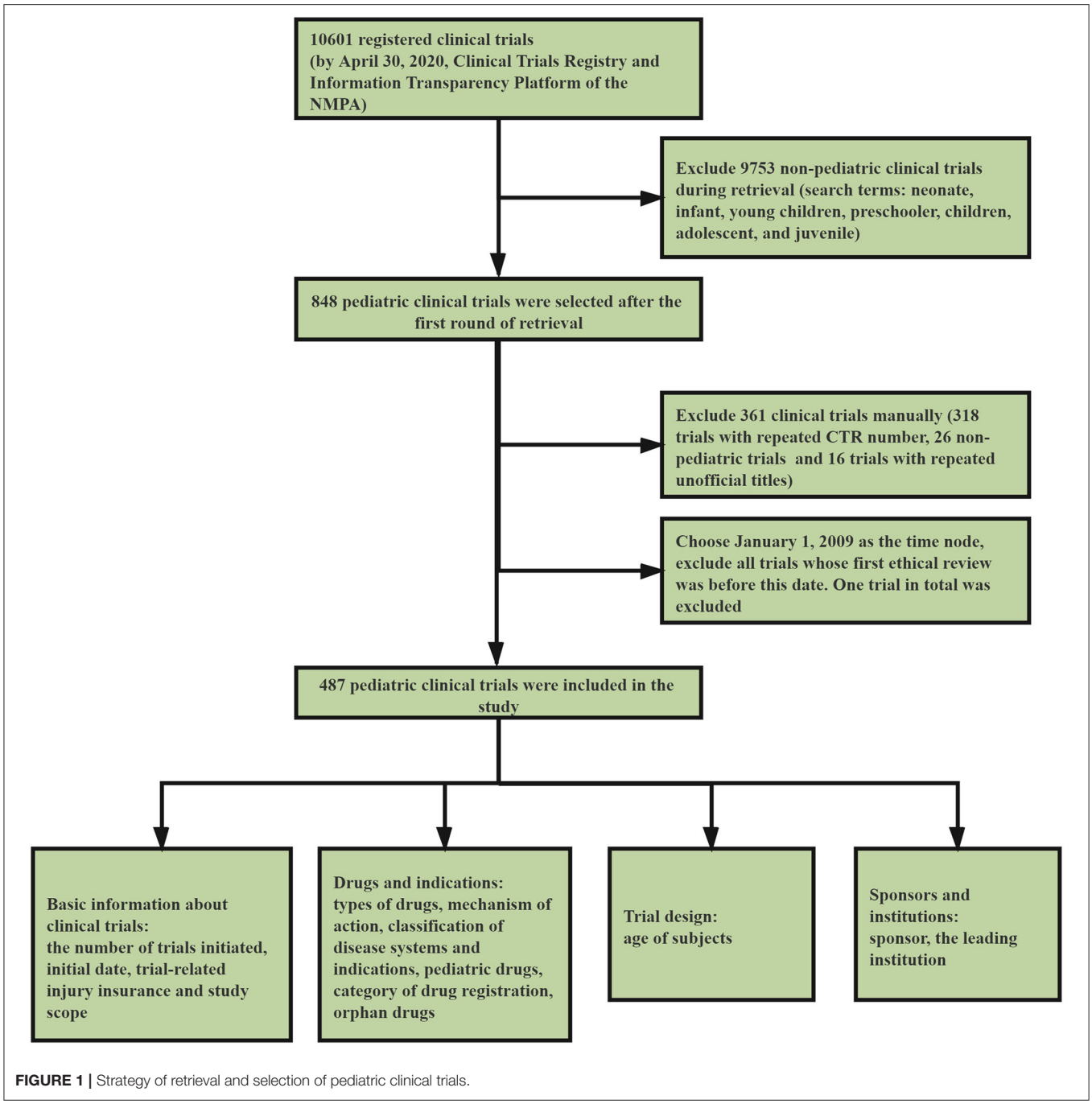

FIGURE 1 | Strategy of retrieval and selection of pediatric clinical trials.

reflected by the number of clinical trials for different drugs, drugs in different study phases, and initial registration date and development trends. For clinical trial quality, we used disease system classification and indications and drug registration types to reflect the innovation aspect of the clinical trial. Trial-related injury insurance reflected the clinical trial design normalization. Study scope reflected the clinical trial impact. Clinical trials of pediatric and orphan drugs reflected the specificity of pediatric clinical trials. The above indicators reflect the quality trend of pediatric clinical trials in China. Finally, the resource allocation of pediatric clinical trials was reflected by clinical trial sponsors and institutions. A simple regression model was used to calculate the annual fluctuation rates of the indicators. The homogeneity of variance test was used to compare whether the same index had statistical differences under different statistical diameters. The initial year of the trial was determined by the date of its first ethical review. Two-tailed $P < 0.05$ were considered significant.

RESULTS

Basic Information Regarding Pediatric Clinical Trials in China

General Conditions

From 2009 to April 2020, a total of 487 pediatric clinical trials were conducted in mainland China, of which 246 (50.5%) were ongoing, 226 (46.4%) had been completed, and 15 (3.1%) had been voluntarily suspended by their sponsors. Of the 487 trials, 43 were in Phase 1 (8.8%), 36 in Phase II (7.4%), 153 in Phase III (31.4%), and 47 in Phase IV (9.7%), 177 (36.3%) were BE studies, and the last 31 (6.4%) fell into other categories (**Figure 2A**). When classified in terms of drug type, chemical drugs were involved in 303 trials (62.2%); natural medicines in 16 trials (3.3%); therapeutic biological products in 69 trials (14.2%), and prophylactic biological products in 99 trials (20.3%) (**Figure 2B**).

Initial Registration Date and Development Trends

From 2009 to 2019, the number of conducted trials increased annually ($P < 0.0001$), with an average annual increase rate of 44.7%. Since 2016, the number of pediatric-related clinical trials began to rise significantly, with an annual increase of more than 20 trials. The increase was significant in 2017 and 2018 with an annual increase of 30 trials. Conversely, in 2019, the increase began to slow. In terms of the types of drugs involved in pediatric trials, chemical drugs showed a significant increase, with an average annual increase rate of 46.3% ($P = 0.01$); natural medicines, therapeutic biological products, and prophylactic biological products showed relatively small changes, with average annual increase rates of 10.7% ($P = 0.3078$), 27.1% ($P = 0.00012$), and 15.8% ($P = 0.0025$), respectively, between 2010 and 2019.Trials on both chemical drugs and prophylactic biological products began to significantly increase in 2016 **(Figure 3A)**. In terms of study phases, there were few Phase I, II, and IV trials, with little fluctuation, while Phase III trials and BE studies both saw significant increases in 2016. Phase III trials had an average annual increase rate of 28.7% ($P = 0.0004$) (2010–2019) and BE studies had an average annual increase rate of 53.6% ($P = 0.0016$) (2011–2019) **(Figure 3B)**.

Trial-Related Injury Insurance

Of the 487 clinical trials, 218 provided trial-related injury insurance to the participants, with an overall coverage rate of 44.8%. The coverage rate of the international multi-center trials, however, was 88.5%, much higher than that of the domestic trials (8.5%) ($F = 54.0$, $P < 0.001$) (**Table 1**). From 2010 to 2019, the insurance coverage rate of pediatric clinical trials in China showed an upward trend, with an average annual increase rate of 35.3% ($P = 0.0019$). The highest insurance coverage rate was observed in Phase III trials (57.5%), followed by BE trials (41.2%). The insurance coverage rates of Phase I, II, and IV trials were 39.5, 33.3, and 36.2%, respectively (**Table 2**).

Study Scope

Of the 487 trials, 258 were multi-center trials (52.3%) including 61 international multi-center trials (12.5%). The number of international multi-center trials increased over time, with an average annual increase rate of 37.9% ($P = 0.0069$) from 2012 to 2019. While the average number of international multi-center trials conducted per year from 2009 to 2016 was only 1.2, and drastically increased to 17 from 2017 to 2019. International multi-center trials began to increase significantly in 2017. In terms of study phases, Phase III trials contributed the highest proportion of international multi-center trials, with 49 trials accounting for 32.0%.Phase II trials ranked second, with seven trials accounting for 19.4% (**Table 3**). In terms of drug type, trials on chemical drugs contributed the highest proportion of international multi-center trials, with 54 trials accounting for 17.8%. In addition, six international multi-center trials on therapeutic biological products were registered, accounting for 8.7%. There was only one international multi-center trial on prophylactic biological products (1.0%) and no international multi-center trials on natural medicines (**Table 4**).

Age of Subjects

Since it is a design requirement that all BE study subjects should be adults, the 177 BE studies were first excluded. Then, subjects were divided into five age groups, neonates (age < 28 days), infants (28 days < age < 24 months), children (2 years < age < 11 years), adolescents (12 years < age < 18 years), and adults (age > 18 years). After excluding the BE studies, 27 of the remaining 310 trials involved adult subjects only, accounting for 8.7%. The remaining 91.3% involved subjects < 18 years of age, while 55.2% (171 trials) only involved subjects < 18 years of age (**Table 5**). More specifically, 26, 133, 208, 185, and 139 trials involved neonate, infant, children, adolescent, and adult subjects, respectively (**Figure 4**).

Drugs and Indications

Classification of Disease Systems and Indications

In accordance with the classification standards in the *Chinese National Formulary,* we classified all investigational products in terms of disease systems and indications (5). The number of trials for each classification was calculated (as some investigational products were tested for several indications, the number of investigational products classified in this way was higher than the actual number of tested products). Infectious disease was the most studied therapeutic area, with 108 clinical trials (22.2%). The next four most common therapeutic areas, in descending order, were agents for preventive purposes (99 trials, 20.3%), neurological and psychiatric diseases (71 trials, 14.6%), respiratory diseases (50 trials, 10.3%), and endocrine and inherited metabolic diseases (38 trials, 7.8%). Trials involving the five disease systems mentioned above accounted for 75.2% of all pediatric clinical trials (**Figure 5**).

As for indications, the trials on prophylactic biological products were first excluded, hence 388 trials remained, of which indications investigated in more than 10 trials included epilepsy (39 trials, 10.1%), asthma (33 trials, 8.5%), influenza (24 trials, 6.2%), growth retardation in children (24 trials, 6.2%), HIV infection/chronic hepatitis B (22 trials, 5.7%), HIV infection (19 trials, 4.9%), bacterial infectious diseases (14 trials, 3.6%), anesthesia (14 trials, 3.6%), hemophilia A (13 trials, 3.4%), chronic hepatitis B (11 trials, 2.8%), immune rheumatic diseases

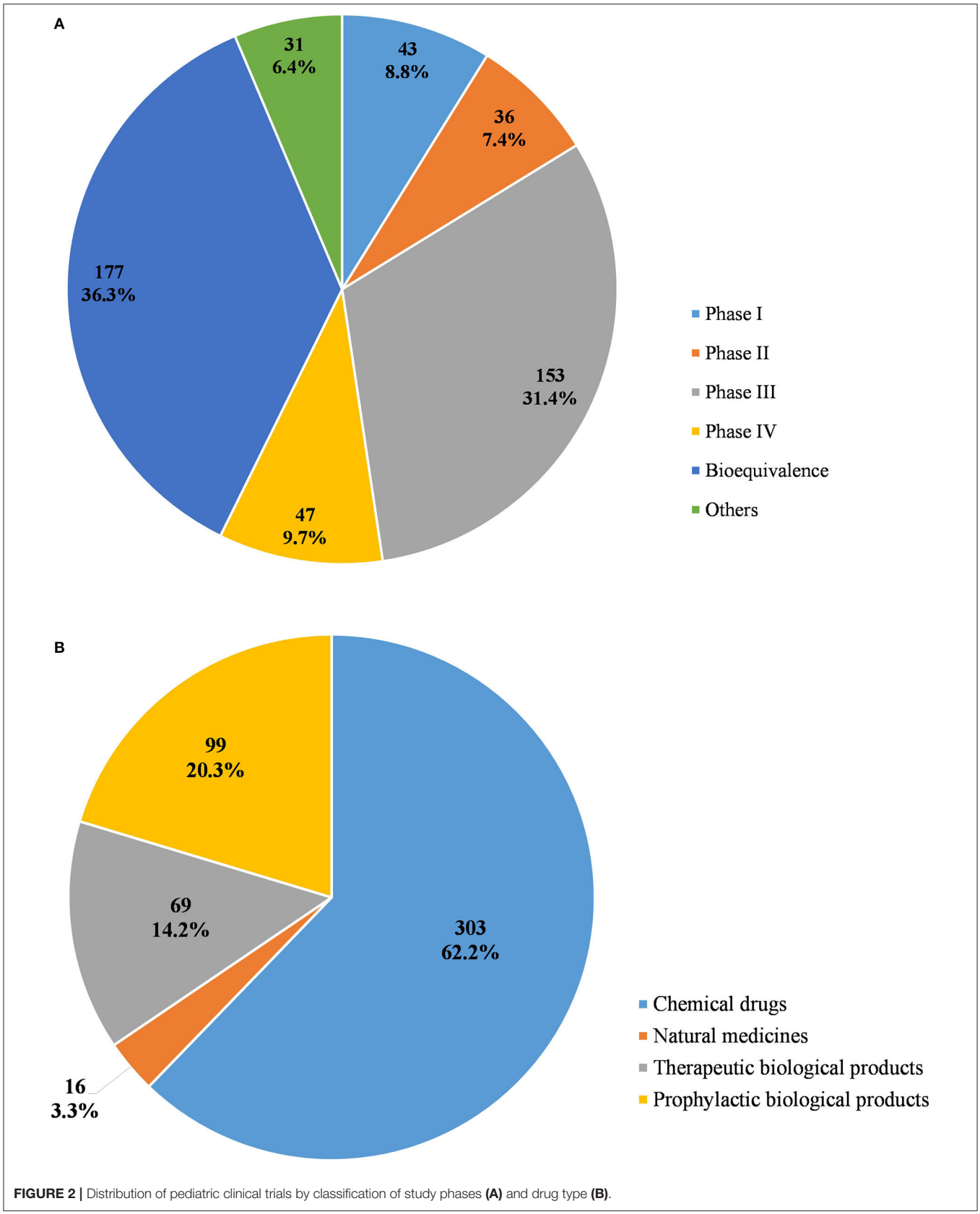

FIGURE 2 | Distribution of pediatric clinical trials by classification of study phases **(A)** and drug type **(B)**.

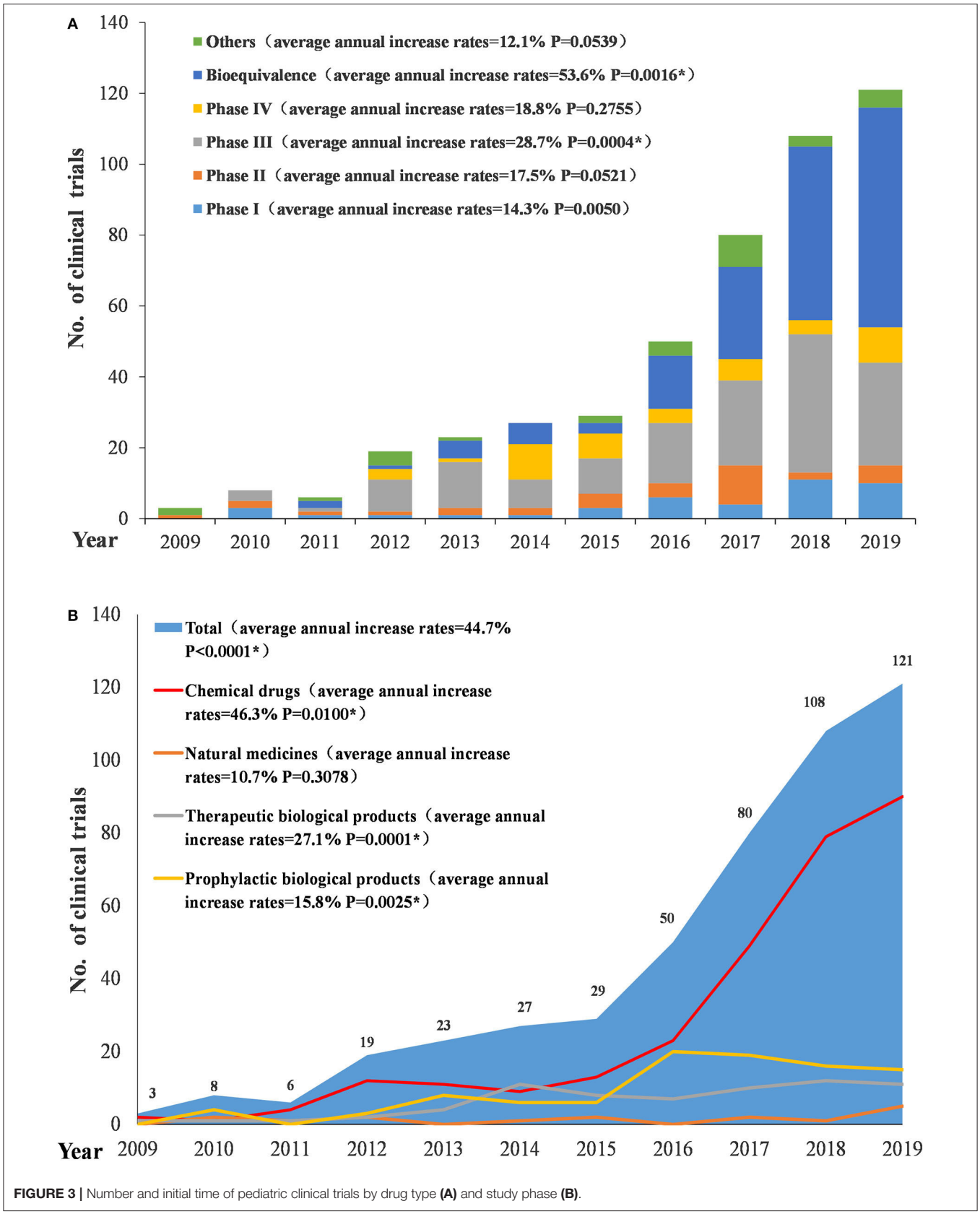

FIGURE 3 | Number and initial time of pediatric clinical trials by drug type **(A)** and study phase **(B)**.

TABLE 1 | Domestic and international multi-center trial-related injury insurance.

Trial scope	No. of injury insurance trials (each scope total trials)	%
Domestic	164 (426)	38.5
International multi-center	54 (61)	88.5
Total	218 (487)	44.8

TABLE 2 | Different phase trial-related injury insurance.

Trial phase	No. of injury insurance trials (each phase total trials)	%
Phase I	17 (43)	39.5
Phase II	12 (36)	33.3
Phase III	88 (153)	57.5
Phase IV	17 (47)	36.2
BE study	73 (177)	41.2
Others	11 (31)	35.5
Total	218 (487)	44.8

TABLE 3 | Different trial phase scope.

Trial phase	No. of Domestic trial (%)	No. of international multi-center trial (%)	Total no. of trials
Phase I	43 (100.0)	0 (0.0)	43
Phase II	29 (80.6)	7 (19.4)	36
Phase III	104 (68.0)	49 (32.0)	153
Phase IV	46 (97.9)	1 (2.1)	47
BE study	175 (98.9)	2 (1.1)	177
Other	29 (93.5)	2 (6.5)	31
Total	426 (87.5)	61 (12.5)	487

TABLE 4 | Scope of trials for different drug types.

Drug type	No. of Domestic trial (%)	No. of international multi-center trial (%)	Total no. of trials
Chemical drugs	249 (82.2)	54 (17.8)	303
Natural medicines	16 (100.0)	0 (0.0)	16
Therapeutic biological products	63 (91.3)	6 (8.7)	69
Prophylactic biological products	98 (99.0)	1 (1.0)	99
Total	426 (87.5)	61 (12.5)	487

(10 trials, 2.6%), and attention deficit hyperactivity disorder (10 trials, 2.6%). In total, 233 trials involved the indications mentioned above, accounting for 60.0% of the 388 trials. There are 22 kinds of indications involving more than five clinical trials, the number of clinical trials is 299, accounting for 77.1% (**Table 6**).

TABLE 5 | Distribution of clinical trials by different age groups.

Age groups of subjects	No. of trials	%	
Subjects included adults	Adults	27	8.7
	neonates, infants, children, adolescents, adults	13	4.3
	infants, children, adolescents, adults	23	7.4
	children, adolescents, adults	41	13.2
	adolescents, adults	35	11.3
Subjects included no adults	infants	32	10.3
	infants, children	38	12.3
	infants, children, adolescents	19	6.1
	neonates	5	1.6
	neonates, infants	2	0.6
	neonates, infants, children	2	0.6
	neonates, infants, children, adolescents	4	1.3
	children	19	6.1
	children, adolescents	49	15.8
	adolescents	1	0.3
Total	310	1	

Classification System for Registration of Chemical Drugs in China

In accordance with the Reform Scheme of the Classification System for Registration of Chemical Drugs issued by the CFDA in March 2016, and the Provisions for Drug Registration, which came into force on July 1, 2020, the chemical drugs were classified into innovative drugs, modified new drugs, and generic drugs (6, 7) (**Table 7**).

As **Figures 6–8** show, in the 303 clinical trials on chemical drugs, 57 were on innovative drugs, accounting for 18.8%. However, only four trials on innovative drugs were sponsored domestically (domestic innovative drugs) (7.0%), far fewer than the 53 trials sponsored overseas (imported innovative drugs) (93.0%). From 2011 to 2019, trials on innovative drugs in mainland China showed an upward trend, with an average annual increase rate of 41.4% ($P = 0.0038$). The number of trials on innovative drugs has sharply increased increase in 2017 (500.0%) compared to 2016.

As for modified new drugs, 35 trials were conducted, accounting for 11.6%. Of these, 24 were sponsored domestically (domestic modified drugs) (68.6%), while another 11 trials were sponsored overseas (imported modified drugs) (31.4%). Before 2017, the number of trials on modified new drugs followed a steady trend while a drastic increased was reported in 2018, with an increase of 1,000.0% compared to 2017.

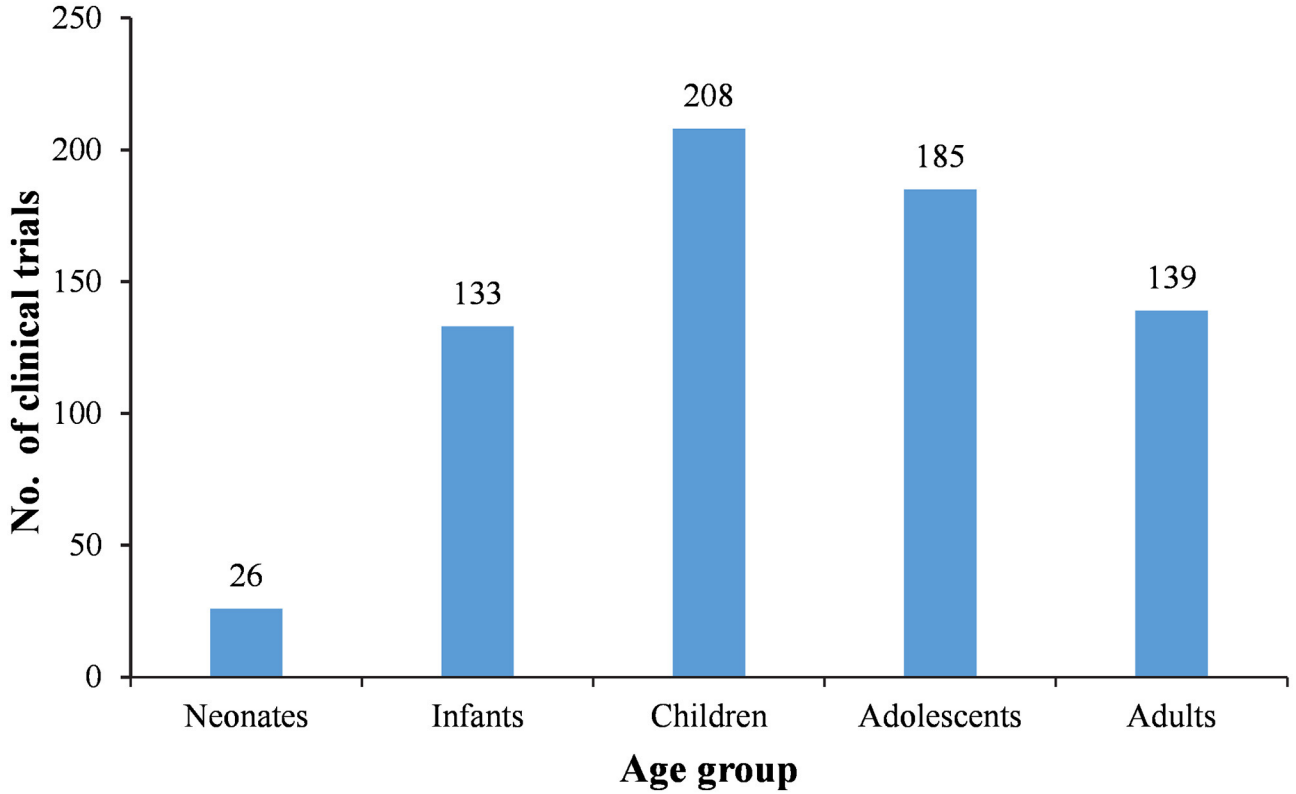

FIGURE 4 | Distribution of pediatric clinical trials by age group.

As for generic drugs, 211 clinical trials were conducted, accounting for 69.6%. Of these, 203 were sponsored domestically (domestic generic drugs) (96.2%), far more than the eight trials sponsored overseas (imported generic drugs) (3.8%). The number of trials on generic drugs also increased over time, with an average annual increase rate of 50.6% ($P = 0.0003$). Clinical trials on generic drugs began to increase significantly from 2016, with an increase of 185.7% compared to 2015. The increase rate slowed from 2017 to 2019 but retained an average rate of 47.0%.

Pediatric Drugs

After excluding trials on prophylactic biological products, the 388 remaining trials were further analyzed, and drugs indicated only for children were defined as pediatric drugs. Of the 388 clinical trials, 85 were on drugs especially designed for pediatric use, only accounting for 21.9%. The numbers of trials on various types of pediatric drugs are presented in **Table 8**. For the chemical drugs, pediatric clinical trials on psychotropic and antipsychotic drugs were the most common (19 trials, 44.2%), indicated for epilepsy and attention deficit hyperactivity disorder. This was followed by trials on anti-tumor agents (six trials, 14.0%) and anti-infective drugs (four trials, 9.3%). Trials on traditional Chinese medicines and natural medicines were mainly indicated for respiratory diseases (five trials, 41.7%). Most pediatric trials conducted on therapeutic biological products focused on growth hormones (27 trials, 90%). Overall, clinical trials on drugs for pediatric use showed an upward trend over time, with an average annual increase rate of 18.2% ($P = 0.0003$). The increase was especially significant in 2017, when the number of pediatric clinical trials increased by 10 compared to 2016, with an increase rate of 166.7%.

Orphan Drugs

In accordance with the First *List of Rare Diseases* released in May 2018, and the *List of Reference on Rare Diseases in China*, clinical trials on drugs indicated for rare diseases were screened (8, 9). Of the 487 clinical trials, 45 were indicated for rare diseases with 29 orphan drugs involved. Of the 45 trials for rare diseases, 23 were indicated for hemophilia, accounting for 51.1%. Further analysis of the other 22 trials showed that the next most common indications were Dravet syndrome and pulmonary artery hypertension, with three trials each. This was followed by spinal muscular atrophy, Tourette syndrome, and Lennox-Gastaut syndrome, with two trials each. Of the 45 trials, 24 were conducted on chemical drugs while the other 21 were on therapeutic biological products. In terms of sponsorship, 20 trials were sponsored by domestic pharmaceutical companies, accounting for 44.4%, while the other 25 were sponsored by overseas companies, accounting for 55.6%. Clinical trials on orphan drugs also showed an upward trend over time, with an average annual increase rate of 27.1% ($P = 0.0003$).

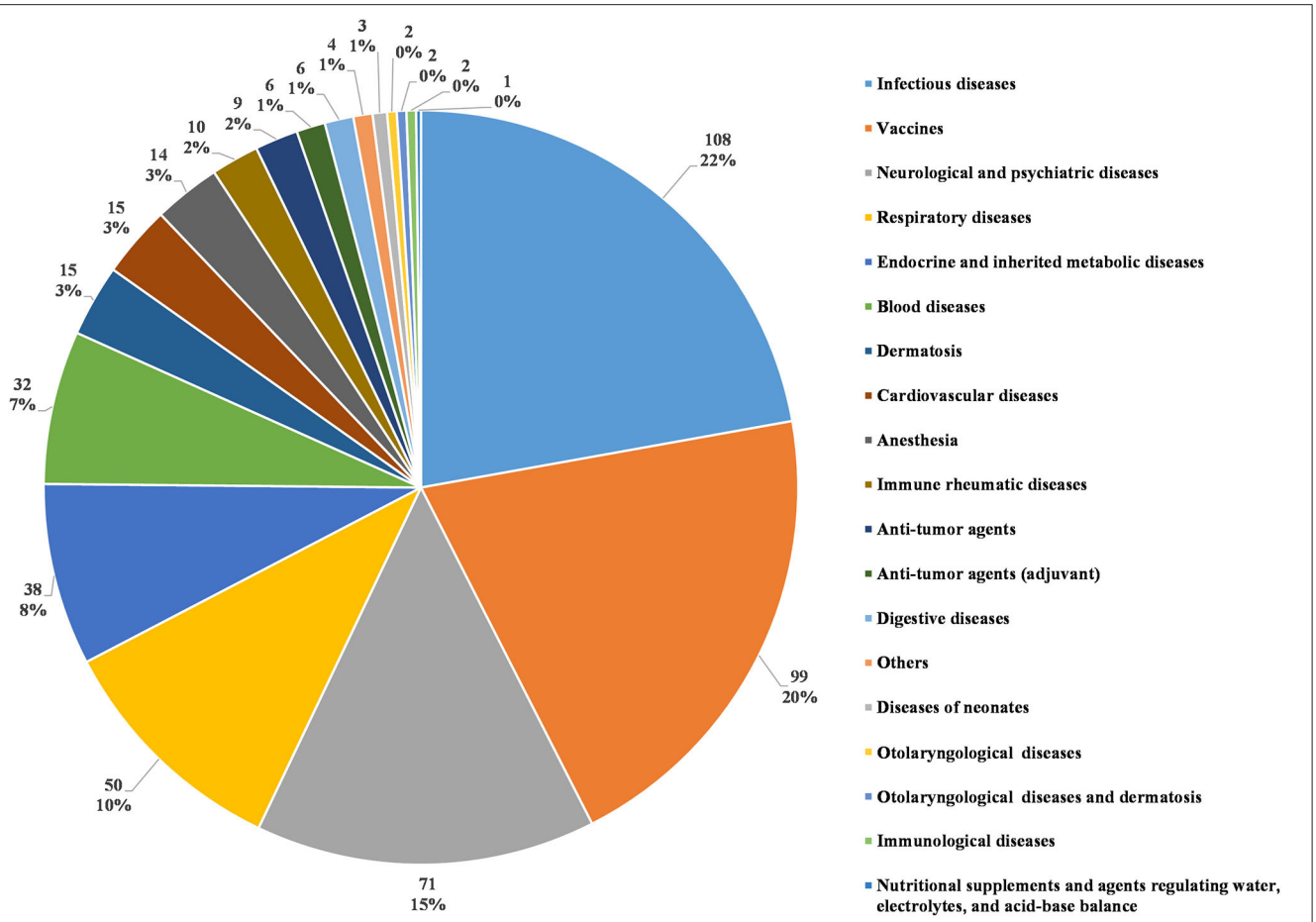

FIGURE 5 | Distribution of pediatric clinical trials by disease system.

Sponsors and Institutions

Sponsor

Of the 487 pediatric clinical trials conducted from 2009 to 2020, 378 trials (77.6%) were sponsored by pharmaceutical companies in China, while another 105 (20.3%) were sponsored by overseas and sino-foreign joint ventures. Only four trials (0.8%) were sponsored by research institutions in China (**Figure 9**). The domestic pharmaceutical companies most frequently conducted BE studies, with a total of 172 trials (45.5%). This was followed by Phase III trials, with 81 trials conducted (21.4%). The overseas and sino-foreign joint ventures most frequently conducted Phase III trials, with a total of 71 trials (67.6%). This was followed by Phase IV trials, with 14 trials conducted (15.2%) (**Table 9**).

Leading Institutions

From 2009 to 2019, 144 institutions participated in pediatric clinical trials in mainland China as leading unit institutions. Among these, 89 only participated in BE studies, and 17 (mainly local Centers for Disease Control and Prevention) only participated in studies on prophylactic biological products. East China had the highest number of leading unit institutions (49, 34.0%), North China had 34 leading unit institutions (23.6%), Central China had 27 (18.8%), South China had 11 (7.6%), Southwest China had 10 (6.9%), Northeast China had 8 (85.6%), and Northwest China had 5 (3.5%) (**Figure 10**).

DISCUSSION

Since children belong to a medically unique group, it is of great significance to protect their health. However, shortages of pediatric drugs are now a worldwide challenge, also experienced in China. Research on drug use in pediatric patients from 78 hospitals in seven locations in mainland China from 2013 to 2014 shows that drug types that can be used in pediatric patients only accounted for 31.04% of the drugs used, and drugs specifically designed for children only accounted for 0.7% (10). In addition, off-label drug use in the pediatric population in China is of great concern. A survey conducted by the Children's Hospital of Fudan University shows that 63.8% of pediatricians gave off-label prescriptions at least once and 92.45% of pharmacists dispensed off-label prescriptions at least once (11). Off-label drug use is common in the pediatric population at all ages. Owing to high costs and low profits, most Chinese pharmaceutical companies are reluctant to develop pediatric drugs and carry

TABLE 6 | Distribution of clinical trials by indications.

Indications	No. of trials	%
Epilepsy	39	10.1
Asthma	33	8.5
Influenza	24	6.2
Growth retardation in children or microsomia	24	6.2
HIV infection/chronic hepatitis B	22	5.7
HIV infection	19	4.9
Bacterial infectious diseases	14	3.6
Anesthesia	14	3.6
Hemophilia A	13	3.4
Chronic hepatitis B	11	2.8
Immune rheumatic diseases	10	2.6
Attention deficit hyperactivity disorder	10	2.6
Respiratory tract infections in children	9	2.3
Mucous sputum of respiratory tract	8	2.1
Hyperlipidemia	8	2.1
Acute lymphoblastic leukemia	7	1.8
Common cold and fever	6	1.5
Cough in children	6	1.5
Atopic dermatitis	6	1.5
Hemophilia	6	1.5
Adjuvant chemotherapy	5	1.3
Schizophrenia or bipolar disorder	5	1.3
Total	**299**	**77.1**

out the relevant trials. Therefore, low motivation for pediatric drug development and a lack of pediatric clinical trials may be the major causes of the above-mentioned challenges. Through a development process evaluation of the quantity and quality of pediatric drug clinical trials in China in the past decade, and considering the relevant policies issued by the Chinese government, we further analyzed and discussed the gains and losses of the development experience of pediatric drug clinical trials in China in the past decade.

Pediatric Clinical Trials and Drug R&D Are Encouraged by National Policy

To encourage the development of pediatric drugs and ensure children's access to such drugs, the Chinese government has launched a package of incentive policies and regulations over the past decade (**Figure 11**).

In 2011, the State Council issued the National Programme for Child Development in China (2011–2020), which proposed to "encourage the development and manufacture of drugs specifically for pediatric use."(12) Since 2019, the Significant New Drugs Development Project under the 11, 12, and 13th Five-Year Plans has continuously supported the development of pediatric clinical trials. In 2014, six government departments, including the former National Health and Family Planning Commission, jointly issued Opinions on Ensuring the Safety and Availability of Pediatric Medicines, which recommended the establishment of special approval tracks for pediatric drugs and encouraged research and development (R&D) and clinical trials in the pediatric population, to ensure the availability of pediatric drugs (13). Moreover, in 2016 the State Council issued Guiding Opinions on Promoting the Healthy Development of the Pharmaceutical Industry. It suggested that it is of vital importance to develop appropriate dosage forms and new products based on the physiological characteristics of children to meet pediatric clinical needs (14). In 2017, the General Office of the Communist Party of China Central Committee and the State Council released Opinions on Deepening the Reform of the Review and Approval System to Encourage Innovation of Drugs and Medical Devices.

In this document a period of data exclusivity for clinical trials on pediatric drugs was proposed. The National Essential Medicines List, updated in 2018, added 22 pediatric drugs. Encouragingly, in the 2018 edition of the list, a separate category was introduced for pediatric drugs for the first time, which implies that more pediatric drugs will be incorporated into the list in the future (15). The Drug Administration Law of the People's Republic of China, amended in 2019, requires the government to take effective measures to encourage the R&D and innovation of pediatric drugs (16).

Against this backdrop, the National Medical Products Administration (NMPA), as the regulatory authority over drug development and clinical trials in China, has launched a series of policies to encourage the development of pediatric drugs and relevant trials **(Figure 11)**. In 2013, the NMPA issued Opinions on Continuing the Reforms in Drug Review and Approval and Further Encouraging Pharmaceutical Innovation, which grants priority review to innovative and generic pediatric drugs with proper formulations and dosages based on the physiological characteristics of children (17). In 2014, the NMPA issued the first technical guideline on pediatric clinical trials, guiding investigators through how to conduct pharmacokinetic studies on the pediatric population (18). In 2015, the NMPA issued the Notice on Policies of Drug Registration, Review and Approval, which proposed the establishment of a special review track for pediatric drugs with an accelerated review process (19). In 2016, the former National Health and Family Planning Commission, CFDA, and Ministry of Industry and Information Technology jointly issued the List of Pediatric Drugs Encouraged for R&D and Registration (the first batch). Since 2016, three batches of the list have been released, covering a total of 105 pediatric drugs (20–22). In 2018, the NMPA released the Notice on Adjustment of Review Process of Clinical Trials on Medical Devices, replacing the former qualification certification with a record-keeping management system. (23) In the same year, the Measures for Data Protection for Clinical Trials (Provisional) was issued, which granted a 6-year data exclusivity period to pediatric drugs to protect the interests of innovators (24). In 2019, the NMPA issued the Regulations for the Administration of Drug Clinical Trial Institutions, which officially changed the accreditation of drug clinical trial institutions to record-keeping management (25). Apart from government policies, a series of technical guidelines have been established since 2014, including the Guidelines for Pharmacokinetics Study in Pediatric Population, Guidelines

TABLE 7 | Classification system for registration of chemical drugs.

Classification	New classification	Definition/scope	Old classification	Definition/scope
Innovative drugs	Class 1	Innovative drugs which have never been marketed within or outside China: compounds with clear and new chemical structures; with pharmacological effects and clinical value, that can be put into clinical practice.	Class 1, 1.1	Drugs not marketed within or outside China: drug substances and preparations produced by synthesis or semi-synthesis methods.
			Class 1, 1.2	Drugs not marketed within or outside China: new effective monomers and their preparations extracted from natural materials or by fermentation.
Modified new drugs	Class 2, 2.1	Drug substances and preparations with obvious clinical advantages: optical isomers of known active ingredients, optical isomers produced by splitting or synthesis methods; esterification or salt formation of known active ingredients (including salts containing hydrogen bonds or coordination bonds); modification of acid radical, base, or metal elements of known active ingredients of salt drugs; or other non-covalent bond derivatives (such as complex, chelates, or inclusion compounds).	Class 1, 1.3	Drugs not marketed within or outside China: optical isomers of known drugs and preparations; optical isomers produced by resolution or synthesis methods.
			Class 4	Drug substances and preparations with modifications of acid radical, base, or metal elements of already marketed salt drugs, without influencing their pharmacological effects.
	Class 2, 2.2	Preparations of known active ingredients with new dosage forms (including new drug delivery systems), formulations or routes of administration; with obvious clinical advantages.	Class 2	Preparations not marketed within or outside China: with changes to route of administration.
			Class 5	Preparations with changes to the dosage form of products already marketed in China; no changes to routes of administration.
	Class 2, 2.3	New compound preparations of known active ingredients, with obvious clinical advantages.	Class 1, 1.4	Drugs not marketed within or outside China: fewer-component drugs obtained from already marketed multi-component drugs.
			Class 1, 1.5	Drugs not marketed within or outside China: new compound preparations.
	Class 2, 2.4	Preparations of known active ingredients, with new indications.	Class 1, 1.6	Preparations already marketed in China, with new indications added; new indications previously unapproved within or outside China.
Generic drugs	Class 3	Drug substances and preparations with the identical active ingredients, dosage form, strength, indications, route of administration, and dosage to innovative drugs that have been marketed outside China but not in China.	Class 3, 3.1	Drug substances and preparations marketed outside China, and/or preparations with changes to dosage form but not route of administration.
			Class 3, 3.2	Compound preparations marketed outside China, and/or preparations with changes to dosage form but not route of administration.
			Class 3, 3.3	Preparations marketed outside China, with changes to route of administration.
			Class 3, 3.4	Preparations already marketed in China, with new indications added; new indications already approved outside China.
	Class 4	Drug substances and preparations with the identical active ingredients, dosage, strength, indications, route of administration, and dosage to innovative drugs that have been marketed in China.	Class 6	Drug substances or preparations which already have national standards.
Imported innovative drugs	Class 5, 5.1	Imported innovative drugs (including drug substances and preparations) that have been marketed outside China.		
Imported non-innovative drugs	Class 5, 5.2	Imported non-innovative drugs (including drug substances and preparations) that have been marketed outside China.		

TABLE 8 | Distribution of pediatric trials by drug type.

Drug type	No. of clinical trials	No. of clinical trials on drugs for pediatric use	%
Chemical drugs	303	43	14.2
Traditional Chinese medicines and natural medicines	16	12	75.0
Therapeutic biological products	69	30	43.5

for Clinical Trials in Pediatric Population, Guidelines for Extrapolation of Adult Medication Data to Pediatric Population, and Guidelines for Drug Development (Chemical drugs) in Pediatric Population (Tryout). These guidelines systematically analyzed the crucial problems existing in pediatric clinical trials and provide technical support for pediatric drug development (18, 26–28).

Increasing Pediatric Drug Clinical Trials and International Cooperation

Stimulated by these incentive policies, the number of pediatric clinical trials continued to increase from 2009 to 2019, with an average annual increase rate of 44.7%. The increase was especially significant after 2016, when a series of polices encouraging the development and approval of pediatric drugs were launched, various technical guidelines were released, and the record-keeping management system for clinical trial institutions and the default licensing system of clinical trials were implemented was adopted. Pediatric clinical trials conducted from 2016 to 2019 accounted for 73.7% of all the pediatric trials conducted over the past decade.

Since the ethical requirements and standards of pediatric clinical trials varied across different regions of China, it has been difficult to conduct multi-center clinical trials. In 2017, Opinions on Deepening the Reform of Review and Approval Processes to Encourage Innovation of Drugs and Medical Devices was issued, which requires that, once a multi-center clinical trial planned to initiate in China has obtained ethical approval from one leading unit institution, other member institutions shall conduct the review according to the review opinion to avoid repeated reviews (16). This has led to more multi-center clinical trials, and the data we collected confirmed this. According to our statistics, 43.0% of the pediatric clinical trials conducted after the release of the document have been multi-center ones. Subsequently, the NMPA issued the Decision on Adjusting the Relevant Matters Concerning the Registration and Administration of Imported Drugs, which lifted some of the restrictions on international multi-center clinical trials planned to initiate in China. The document stipulates that, when international multi-center clinical trials are completed, the sponsors can submit new drug applications in China directly (29). This greatly encourages foreign pharmaceutical companies to conduct clinical trials synchronously in China, which provides more opportunities for China to participate in international multi-center pediatric clinical trials. Our study shows that international multi-center pediatric trials began to increase significantly in 2017. The average number of international multi-center trials conducted from 2017 to 2019 is 14.1 times higher than that in the preceding years.

The Quality of Pediatric Drug Clinical Trials Needs to Be Further Improved

China has made remarkable progress in conducting pediatric clinical trials over the past decade. However, there remains a scope for improvement with respect to trial quality, as there are still deficiencies in pediatric trials in mainland China. These are mainly reflected in the following aspects.

Lack of Innovation, Rather Concentrated Research Areas, and Prevalent Repetitive R&D

Owing to the high costs of drug development and the relatively small scale of domestic pharmaceutical companies compared to some international ones, domestic pharmaceutical companies often lack the funding and capability to invest in innovative drugs. With the support of incentive policies, the R&D of innovative drugs in China has progressed, which is particularly obvious in areas like small-molecule targeted drugs for tumor treatment and immune checkpoint inhibitors. However, little progress has been made in pediatric drugs since it is harder to convert active pharmaceutical ingredients to final pharmaceutical products and takes longer to see investment return for pediatric medicines. Therefore, most domestic pharmaceutical companies still focus on pediatric generics with mature markets, as they require a lower budget and provide a quicker investment return.

Of the 487 pediatric clinical trials, BE studies accounted for 36.3% and only four of them were sponsored by overseas pharmaceutical companies. This directly reflects the release of the Generic Consistency Evaluation (Quality & Efficacy) by the State Council in 2016. This evaluation requires BE studies to be conducted on all solid-dosage oral pharmaceuticals to test the consistency between generics and the original product. Solid-dosage pharmaceuticals without BE studies can no longer be registered (30). Thus, since 2016, the number of BE studies has increased dramatically. In 2019, BE studies accounted for over half of all the pediatric trials, indicating that generics play a dominant role in pediatric trials.

Our study shows that, of the 303 pediatric trials on chemical drugs, 211 were for generics and 203 of these (96.2%) were sponsored by domestic pharmaceutical companies. In contrast, trials on innovative drugs sponsored by domestic companies were rare. In the 57 trials on innovative drugs, only four (7.0%) were sponsored by domestic companies, far fewer than the 53 trials on imported innovative drugs. In recent years, clinical trials on popular innovative drugs, such as JAK kinase inhibitors, monoclonal antibodies, gene splicing and modification drugs, and DNA repair drugs were carried out in China overwhelming by overseas companies. Consider monoclonal antibodies as an example, there were seven related trials, of which only one was sponsored by a company in mainland China while the rest were all sponsored and developed by overseas companies. Of the

TABLE 9 | Phases of clinical trials by different sponsors.

Sponsor	Phase I	Phase II	Phase III	Phase IV	BE study	Others	Total
Domestic pharmaceutical companies	38	30	81	31	172	26	378
Overseas and sino-foreign joint ventures	4	6	71	16	3	5	105
Domestic research institutions	1	0	1	0	2	0	4

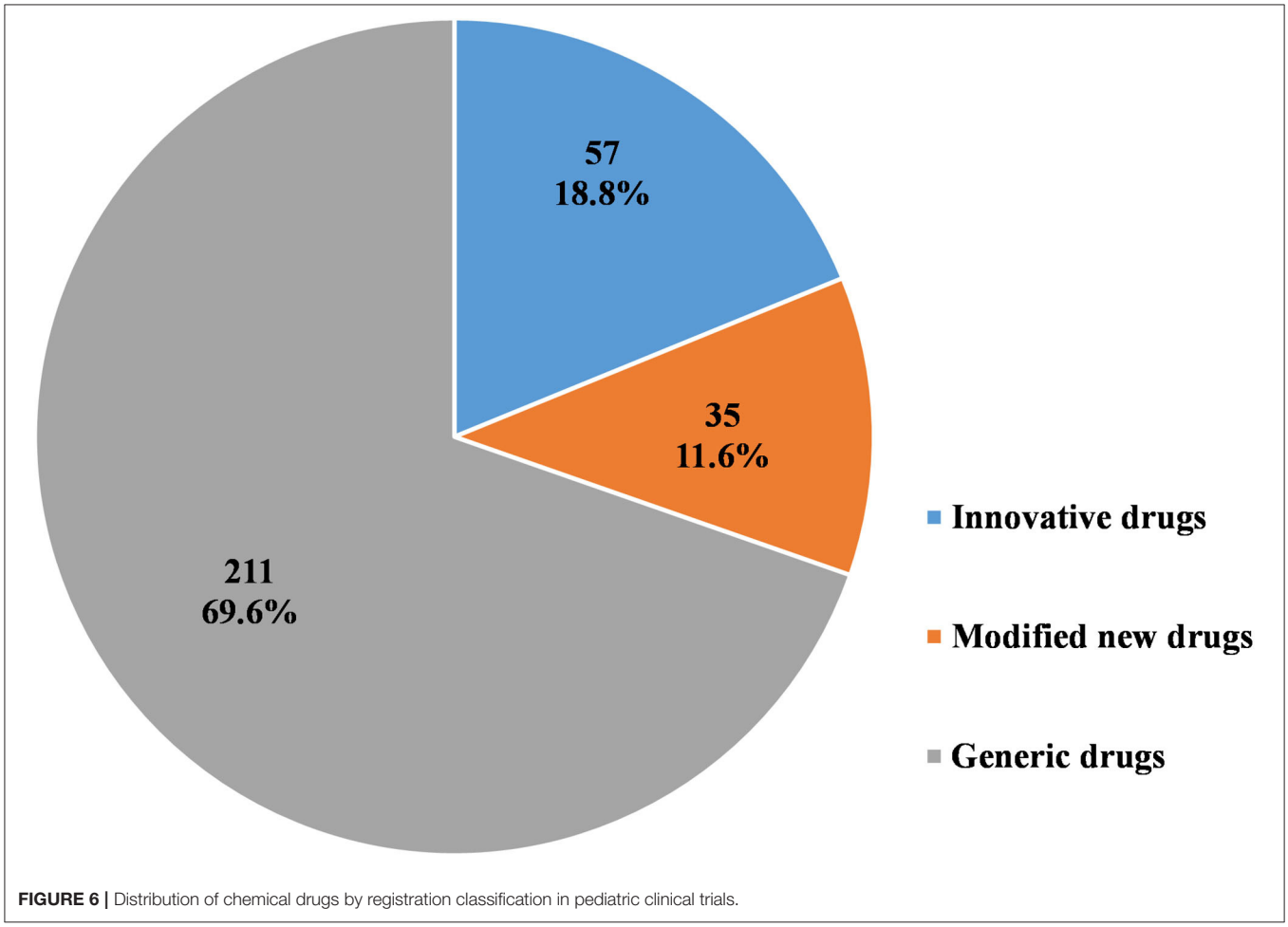

FIGURE 6 | Distribution of chemical drugs by registration classification in pediatric clinical trials.

25 trials on orphan drugs, nine were sponsored by domestic companies, of which only two involved modified new drugs while the rest all involved generics. In contrast, of the 14 trials sponsored overseas, only one was on a generic drug while the others were all on innovative or modified drugs.

Overall, pediatric clinical trials in China mainly focus on infectious, nervous, respiratory, and endocrine diseases and vaccines, research areas that are relatively mature with less R&D risk. In contrast, there were few trials on cancer, immune diseases, or cardiovascular diseases, research areas with no R&D model to follow and thus with a higher risk. However, cancer, immune diseases, and cardiovascular diseases are usually the main causes of death for children in China. (31) Excessive clinical trials concentrated in just a few therapeutic areas result in repeated research studies and limited types of new drugs. Our study found that only four different drugs were involved in the 27 trials on growth hormone, and four others in the 24 trials on antihistamines, giving an average of six to seven clinical trials investigating each drug. In addition, the average number of trials investigating each drug for antivirals, antiepileptics, and coagulation factors was 2.5–3. A total of 21 clinical trials on different dosage forms of montelukast sodium were registered, and as many as 30 trials investigated tenofovir-related single or compound preparations. Too many repeated and unnecessary clinical studies decrease the innovative capacity of pediatric trials in China, eroding the development environment for innovative drugs.

Notably, although there has been no breakthrough for domestic pharmaceutical companies in innovative drugs, the number of modified new drugs for pediatric use has increased

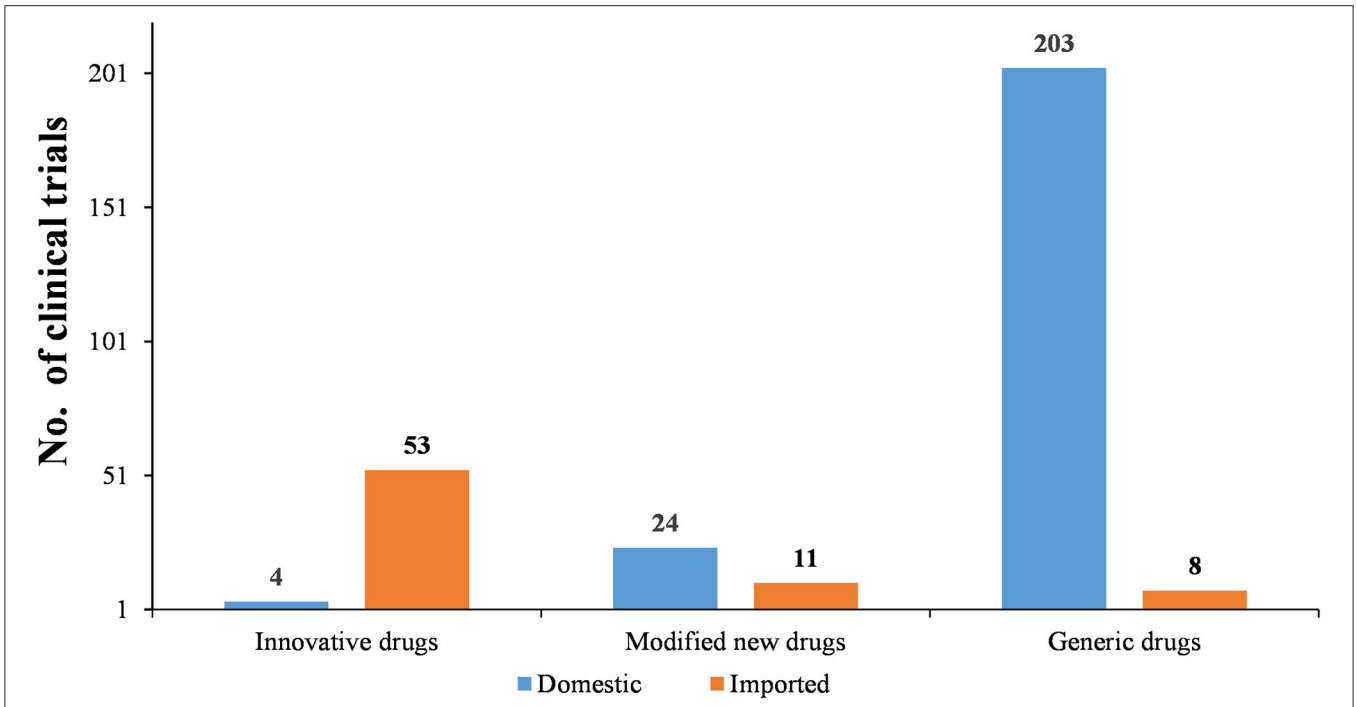

FIGURE 7 | Distribution of domestic and imported chemical drugs in pediatric clinical trials.

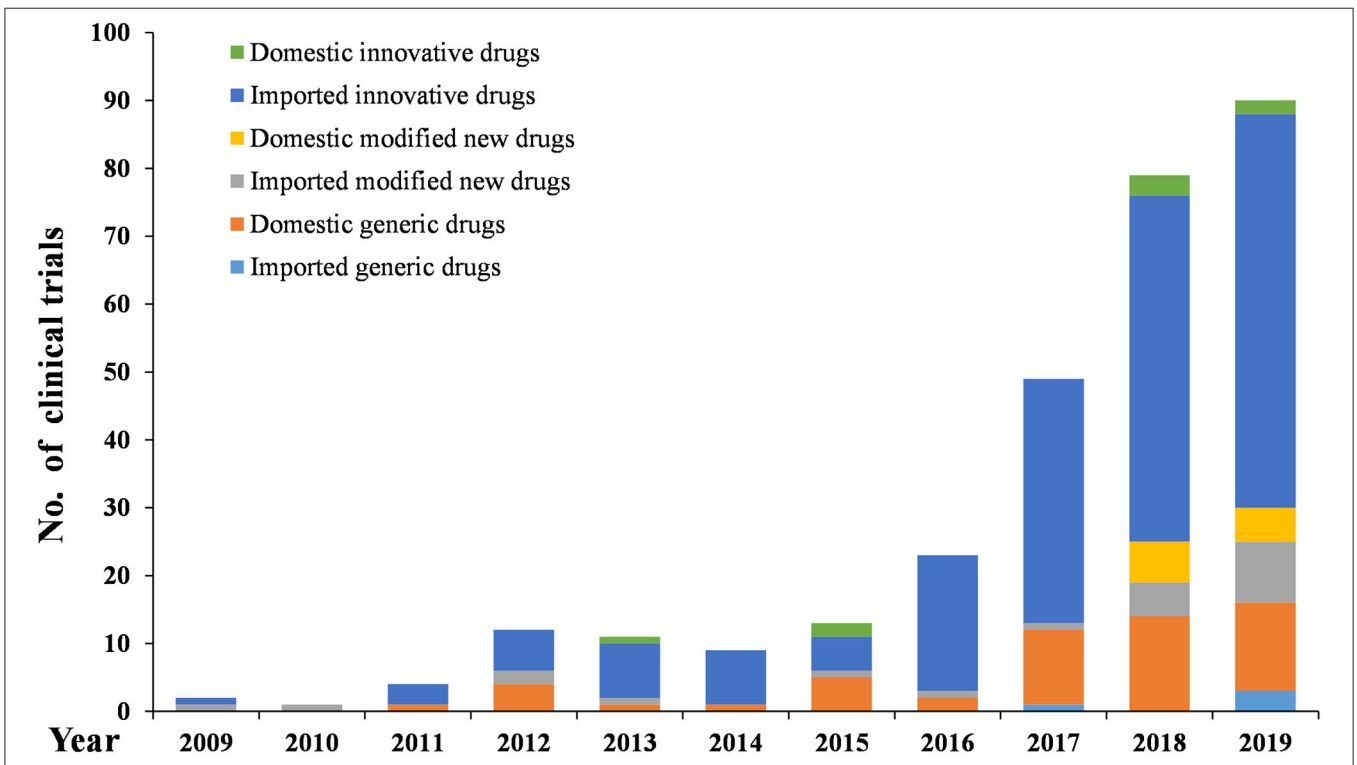

FIGURE 8 | Development trends of different types of chemical drugs in pediatric clinical trials.

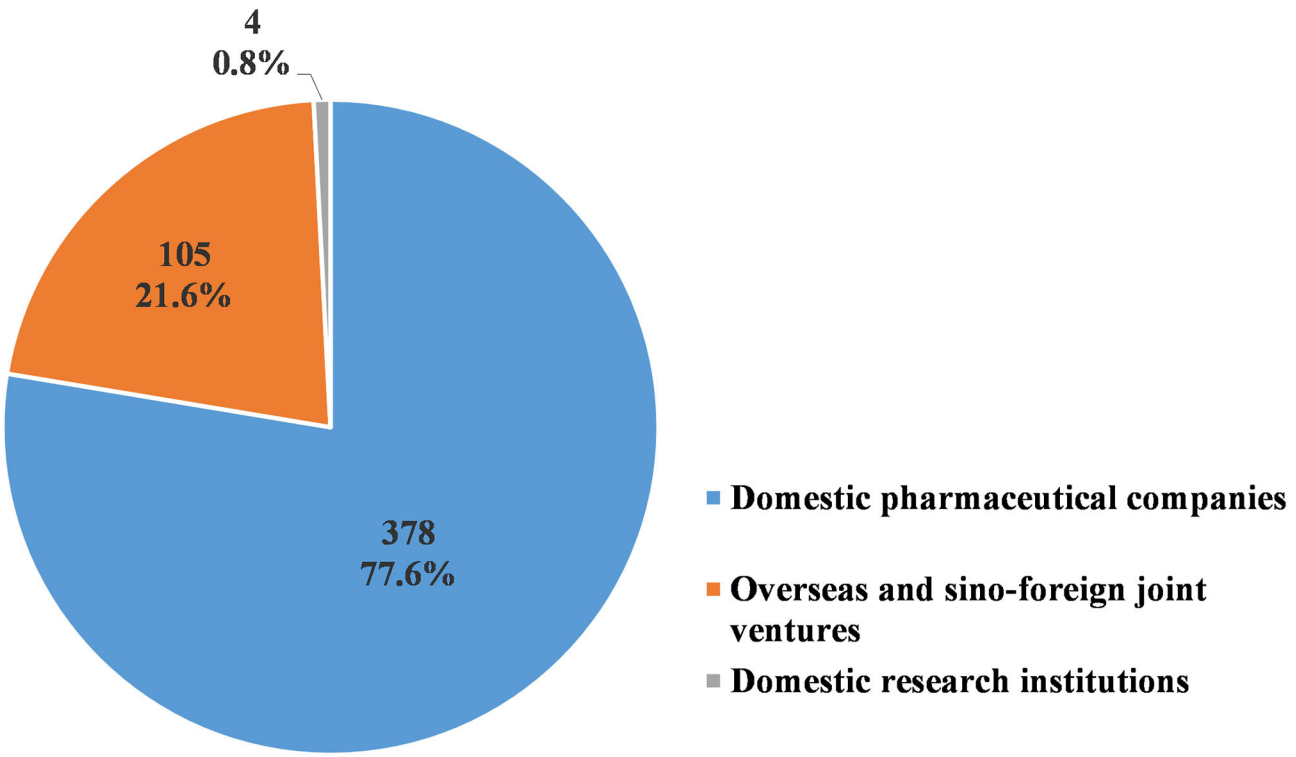

FIGURE 9 | Sponsorship of pediatric clinical trials.

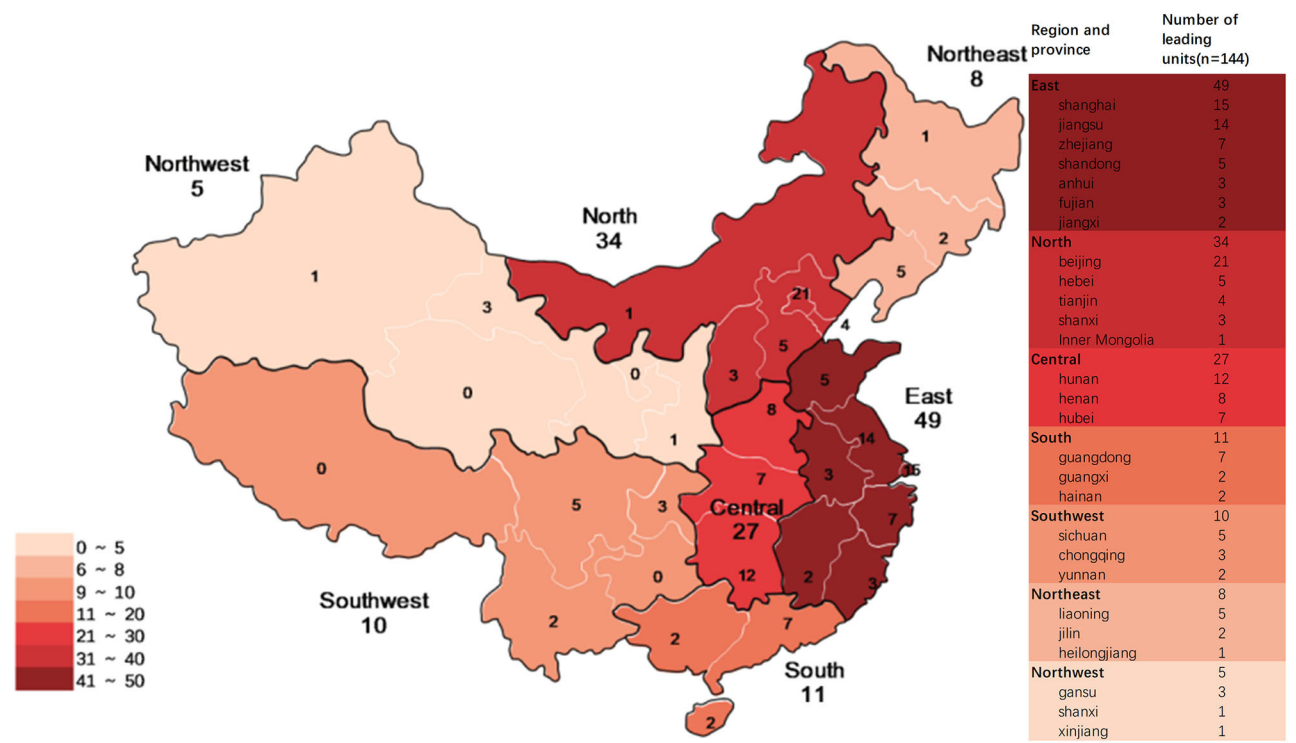

FIGURE 10 | Distribution of leading unit institutions in mainland China.

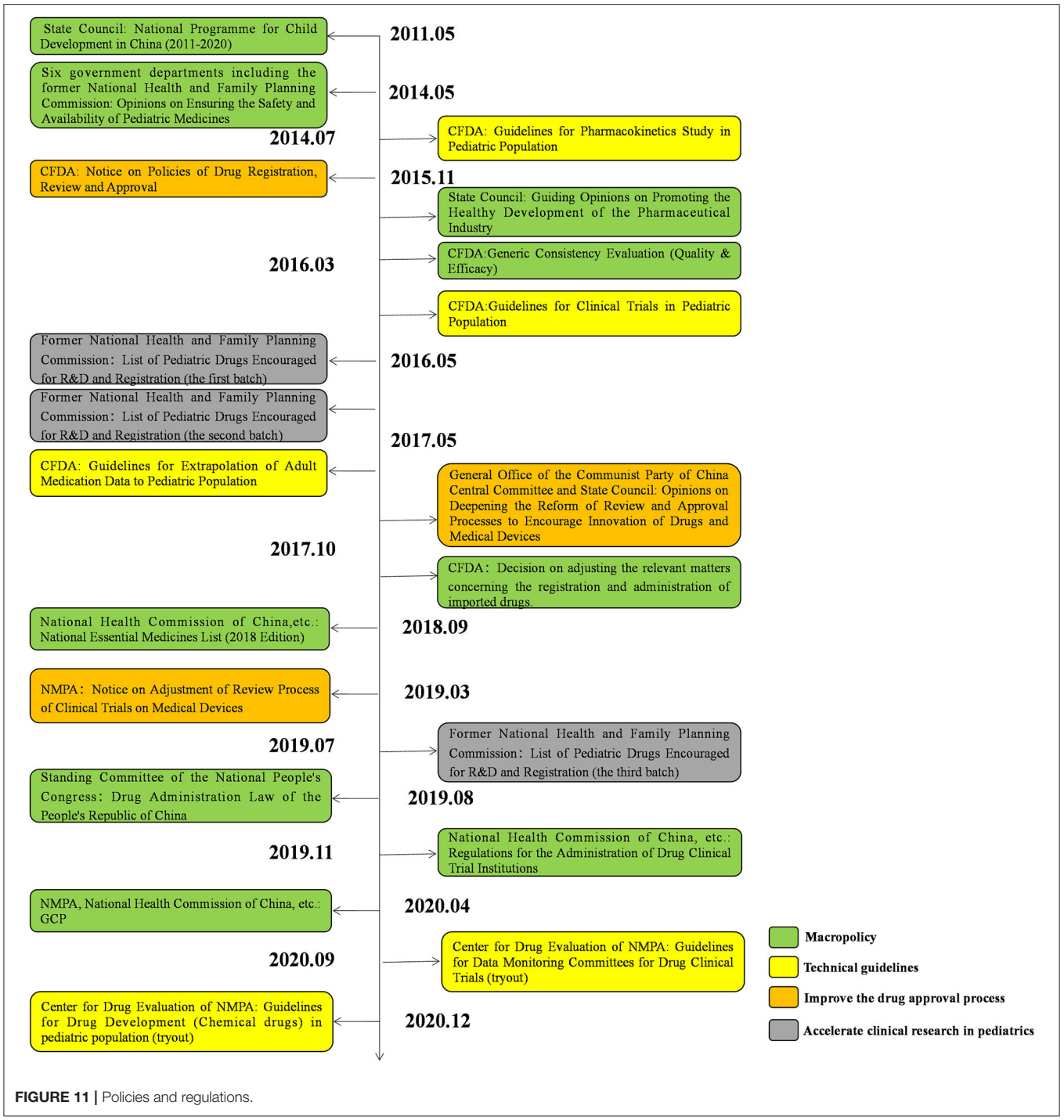

FIGURE 11 | Policies and regulations.

significantly since 2018. The number of trials on modified new drugs for pediatric use in 2018 and 2019 was 14, while the total number of such trials before 2018 was only nine. Modified new drugs improve or optimize the formulation, structure, or dosage form of original products, or add new indications. Compared to innovative drug trials, modified new drug trials, the development of which is also supported by national policies, focus more on "superiority". Modified new drugs have lower risks, higher success rates, higher investment returns, and longer product life cycles. Therefore, at the current stage, developing modified new drugs may be the best choice for companies mainly relying on generics and lacking innovative capacity.

Less Standardized Clinical Trials Design

At present, pediatric clinical trials in China follow the principles and standards of adult trials, regardless of trial design or

methodology. However, children have different physiological characteristics at various development stages, which indicates that pediatric trials, with higher potential safety risks, cannot be the conducted in the same manner as those of adults. According to the Annual Report for National Adverse Drug Reaction Monitoring (2019), there were 1.51 million cases of adverse drug reactions, of which children under the age of 14 accounted for 10.8% (32). It is therefore urgent to grant more attention to pediatric clinical trials from both ethical and scientific perspectives. Trial-related injury insurance can effectively lower safety risks and improve trial quality; however, the situation regarding this aspect in China is not optimistic.

Trial-related insurance plays an important role in protecting the interests of participants. It also serves as an important risk-sharing mechanism for sponsors and helps to avoid unnecessary disputes between participants, hospitals, and ethical committees. Moreover, trial-related insurance can reassure parents, alleviating concerns regarding the potential risks of clinical trials, which helps with the recruitment of child subjects. To date, China has not made any compulsory provisions that require sponsors to provide insurance. The newly revised Good Clinical Practice, published in 2020, only requires that "Sponsors should provide trial-related legal and economic insurance or guarantees to investigators and institutions" (33). The data we collected show that, for the 487 pediatric clinical trials, the overall insurance coverage rate was 44.8%, much lower than that of anti-tumor clinical trials (79.8%) (34). The insurance coverage rate of clinical trials sponsored by overseas companies (87.7%) was much higher than that of domestically sponsored trials (32.8%), and the coverage rate of international multi-center trials (88.5%) was also much higher than that of domestic trials (38.5%). The relatively low insurance coverage rate in China results from the absence of relevant regulations, weak public awareness of rights protection, and an immature commercial insurance industry, among other factors. However, the insurance rate of domestic pediatric trials has been increasing over the past decade, with an average rate of 42.7% from 2017 to 2019. In 2020, of the 11 domestic pediatric trials, eight have provided insurance, with a coverage rate of 72.7%. With the introduction of more relevant laws and improvements in public awareness of rights protection, the gap in trial-related insurance coverage between China and the international community can be narrowed further.

Uneven Distribution of Pediatric Clinical Trials

In addition, with government policies supporting pediatric drug development and clinical trials, the number of clinical institutions with pediatrics is also increasing. By December 2019, 158 clinical institutions had been approved to conduct pediatric trials. There was a surge in the number of clinical institutions with pediatric approval from 2017 to 2019. During this period, 91 new institutions were approved, accounting for 57.6% of all approvals. The surge may be owing to the issue of the Generic Consistency Evaluation by the CFDA in 2016.

Our study found that 61.8% of the pediatric clinical institutions only carried out BE studies. Pediatric clinical institutions in China still face two main challenges: First, there remains an insufficient number of clinical institutions with pediatric capacity, accounting for only 17.7% of all the clinical institutions by December 2019. Second, similar to the distribution of leading unit institutions, the distribution of clinical institutions with pediatrics is imbalanced, with most institutions in East China and North China, followed by Central China, South China and Southwest China, Northwest China, and Northeast China (in descending order). This difference does not reflect demographic factors or patient distributions, instead, indicate the uneven distribution of clinical medical resources in China. Thus, it is important for policy makers to coordinate the distribution of medical resources while acknowledging the leading role of some areas.

Shortage of Pediatric Drug R&D, Priority Review, and Approval Policies Have Not Yet Fully Played Its Role

Clinical trials are the basis for drug marketing, and a highly efficient review and approval system is an important guarantee for the successful marketing of pediatric drugs. With the rapid development of pediatric clinical trials in China and the implementation of relevant priority review and approval policies, the speed by which pediatric drugs are marketed in China has increased in recent years. However, compared with Japan, Europe, United States, and other regions, there is still further improvement to be made. Taking pediatric drugs marketed through the priority review and approval policy as an example, in the past five years, a total of 29 pediatric drugs, accounting for 8.5% among all priority review and approval drugs (343), have been rapidly approved in China for marketing through this policy. (35) In the past two decades, Japan has passed a similar policy named "public knowledge-based applications" *(Kouchi-shinsei* in Japanese*)*, and 74 pediatric drugs have been approved under this policy, accounting for 33.8% of all approved drugs (219) in the project, which is still higher than that (8.5%) in China. (36) EU data show that 25% of all new medicines released in the EU were aimed for children during 2007–2017 (37). Although there are no specific data on the marketing of pediatric drugs in the US, according to the statistics of the Food and Drug Administration, under the strong promotion of the *Best Pharmaceuticals for Children Act* and the *Pediatric Research Equity Act*, pediatric clinical trials based on the original trials have been re-conducted on as many as 792 drugs, and the pediatric sections on package inserts of 854 drugs have been revised. (38) Correspondingly, the 487 clinical trials included in our research involved only 198 drugs. However, we should also note that as increasing support has been provided by the Chinese government to the pediatric drug accessibility, research and development on and review and approval of pediatric drugs have been accelerated in recent years. In 2020, the NMPA approved a total of 26 pediatric drugs, with a yearly increase of 36.8%. In the first half of 2021, 14 pediatric drugs have been approved for marketing, and dozens of pediatric drugs and varieties for adding indications or usage and dosage are under review, among which 22 varieties have been included in the priority review and approval sequence (39).

LIMITATIONS

The raw data used in this study were derived from the only mandatory clinical trial registry platform in mainland China and we conducted a systematic review of the pediatric clinical trials registered on this platform over the past decade. However, the study also has some limitations. Although it is compulsory for sponsors to register information regarding their clinical trials on the platform and the information submitted are reviewed and verified by the CFDA, which ensures data integrity and reliability to a large extent, there was no such requirement before September 2013. That is, clinical trials completed before 2013 may not be included in the platform database. In addition, despite being required to submit the initial registration at least 30 days before the first subject is enrolled, the submission time of trials can differ. Therefore, this study defined the initial year of a trial by the date of its first ethical review, which differs from other similar papers in China.

CONCLUSIONS AND OUTLOOK

It was proposed in the National Programme for Child Development in China (2011–2020) that children are the future of mankind, and child health is the foundation of national health and an important guarantee for sustainable economic and social development (9). Therefore, the Chinese government has been committed to promoting the development of pediatric drugs. Over the past decade, China has made constant progress in improving the R&D environment for pediatric drugs and conducting more pediatric trials. However, there remains a wide gap in pediatric drug development between China and developed countries, and limitations such as study duplication, a lack of innovation, and poor research design remains a challenge in mainland China. Currently, China's national policies are continuously tilting in favor of innovative drugs. Influenced by medical reform policies such as volume-based procurement, generic consistency evaluation, and healthcare cost control, the profitability of generic drugs is decreasing annually and the transformation and upgrading of the pharmaceutical industry is imminent. Since the NMPA joined the ICH, China has taken actions to further harmonize with international regulatory standards to conduct safer, more effective, and higher quality clinical drug trials. Thus, it can be believed that, with improvements in regulatory policies and the innovative capacity of the pharmaceutical industry, China, as the world's second largest pharmaceutical market, will contribute more substantially to the global development of pediatric drugs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

W-WW, QW, and JX designed, planned, and led the study. W-WW, XJ, and HW undertook the literature search and with FC applied the eligibility criteria. W-WW, QD, G-dZ, and ML retrieved the clinical information from the Chinese Clinical Trials Registry and Information Transparency Platform. W-WW, S-sW, M-mN, and Q-qL undertook data extraction. W-WW, XJ, and HW designed and applied the statistical methods utilized. W-WW, QW, and HW wrote the original draft of the paper. All authors participated in the preparation, review and editing process of this paper, and have approved the final article.

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REFERENCES

1. White Paper on the Investigation of Pediatric Drug Use Safety. (2016). Available online at: https://www.ruiwen.com/gongwen/diaochabaogao/99076.html (accessed April 30, 2020).
2. Li J, Yan K, Kong YT, Ye XF, Ge MM, Zhang CF. A cross-sectional study of children clinical trials registration in the world based on ClinicalTrials.gov establishment. *Chin J Evid Based Pediatr*. (2016) 11:3–7. doi: 10.3969/j.issn.1673-5501.2016.01.002
3. Zhang GD, Yang Y, Zhao RL. Characteristics Analysis of Pediatric Drug Clinical Trials Registered in Chinese Clinical Trial Registry. *China Pharmacy*. (2020) 31:2055–60. doi: 10.6039/j.issn.1001-0408.2020.17.02
4. Hao GX, Yuan XX, Guo W, Quan XY, Qi XJ, Wang TY, Zhao W. Paediatric drugs trials in China. *BMJ Paediatrics Open*. (2020) 4:e000618. doi: 10.1136/bmjpo-2019-000618
5. National Health Commission of the People's Republic of China. Chinese National Formulary. (2010). Available online at: http://www.nhc.gov.cn/cms-search/xxgk/getManuscriptXxgk.htm?id=45875 (accessed April 30, 2020).
6. National Medical Products Administration. Provisions for Drug Registration. (2020). Available online at: https://www.nmpa.gov.cn/xxgk/fgwj/bmgzh/20200330180501220.html (accessed April 30, 2020).
7. National Medical Products Administration. Reform Scheme of the Classification System for Registration of Chemical Drugs. (2016). Available online at: https://www.nmpa.gov.cn/yaopin/ypggtg/ypqtgg/20160309151801706.html (accessed April 30, 2020).
8. National Health Commission of the People's Republic of China. First List of Rare Diseases. (2018). Available online at: http://www.nhc.gov.cn/cms-search/xxgk/getManuscriptXxgk.htm?id=393a9a37f39c4b458d6e830f40a4bb99. (accessed April 30, 2020).
9. List of Reference on Rare Diseases in China. (2018). Available online at: http://www.cord.org.cn/. (accessed April 30, 2020).

10. Yiyun LI, Zhi'ang WU, Xin HU. Analysis of drug use in pediatric patients from 78 sample hospitals in 7 regions of China from 2013 to 2014. *China Pharmacy*. (2016) 27:4058–61. doi: 10.6039/j.issn.1001-0408.2016.29.07
11. Mei M, Wang L, Liu E, Li Z, Guo Z, Zhang X, Xu H. Current practice, management and awareness of pediatric off-label drug use in China-A questionnaire based cross sectional survey. *Chin J Evid Based Pediatr*. (2017) 12:289–94. doi: 10.1186/s12887-019-1664-7
12. People's Republic of China of State Council, National Health Commission of the People's Republic of China (NHCPRC). National Programme for Child Development in China (2011–2020). (2011). Available online at: http://www.nhc.gov.cn/fys/s7900/201108/0990d658c2a74a7dae622684d24b2985.shtml. (accessed April 30, 2020).
13. National Health Commission of the People's Republic of China. Opinions on Ensuring the Safety and Availability of Pediatric Medicines. (2014). Available online at: http://www.nhc.gov.cn/yaozs/s3581/201405/e51354d631944fa68aac0c4d9585f291.shtml (accessed April 30, 2020).
14. People's Republic of China of State Council. Guiding Opinions on Promoting the Healthy Development of the Pharmaceutical Industry. (2016). Available online at: http://www.gov.cn/zhengce/content/2016-03/11/content_5052267.htm (accessed April 30, 2020).
15. People's Republic of China of State Council. Opinions on Deepening the Reform of the Review and Approval System to Encourage Innovation of Drugs and Medical Devices. (2017). Available online at: http://www.gov.cn/zhengce/2017-10/08/content_5230105.htm (accessed April 30, 2020).
16. People's Republic of China of State Council. Drug Administration Law of the People's Republic of China. (2019). Available online at: http://www.gov.cn/xinwen/2019-08/26/content_5424780.htm (accessed April 30, 2020).
17. National Medical Products Administration. Opinions on Continuing the Reforms in Drug Review and Approval and Further Encouraging Pharmaceutical Innovation. (2013). Available online at: https://www.nmpa.gov.cn/zwgk/xwfb/20130226195001883.html (accessed April 30, 2020).
18. National Medical Products Administration. Guidelines for Pharmacokinetics Study in Pediatric Population. (2014). Available online at: https://www.nmpa.gov.cn/directory/web/nmpa/xxgk/fgwj/gzwj/gzwjyp/20140711112001393.html (accessed April 30, 2020).
19. National Medical Products Administration. Notice on Policies of Drug Registration, Review and Approval. (2015). Available online at: https://www.nmpa.gov.cn/directory/web/nmpa/xxgk/ggtg/qtggtg/20151111120001229.html (accessed April 30, 2020).
20. National Health Commission of the People's Republic of China. List of Pediatric Drugs Encouraged for R&D and Registration (the first batch). (2016). Available online at: http://www.nhc.gov.cn/yaozs/s3581/201605/b0ea217312314c5098d905094f7e67ee.shtml (accessed April 30, 2020).
21. National Health Commission of the People's Republic of China. List of Pediatric Drugs Encouraged for R&D and Registration (the second batch). (2017). Available online at: http://www.nhc.gov.cn/yaozs/s3581/201705/b9874725a6a04e2ebbc8a969a4604609.shtml (accessed April 30, 2020).
22. National Health Commission of the People's Republic of China. List of Pediatric Drugs Encouraged for R&D and Registration (the third batch). (2019). Available online at: http://www.nhc.gov.cn/yaozs/s7656/201908/9a10b2382fe94d84817d9044d90dda15.shtml (accessed April 30, 2020).
23. National Medical Products Administration. Notice on Adjustment of Review Process of Clinical Trials on Medical Devices. (2019). Available online at: https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20190401164701503.html (accessed April 30, 2020).
24. National Medical Products Administration. Measures for Data Protection for Clinical Trials (Provisional). (2018). Available online at: https://www.nmpa.gov.cn/directory/web/nmpa/xxgk/zhqyj/zhqyjyp/20180426171801468.html (accessed April 30, 2020).
25. National Medical Products Administration. Regulations for the Administration of Drug Clinical Trial Institutions. (2019). Available online at: https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20191129174401214.html (accessed April 30, 2020).
26. National Medical Products Administration. Guidelines for Clinical Trials in Pediatric Population. (2016). Available online at: https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20160307164401912.html (accessed April 30, 2020).
27. National Medical Products Administration. Guidelines for Extrapolation of Adult Medication Data to Pediatric Population. (2017). Available online at: https://www.nmpa.gov.cn/directory/web/nmpa/xxgk/ggtg/qtggtg/20170518163201802.html (accessed April 30, 2020).
28. Center for Drug Evaluation, National Medical Products Administration. Guidelines for Drug Development (Chemical drugs) in pediatric population (tryout). (2020). Available online at: http://www.cde.org.cn/news.do?method=largeInfo&id=b40a4d0fd292259b (accessed January 30, 2021).
29. National Medical Products Administration. Decision on adjusting the relevant matters concerning the registration and administration of imported drugs. (2017). Available online at: https://www.nmpa.gov.cn/yaopin/ypjgdt/20171010213601206.html (accessed April 30, 2020).
30. People's Republic of China of State Council. Generic Consistency Evaluation (Quality & Efficacy). (2016). Available online at: http://www.gov.cn/zhengce/content/2016-03/05/content_5049364.htm (accessed April 30, 2020).
31. Wu W, Tang Z, Chen J, Gao Y. Pediatric drug development in China: Reforms and challenges. *Pharmacological Research*. (2019) 148:104412. doi: 10.1016/j.phrs.2019.104412
32. Center for Drug Reevaluation, National Medical Products Administration. National Center for ADR Monitoring, China. Annual Report for National Adverse Drug Reaction Monitoring (2019). (2020). Available online at: http://www.cdr-adr.org.cn/tzgg_home/202004/t20200410_47300.html (accessed April 30, 2020).
33. National Medical Products Administration, National Health Commission of the People's Republic of China. Good Clinical Practice. (2020). Available online at: https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20200426162401243.html (accessed April 30, 2020).
34. Li N, Huang HY, Wu DW, Yang ZM, Wang J, Wang JS, et al. Changes in clinical trials of cancer drugs in mainland China over the decade 2009-18: a systematic review. *Lancet Oncol*. (2019) 20:e619–26. doi: 10.1016/S1470-2045(19)30491-7
35. Center for drug evaluation, NMPA, Report on drug Evaluation in 2020. (2021). Available online at: http://www.cde.org.cn/news.do?method=largeInfo&id=cb377a202489c901 (accessed Aug 16, 2021).
36. Maeda H, Fukuda Y, Uchida M. Assessment of drugs approved by public knowledge-based applications (*Kouchi-shinsei*) during the last two decades in Japan. *Clin Pharmacol Ther*. (2021). doi: 10.1002/CPT.2332
37. European Parliament and the Council of the European Union, State of Paediatric Medicines in the EU: 10 Years of the EU Paediatric Regulation. (2017). Available online at: https://ec.europa.eu/health/sites/default/files/files/paediatrics/docs/2017_childrensmedicines_report_en.pdf (accessed Aug 16, 2021).
38. U.S. FOOD&DRUG ADMINISTRATION.New Pediatric Labeling Information Database. (2021). Available online at: https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase (accessed Aug 16, 2021).
39. National Medical Products Administration.Jiao Hong emphasize in the drug trial center on-site office to commit to hard soul to do the children's medication review and approval, NMPA. (2021). Available online at: https://www.nmpa.gov.cn/yaowen/ypjgyw/20210726213505143.html (accessed Aug 16, 2021).

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ORIGINAL RESEARCH
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Process Evaluation of an Online SUpport PRogram for Older Hearing Aid Users Delivered in a Cluster Randomized Controlled Trial

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Objectives: To evaluate the process of implementing a web-based support program (SUPR) for hearing aid users in the Dutch dispensing setting in order to allow interpretation of the randomized controlled trial's results (positive effects on hearing-aid related outcomes; no effects on psychosocial outcomes).

Design: Measures: context of implementation, recruitment, SUPR's: reach, implementation fidelity, dose delivered, dose received, satisfaction, and benefit. Data collection: quantitative and qualitative.

Study Sample: One hundred thirty-eight clients (mean age 68.1 years; 60% male) and 44 dispensers completed questionnaires. Five clients and 6 dispensers participated in interviews and focus groups.

Results: Clients and dispensers were generally satisfied with SUPR's usefulness. SUPR-videos were watched by 7–37% of the clients. Around half of the dispensers encouraged clients to watch them or informed them about SUPR. Some clients found the SUPR-materials suboptimal, and changes in personnel and limited dispenser-training were barriers acting on a contextual level.

Conclusions: This study identified several factors that contributed to the success of SUPR. Others factors, acting on various levels (e.g., intervention material, dispensers, and implementation context), were suboptimal and may explain the absent psychosocial effects. The identified factors are important to consider in further development of SUPR, and in other web-based support programs.

Keywords: process evaluation, communication program, eHealth, hearing aid users, implementation, hearing aid dispensing practice, self-management

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INTRODUCTION

Hearing aid (HA) fitting is a central component of aural rehabilitation (AR) (1). HA use has been found to ameliorate the adverse psychological, social, and emotional effects of hearing loss, thereby improving health-related quality of life (2). Still, HAs cannot restore normal hearing levels (3), and residual activity limitations and participation restrictions often remain (4). This is an important

reason why a substantial percentage of HA users (i.e., 3–24%) use them <1 h per day or not at all (5–10). Other factors that contribute to low HA use include difficulties in handling and maintaining the HAs, and feelings of embarrassment and stigma associated with wearing HAs (11).

It has therefore been suggested that AR should use a holistic rather than a biomedical (or impairment) approach. This means that AR should include aspects that go beyond HA fitting, like support in the use of communication strategies, acceptance of hearing loss, and HA handling skills (3, 12). These aspects have been incorporated into several group and individual educational programs developed for adults with hearing loss and are typically offered as an addition to HA fitting (1). They usually provide a combination of training in communication strategy use, instruction in HA management, or counseling aimed at supporting the individual's emotional coping with the consequences of hearing loss (12). While educational group programs are often led by clinicians, individual programs are usually self-directed and supported by audiovisual or written materials (13). In recent years, a promising alternative to deliver these programs has emerged, i.e., *via* eHealth technologies (14). Delivery of communication programs *via* eHealth allows for services that can improve (cost-) effectiveness and access to hearing care (15), because they can be delivered at the intensity the patient prefers, in an automated fashion (with limited efforts for health care professionals), and with a wide reach (16).

An example of an effective web-based educational communication program is the online program by Thoren et al. (17). This program included self-study in hearing anatomy, HAs and communication strategies, professional online interaction, and online contact with peers. The program reduced hearing-related participation restrictions and activity limitations in a sample of experienced Swedish HA users who were recruited *via* local advertisements and the internet (17). More recently, the program was expanded with telephone support and tested in a clinical setting, i.e., in three Swedish hearing clinics (18). That study showed improvements in the use of communication skills at 6 months follow-up (18). Another example of a web-based program is that by Ferguson et al. (19), who created Reusable Learning Objects (RLOs, i.e., short interactive videos) covering information on HA care, communication strategies, and adaptation to wearing HAs. The program was found to be successful in improving HA use and practical HA skills in first-time HA users attending the Nottingham Audiology Service (19). Thus, these findings provide evidence for the effectiveness of web-based interventions for HA users. However, the effects have not yet been evaluated using a real-life research design, and the long-term effects (i.e., up to at least 1-year post-intervention) are unknown.

Our research team recently contributed to the development of a web-based SUpport PRogram (called SUPR) for adult (50+) HA users and their communication partners (CPs) to be offered in a hearing aid dispensing (HAD) setting in addition to a usual HA fitting trajectory. The CP could be any person the client communicates with on a regular basis, i.e., a partner, child, neighbor, or caregiver. SUPR's main aims are to increase HA users' use of communication strategies and a range of secondary outcome measures (see later). SUPR is based on the home education program by Kramer et al. (20), which was shown to be successful in improving quality of life, and communication strategy use at a 6-month follow-up. In 2015, SUPR was created in order to deliver the videos *via* the internet, and the home education program element was supplemented with HA instruction videos and peer testimonials. **Figure 1** displays each of SUPR's elements, along with the outcome measures and groups (person with hearing loss or CP) that each of them targeted. The primary outcome included the use of communication strategies by the HA user. All other measures were considered secondary outcomes. All measurement instruments can be reviewed in the effectiveness paper (see below). The full description of the developmental process of SUPR is reported in a lessons learned paper (21).

In a previous study (22), we reported on the effectiveness of SUPR through a cluster randomized controlled trial (cRCT), including 343 clients from 70 HAD practices. The design of the cRCT is described further in the following section (under Materials and Methods) and the study protocol (23). We found no differences in the course of the use of communication strategies between SUPR recipients and controls. For the secondary outcomes, also no effects were found on the psychosocial outcomes (e.g., personal adjustment to hearing loss), but SUPR recipients showed significantly higher self-efficacy for HA handling and HA satisfaction in the long term (i.e., at 1-year follow-up) than controls. Also, SUPR recipients had significantly greater HA use than the controls in the short term (i.e., immediately post-intervention). There were no differences in effects between first-time and experienced clients for any of the outcomes (22). In order to gain more insight into our trial's results and to provide guidance for future use of web-based communication programs like SUPR in clinical practice, we conducted a process evaluation (PE) alongside SUPR's cRCT. Although the PE results were briefly summarized in the lessons learned paper mentioned earlier (21), it did not include the full scope of the results, nor did it include any information on the methodology of the PE study. These aspects are explained in detail in the current paper.

Although an RCT is considered a proper design for establishing the effectiveness of an intervention, they are also criticized for being a "black box," since it can be difficult to understand why an intervention was a success or failure (24). More specifically, PE studies can help distinguish between implementation and intervention success (or failure), and point to aspects of the intervention that may need to be improved to increase its success. It is therefore generally recommended to perform a PE study alongside an RCT (25, 26). To our knowledge, only two studies that reported on the effectiveness of a web-based AR intervention performed a PE (19, 27). Ferguson et al. (19) evaluated the implementation of RLOs, by assessing accessibility and adherence to, and uptake and acceptability of, the RLOs. A key finding was that all seven RLOs were watched by over 90% of the HA users enrolled (*adherence*) and these were rated as highly useful (*acceptability*). Based on these positive results the authors considered the RLOs a valuable supplement to usual HA care. Recently, Ratanjee-Vanmali et al. (27) conducted a PE to evaluate uptake, patient experience, and satisfaction of a hybrid (web-based and face-to-face) hearing health service model for

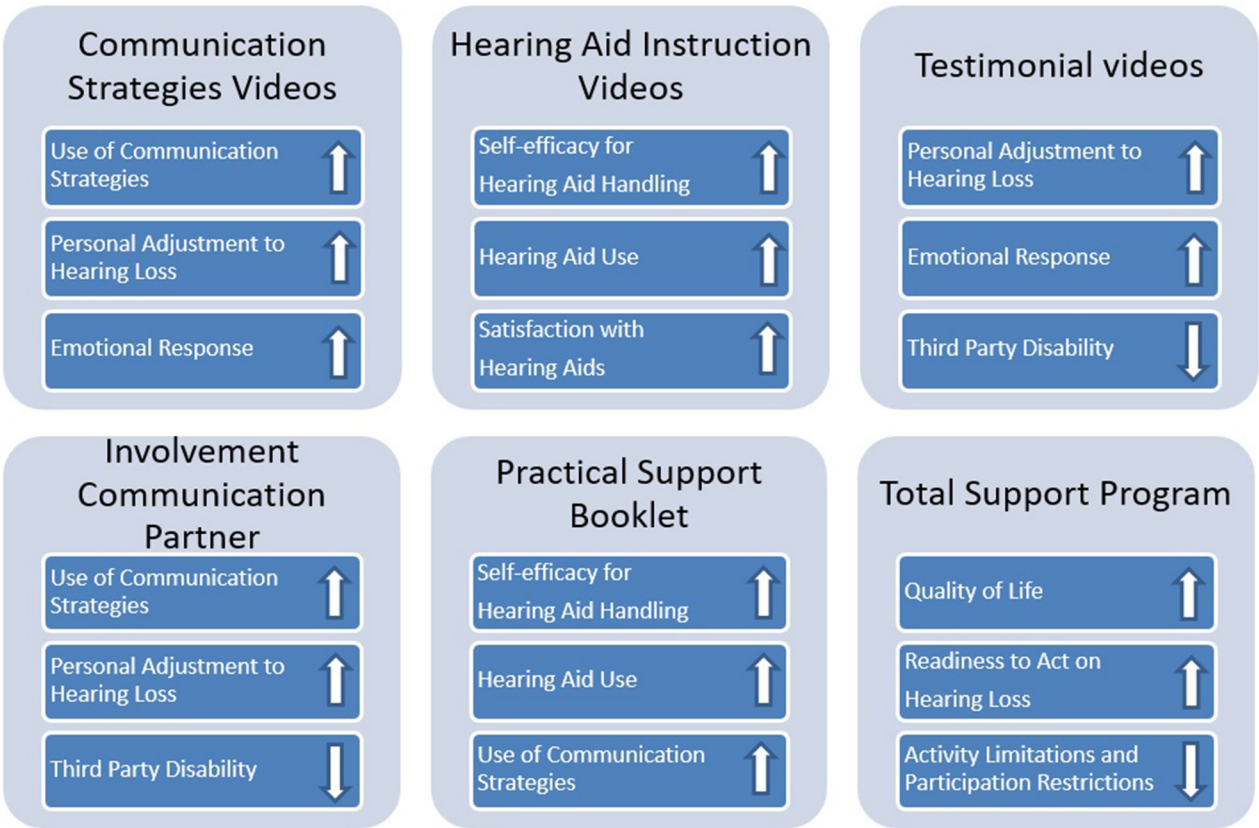

FIGURE 1 | Links between the different SUPR elements and outcome measures. An "up" arrow indicates that the element aimed to improve the particular behavior or appraisal, while a "down" arrow indicates that it aimed to reduce the particular hearing disability.

adult patients with hearing loss. Positive patient experiences and satisfaction were measured, demonstrating the potential of the hybrid service model in clinical practice.

The aim of this PE study was to evaluate the perspectives of SUPR users (clients) and SUPR implementers (HA dispensers; henceforth: dispensers) on eight components, based on Linnan et al. (28) PE framework. These components included: (1) *context* (aspects influencing intervention implementation), (2) *recruitment* (procedures used to attract potential participants), (3) *reach* (target population participating in the intervention), (4) *dose delivered* (components of the intervention delivered to participants), (5) *dose received* (participants' use of and engagement with the intervention materials), (6) *fidelity* (quality of intervention implementation), (7) *satisfaction* with the intervention, and (8) *perceived benefit* of the intervention materials.

MATERIALS AND METHODS

cRCT Description

A full description of the methods and results of the cRCT is reported elsewhere (22, 23). The study was approved by the Dutch Institutional Review Board of the VU Medical University Center Amsterdam. In brief, 34 HAD practices were randomized to the control arm and 36 to the intervention arm. Between February and September 2016, dispensers of these HAD practices recruited clients who were about to enter an HA evaluation period. In total, 343 participants (mean age 68.1 years; SD 8.5; 60% male) were included, and all provided online consent to participate in the study. cRCT outcomes were measured *via* an online survey platform at baseline (T0, when participants had not yet obtained HAs), immediately after SUPR completion (T1, this was 6 months after the client had purchased HAs), 6 months after SUPR completion (T2), and at 12 months after SUPR completion (T3).

Intervention Description: Care as Usual (Control) and SUPR (Intervention)

Care as Usual (Control)

The control group received care as usually provided in the HAD company, i.e., HA fitting only. Care as usual included four appointments with the dispenser. In the first appointment, a screening pure tone audiogram (air conduction only) was performed and the client's goals and wishes related to use of the HAs were discussed. Additionally, clients were advised to appoint a CP and bring them along to the subsequent appointments. The next appointment included full audiometric assessment (i.e., pure tone audiometry including air- and bone conduction and speech audiometry). Based on a protocol

as described by Dreschler and de Ronde-Brons (29), the HAs best suited for the client were selected and fitted immediately (if in stock) or at a subsequent appointment. Once the HAs were fitted, the dispenser demonstrated how to insert and clean the HAs and how to change the batteries. This was followed by a HA trial period of ∼4 weeks. In this period, the client could decide whether or not to purchase the HAs. If so, a next "purchase appointment" was scheduled. Based on the client's needs, fine-tuning appointments were scheduled during the trial period or after the purchase. Clients were also able to visit the HAD practice every working day during the "service-hour" (4–5 pm), to have problems or questions related to their HAs addressed.

SUPR

A full description of the development and implementation of SUPR is described in Meijerink et al. (21). In brief, SUPR is an educational support program consisting of the following elements:

- Practical Support Booklet, which clients received at their first appointment with the dispenser. Clients were asked to take notes related to their specific goals and needs and to describe their experiences with the HA. Additionally, the Booklet contained tips and information on HA use and maintenance, and tips for using communication strategies.
- Seventeen emails in total were delivered over 6 months. The email delivery schedule is presented in **Table 1**. Eleven emails contained links to educational videos, four contained written communication tips, and two covered information on how to contact the HAD practice customer contact center (see point 3). There were three types of videos: (1) three instruction videos with training modules on the use and maintenance of HAs; (2) five videos with training modules on communication strategies and personal adjustment. These videos demonstrated the difficulties that the main character (a person with hearing loss) experienced in daily life, and how he could successfully counter them by using communication strategies; (3) three testimonials in which peers talked about their experiences with their hearing loss and HAs.
- The option to contact the HAD practice customer contact center *via* email. In email 12 and 16, clients were asked to share their opinion regarding their HAs and their progress with SUPR.
- Involvement of a CP. Similar to the clients in control group, clients were advised to appoint a CP and bring him/her along to all appointments. Clients were additionally instructed to actively involve their CP as much as possible throughout SUPR, for instance by watching the educational videos together. CPs were also encouraged to use the Practical Support Booklet to write down their goals and experiences with the HAs of their loved ones.

TABLE 1 | Email delivery schedule of SUPR's online elements.

Phase	Time	Email	Topic
Trial period	Week 1	1	Explanation of SUPR (no link)
	Week 2	2	Link to testimonial video: "First experiences with HAs"
	Week 3	3	Link to instruction video: "How to insert HAs"
	Week 4	4	Link to testimonial video: "Together, we hear more"
Purchase of HA	Week 5	5	Link to tips on how to maintain your HAs (text only)
	Week 6	6	Link to instruction video: "How to make life easier and safer – Assistive listening devices"
	Week 7	7	Link to video on communication strategies and personal adjustment: "The Conversation"
	Week 9	8	Link to instruction video: "Maintenance and cleaning of your HAs"
	Week 11	9	Link to video on communication strategies and personal adjustment: "The Birthday Party"
	Week 13	10	Link to communication tips (text only)
	Week 15	11	Link to video on communication strategies and personal adjustment: "On the Streets"
	Week 17	12	Contact with the HA dispenser
	Week 19	13	Link to video on communication strategies and personal adjustment: "At the Doctor's"
	Week 21	14	Link to testimonial video: "Inspired by others"
	Week 23	15	Link to video on communication strategies and personal adjustment: "The Meeting"
	Week 25	16	Link to compilation of tips and contact with the HA dispenser
	Week 27	17	Goodbye and thank you (no link)

SUPR, support program; HA, hearing aid.

Training of HA Dispensers

To deliver SUPR according to protocol, all dispensers completed an e-learning course and had to attend a 2-day live (in person) training. The aim of the e-learning course was to teach dispensers how to engage the CPs during the clients' appointments in the dispenser practice, and in SUPR. The aim of the first training day was to educate the dispensers about the content of SUPR (how it was developed and what components it covered), and to teach them how to explain the goal and importance of SUPR to their clients and CPs. During the second training day the dispensers practiced how to use the Booklet during a conversation with a client and his/her CP.

Data Collection and Analysis

We used a mixed-methods research design for this PE applying both quantitative and qualitative methods to collect data on the eight components which are specified in **Table 2**. Note that data collection only occurred among clients and dispensers who participated in the SUPR arm of the cRCT. The cRCT participants, and thus also the sample for the current study, included both first-time and experienced hearing aid users. However, because we did not find any differences in effects between first-time and experienced clients in the cRCT study (22), these groups were merged for the current study.

Quantitative Data Collection

Four sources for quantitative data collection were used:

1. PE questionnaires for clients (**Supplementary Material 1**) and dispensers (**Supplementary Material 2**). The

TABLE 2 | Description of the SUPR-intervention process evaluation parameters, the outcome indicators, and the data sources.

Parameter	Definition	PE outcome indicators	Data sources
Recruitment and reach	Recruitment of participants for the study and the proportion of the target population (clients in the intervention group) opting in to receive the SUPR-emails	• Number of invited clients for the SUPR-study • Reasons why clients declined to participate • % of clients consenting • % of clients meeting inclusion criteria • % of clients opting in to receive the SUPR-emails	• Logs of HA dispensers • Researcher records • Database of the HAD company
Context	Factors influencing the implementation of SUPR in the HAD practices	• Dispensers' barriers to and facilitators of SUPR's implementation • % of dispensers who followed the 2-day live-training • The extent to which dispensers: • indicated to have gained enough knowledge to be able to implement SUPR • felt they were sufficiently supported by the HAD headquarters • indicated to be motivated to carry out SUPR in practice	• Focus groups with dispensers • PE questionnaire for dispensers (item 5) • PE questionnaire for dispensers (items 5–7)
Fidelity	The extent to which dispensers executed SUPR as was intended by the developers	• The extent to which dispensers complied with the instruction to: • discuss the clients' goals and experiences written down in the Practical Support Booklet • inform them about SUPR • encourage clients to watch the videos	• PE questionnaire for dispensers (items 2–4)
Dose delivered	The extent to which the different materials of SUPR were delivered	• % of clients to whom the dispensers had handed out the Practical Support Booklet • % of SUPR emails that were delivered to the clients	• PE questionnaire for dispensers (item 1) • Database of the HAD company
Dose received	The extent to which clients actively engaged with, and/or used the intervention materials of SUPR	• *Booklet* • % of clients who received the Practical Support Booklet • The extent to which: clients used the booklet to: • write down their goals and experiences with the HAs • to obtain tips and information • *Videos* • % of clients in the intervention group who started to watch a video • % of clients who watched the full video (of those who started to watch the video) • Average viewing time per video • *CP* • % of clients who reported to have a CP • % of clients who reported to choose a CP to be involved in SUPR and appointments • The extent to which clients indicated their CPs to: • have watched the educational videos • have used the Practical Support Booklet	• questionnaire for clients (item 1) • PE questionnaire for clients (items 2 and 3) • Database of the HAD company and Quadia • Quadia • PE questionnaire for clients (item 6 and 7) • PE questionnaire for clients (items 8, 10, 14, 18)
Satisfaction	Clients' and dispensers' opinions about the different materials of SUPR	• The extent to which dispensers thought SUPR (in general) was useful • Opinions about the different materials of SUPR • The extent to which clients: • thought a particular material of SUPR was useful • would recommend a particular material of SUPR to family, friends, and colleagues • thought that SUPR was worth the trouble	• PE questionnaire for HA dispensers (item 12) • Focus group and interviews with clients and dispensers • PE questionnaire for clients (items 4, 5, 11, 12, 15, 16, 19, 20) • T1 questionnaire of the cRCT (IOI-AI, item satisfaction)
Perceived benefit	Clients' and dispensers' perceived benefit of SUPR	The extent to which clients thought SUPR: • was effective in terms of improving communication, adjustment to hearing impairment, and HA use • helped in a situation where clients most wanted to hear better • The extent to which dispensers thought SUPR was effective in terms of the clients' ability to improve their communication, adjustment to hearing loss, HA use, and the involvement of the CP in the HA trajectory	• PE questionnaire for clients (items 21–23) • T1 questionnaire of the cRCT (IOI-AI, item benefit) • PE questionnaire for dispensers (items 8–11)

SUPR, support program; HAD, hearing aid dispensing; HA, hearing aid; PE, process evaluation; CP, communication partner; cRCT, cluster randomized controlled trial; IOI-AI, International Outcome Inventory – Alternative Interventions (30).

questionnaires were specifically developed for this study. They are based on the PE questionnaires used by Gussenhoven et al. (31). PE data from clients were collected post-intervention. The follow-up questionnaires used in the cRCT were used for this purpose (i.e., the PE questions were added to the outcome measures collected for the cRCT). Recruitment and response rates are described under "Quantitative results, recruitment and reach." PE data from dispensers were also collected post-intervention. Dispensers of 35 practices allocated to the SUPR arm were invited to fill out the PE questionnaire for dispensers (one HAD was permanently closed at the time of the PE and hence 35 of the 36 practices participating in the cRCT contributed to this PE study). In total, 61 dispensers agreed to participate, of which 44 completed the PE questionnaire. Note that the number of dispensers was higher than 35, as in some practices more than one dispenser was active. A researcher of the study team (J.F.J.M) contacted all HAD practices in the SUPR group to invite the dispensers to fill in the PE questionnaire.

2. Logs of dispensers. Dispensers had to log the number of clients they had invited to participate in the cRCT during the recruitment period. These logs were used to compare them to the number of participants who were eligible and consented to participate. When clients declined to participate, the dispensers also had to log their reasons for decline.
3. Data on clients' online behavior using the HAD company database (a portal storing online client behavior) and the Quadia database (Quadia was the HAD company's supplier of online video content). For each SUPR email, the number of clients clicking the link to the videos' website was available. Note that a click on the link did not mean that these people also actually clicked on the video's "start video" button to watch it. The percentage of clients who started to watch a video relative to participants who clicked on the link in an email was provided by Quadia. By combining the data from the HAD company database and Quadia, we calculated the proportion of SUPR participants who started watching the videos, relative to the total number of participants in the intervention group. To illustrate, if 104 people out of the total of 180 participants in the intervention group clicked on the link in email 3 (HAD company database) and 64% of those 104 clicked on "start video" to watch the video (Quadia), the total proportion of people who started to watch the video linked was 37% [104*0,64 = 66.56. (66.56/180)*100 = 37%]. Note that in Quadia, start percentages were only available for the total HAD company customer database due to privacy reasons. Hence, the group of clients participating in the cRCT could not be selected as a separate sample. We therefore used the proportion of all clients who had clicked on the "start video" button in the period of the cRCT study (February–June 2017) as a proxy.
4. The "satisfaction" and "perceived benefit" items of the International Outcome Inventory – Alternative Interventions [IOI-AI (30)] administered at t1 in the cRCT study were used to assess satisfaction with, and perceived benefit of SUPR. The item scores ranged from 1 to 5, with higher scores indicating better outcomes.

Qualitative Data Collection

In total 96 clients were invited to participate in the qualitative part of the PE study (focus groups or individual interviews). These were clients living in the Dutch provinces Noord-Holland and Groningen. These provinces were chosen to allow variance in participants coming from more urban and rural provinces, respectively. The focus groups took place at a central location in these provinces. Focus groups were preferred, but due to a low response, individual interviews were offered as a secondary option. The invitations were sent by the researchers *via* email. Interested clients were called and informed about the study aims and procedures. In total, 5 clients agreed to participate. Three participated in a focus group, and 2 in individual interviews. Because we aimed to avoid a potential bias of cRCT study participants being influenced by their participation in the qualitative measurements (as data collection was still ongoing at that time), we only invited clients who had recently (<4 months ago) completed SUPR and also met all other in- and exclusion criteria applied in the cRCT (22), but who did not participate in the cRCT. Selecting these clients was possible because at that time, the HAD company had implemented SUPR in all their practices, except the ones participating in the control group of the cRCT.

All dispensers working in the practices allocated to the SUPR-arm were invited to participate in focus groups. Six dispensers agreed to participate and were divided over two focus groups (three participants each). Two focus groups (instead of one) were conducted in order to optimize the range of opinions that would be expressed. Similar to the recruitment of clients, dispensers were firstly approached by email, followed by a telephone call. No in- or exclusion criteria applied.

Semi-structured interview guides were used. Both the individual interviews and focus groups were started by the moderator (J.F.J.M) with the following open-ended question: "What do you think of SUPR?". This was done to probe issues emerging during the interviews. Subsequently, J.F.J.M. briefly explained and showed the SUPR elements to the participants, to refresh their memories and to facilitate further discussion. Also, neutral, encouraging probes were used (i.e., "Could you tell a bit more about that?", or "How was this for you?"). The individual interviews and focus groups took 30–60 min. An assistant took notes and observed the group process (focus groups only). The interviews and focus groups were audio-recorded and transcribed verbatim.

Quantitative Data Analysis

Questionnaire data were analyzed descriptively by calculating frequencies, percentages, and either means (M) and standard deviations (SDs) (for normally distributed scores), or medians (Meds) and interquartile ranges (IQRs) (for non-normally distributed scores). For all PE-questions with a five-point response scale ["totally disagree" (1) to "totally agree" (5)], the lowest (1) and highest (5), response options were converted into a three-point scale ["disagree" (1) to "agree" (3)]. This was done because the lowest and highest response options were rarely chosen. Data were analyzed using SPSS Statistics version 26.0.

Qualitative Data Analysis

Focus group and interview data were analyzed separately for clients and dispensers. Thematic analyses were applied following the six steps as defined by Braun and Clarke (32):

1. Familiarization with data. Transcripts were read multiple times and initial ideas were noted.
2. Generation of initial codes. Commonly occurring patterns across the data set were labeled. This was done by three researchers (J.F.J.M., M.P., and a research assistant) to increase reliability of labeling. Any disagreements were discussed until consensus was reached.
3. Searching for themes. Codes were grouped into potential themes and data (quotes of participants) relevant for that theme were gathered.
4. Reviewing themes. This involved checking the potential themes against the dataset. It included splitting, removing, or combining themes to determine if these properly fitted and explained the data.
5. Defining and naming themes. Step 4 was repeated until clear definitions and names for each theme could be generated.
6. Producing the report. This involved the creation of a story within and across themes to answer the research question.

RESULTS

Quantitative Results

Recruitment and Reach

Approximately 2,276 clients were invited to participate in the cRCT. This number is an estimation based on the reported number of invited participants by the practices that complied with the protocol to log the number of invitations. Five hundred clients (22%) enrolled themselves for the SUPR study *via* the registration webpage. The main reasons for clients to decline study participation were: not owning a device with an internet connection or an email account, not interested in the study, no time to fill in questionnaires, or perceiving it as too troublesome because of age/illness. Fifty percent ($N = 248$ clients) originated from practices allocated to the SUPR arm. Of these, 180 clients met all inclusion criteria and were included in the cRCT (73%; 180/248). Of these 180 clients, 166 (92%) confirmed their willingness to receive the SUPR emails and 138 of them (77%) completed the PE questionnaire. Baseline characteristics of these 180 cRCT and 138 PE participants are shown in **Table 3**. There were no statistically significant differences between the two groups for any of the characteristics, indicating that the PE sample was representative for the cRCT intervention group.

TABLE 3 | Characteristics of clients who participated in the quantitative part of the PE (column 1) and in the trial (intervention arm only, column 2).

	PE participants ($n = 138$)	cRCT participants ($n = 180$)
Male	83 (60)	108 (60)
Age in years, mean (SD)	68.1 (8.0)	68.1 (8.4)
Marital status		
Married	101 (73)	130 (73)
Cohabiting	8 (6)	9 (5)
Widowed	16 (12)	24 (14)
Divorced	7 (5)	7 (4)
Single, never married	6 (4)	7 (4)
Living situation		
Living together with other people	112 (81)	144 (81)
Living alone	26 (19)	33 (19)
Educational level		
Low	29 (21)	38 (22)
Middle	97 (70)	123 (70)
High	12 (9)	16 (9)
Paid job		
Yes	25 (18)	39 (22)
No	113 (82)	138 (78)
Country of birth		
The Netherlands	127 (92)	162 (92)
Other	11 (8)	15 (9)
Better ear average hearing level in dB HL, mean (SD)	42.8 (10.8)	43.0 (11.7)
Type of client		
First-time HAs	90 (65)	116 (64)
Replacement HAs	48 (35)	64 (36)

Values indicate numbers (%) of participants unless stated otherwise.
PE, process evaluation; cRCT, cluster randomized controlled trial; SD, standard deviation; dB HL, decibels hearing level averaged across 1, 2, and 4 kHz; HA, hearing aids.

Context

The PE questionnaire results showed that all dispensers indicated to have followed the 2-day training. Of them, 61% agreed that enough *knowledge* was gained during the training in order to be able to adequately implement SUPR, against 34% who disagreed and 5% who were neutral. Thirty-nine percent agreed that sufficient *support* was provided by the HAD headquarters for them to do so (against 7% who disagreed and 52% who were neutral). Eighty-four percent of the dispensers indicated that they were motivated to carry out SUPR (against 5% who disagreed and 11% who were neutral). Ninety-three percent reported preferring to continue with SUPR in the future (against 2% who disagreed and 5% unwilling to share their opinion).

Dose Delivered

In all, 84% of the dispensers reported to have provided the Practical Support Booklet to at least 70% of their clients; 11% reported to have provided the Practical Support Booklet to 50 or 60% of their clients and 5% could not remember to how many clients they had provided the Booklet. The most frequently reported reason for not handing out the Booklet was: "forgot to hand it out." Regarding the dose delivered of the emails: all 17 emails were delivered to at least 97% of the clients.

Dose Received

Practical Support Booklet

In all, 78% of the clients reported to have received the Practical Support Booklet, against 8% who had not and 15% who could not remember. **Table 4** shows the number of clients who used the Practical Support Booklet to obtain tips and information or to write down goals and experiences with their HAs. The main reason to not (always) write down goals and experiences and to not (always) read the tips and information was "no interest."

Educational Videos

Figure 2 presents the percentage of cRCT participants who started to watch the educational videos, i.e., hit the "start video" button *via* the link provided in the SUPR emails. Videos linked to in email 2 (testimonial video "Your first experience with a HA"), 3 (instruction video "How to insert HAs"), and 8 (instruction video "Maintenance and cleaning of HAs") were watched most often (28, 37, and 24% of the participants started to watch, respectively). The main reason to not have watched all instruction videos (as reported in the PE-questionnaire) was: "I already knew how to handle my HA and/or what kind of assistive listening devices there are." The main reason to not watch (all) videos on communication strategies and the testimonial videos was "no interest." **Figure 2** shows that overall, with every next email, the proportion of participants watching the video decreased. **Table 5** shows the average viewing time per video (column 1), the total video length (column 2), and the percentage of participants who watched the videos until the end (column 3). In general, the percentage of participants watching the entire video was lower for lengthier videos.

TABLE 4 | Use of the practical support booklet among PE participants who indicated having received it ($n = 107$) and the extent to which dispersers ($n = 44$) executed the intervention as was intended.

	Never	Sometimes	Always	I do not know (anymore)
PE participants	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Used the Booklet to obtain tips and information	17 (16)	66 (62)	20 (19)	4 (4)
Used the Booklet to write down goals and experiences	29 (27)	45 (42)	26 (24)	7 (7)
Dispensers	7 (16)	16 (36)	21 (48)	0
Used the practical support booklet to discuss the clients' goals and experiences				
Encouraged clients to watch educational videos	8 (18)	16 (36)	19 (43)	1 (2)

Involvement of the CP

In all, 73% of the clients indicated to have a CP and 72% of them had appointed a CP to attend the appointments and be involved in SUPR. Fifteen percent of the clients indicated that their CPs had used the Practical Support Booklet "always" to read tips relevant to them, 35% indicated that their CP had "never" used it, and 35% indicated that their CP "sometimes" used it. Fourteen percent of the clients had forgotten whether or not their CP had used the Booklet. **Table 6** shows how clients assessed the involvement of their CP in watching the educational videos. Note that this was only assessed in clients who had indicated to have watched at least one educational video in each category of videos.

Fidelity

Table 4 shows the number of dispensers who used the Practical Support Booklet to discuss clients' goals and experiences and encouraged clients to watch the online videos. Dispensers' main reason to not (always) use the Booklet was "clients do not fill in their goals and experiences." The most frequently reported reason for not (always) encouraging clients to watch the videos was "felt no need for it because clients also watch the videos without my encouragement." In all, 58% of the dispensers declared they had explained their clients the goals of the educational videos. The remaining dispensers had: "not addressed them or only asked for their clients' email address to tell that emails containing links to videos would be sent" (28%),

FIGURE 2 | Percentage of cRCT participants in the intervention group ($n = 180$) that started to watch the educational videos (hit the "start video" button) *via* the link provided in the SUPR emails.

"only asked for the email address" (6%), or "had not told anything about the online part of the intervention" (8%).

Satisfaction

Table 7 shows the numbers and percentages of clients who agreed, disagreed, or were neutral, with regard to the usefulness of the different SUPR elements. The mean score on the question asking whether clients would recommend the Practical Support Booklet to others was 4.9 (SD= 3.2) on a rating scale ranging from 0 (not likely) to 10 (extremely likely). For the educational videos the means ranged between 5.7 (instruction videos) and 6.1 (testimonial videos) (SDs 2.7–3.0). The mean score of the IOI-AI "satisfaction" item immediately post-intervention was 3.2 (SD = 1.1) for clients (range 1–5, t1 cRCT follow-up questionnaire). The majority (88%) of the dispensers agreed that the entire SUPR program was useful, against 12% who were "neutral."

TABLE 5 | Online behavior of cRCT participants in the intervention group ($n = 180$).

	Average viewing time	Total video length	Participants finishing the video[a]
	M:S	M:S	%
Instruction videos			
Email 3: "How to insert HAs"	1:44	1:56	70
Email 6: "How to make life easier and safer – assisting listening devices"	2:19	2:56	60
Email 8: "Maintenance and cleaning of HAs"	3:07	3:46	69
Videos on communication strategies and personal adjustment			
Email 7: "Horen en Gehoord Worden" - the Conversation	6:08	9:02	49
Email 9: "Horen en Gehoord Worden" - the Birthday Party	6:57	10:42	42
Email 11: "Horen en Gehoord Worden" - on the Streets	6:18	9:48	40
Email 13: "Horen en Gehoord Worden" - at the Doctor	5:22	7:58	50
Email 15: "Horen en Gehoord Worden" - the Meeting	8:50	18:31	22
Testimonial videos			
Email 2: "First experience with HA"	3:19	4:38	62
Email 4: "Together we hear more"	3:01	4:50	48
Email 14: "Inspired by others"	2:49	3:49	61

M, minutes; S, seconds; HA, hearing aid.

[a]*The percentage represents the number of clients who finished watching the video, divided by the number of clients who started to watch it.*

Perceived Benefit

Table 8 shows the results on the benefit of SUPR perceived from both the clients' and the HA dispensers' perspectives. Clients had a mean score of 3.0 (SD = 1.3) on the IOI-AI item "perceived benefit" immediately post-intervention (range 1–5).

Qualitative Results

Clients

Of the 5 participants, 4 were male. Their mean age was 71 years (SD 2.2). The analyses resulted in the identification of two overarching themes: (1) Experiences with SUPR elements and (2) Experiences with and views on hearing care. These themes and subthemes are described below.

Experiences With SUPR Elements

Participants discussed their experiences with the Practical Support Booklet, the online part of SUPR, the involvement of

TABLE 7 | The extent to which PE participants ($n = 138$) found the SUPR elements useful.

	Element useful?		
	Disagree *n* (%)	Neutral *n* (%)	Agree *n* (%)
Practical support booklet ($n = 106$)	6 (6)	48 (45)	52 (49)
Instruction videos ($n = 86$)	4 (5)	23 (27)	59 (69)
Communication strategies videos ($n = 67$)	2 (3)	25 (37)	40 (60)
Testimonial videos ($n = 42$)	0	16 (38)	26 (62)

TABLE 6 | Assessment of CP involvement in watching the educational videos, as viewed by PE participants who had indicated to have a CP ($n = 100$).

	Did you watch the videos together with your CP?					
	Yes, I usually or always watched the videos together with my CP	Yes, I sometimes watched the videos together with my CP	No, my CP watched the videos at another moment	No, my CP did not watch the videos	No, and I do not know if my CP watched the videos	I do not know (anymore)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n*
Instruction videos ($n = 69$)	12 (17)	5 (7)	8 (12)	32 (46)	12 (17)	0
Videos on communication strategies and personal adjustment ($n = 50$)	9 (18)	4 (8)	11 (22)	22 (44)	4 (8)	0
Testimonial videos ($n = 33$)	7 (21)	5 (15)	3 (9)	16 (49)	2 (6)	0

CP, communication partner.

TABLE 8 | The extent to which PE participants ($n = 138$) and dispensers ($N = 44$) thought SUPR was effective (on a scale from 1 to 5).

	According to clients Mean (SD)	According to dispensers Mean (SD)
Improvement in communication	3.0 (1.2)	3.5 (0.65)
Improvement in HA use	2.9 (1.3)	3.7 (0.57)
Improvement in personal adjustment to hearing impairment	3.0 (1.3)	3.5 (0.59)
Improvement in involvement of CP in clients' HA trajectory	-	3.5 (0.78)

SD, standard deviation; HA, hearing aid; CP, communication partner.

the CP, and suggestions for improvements. Overall, participants perceived SUPR as a useful addition to the HA fitting process, but their opinions on the usefulness of the specific elements varied.

- Experiences with the practical support booklet

All participants declared that they used the Booklet mainly to obtain information during the HA fitting process and/or used it as a reference afterward. They were generally positive about the content. They found it clarifying and useful, although the content sometimes overlapped with information provided by the dispenser. One participant said: "*If I had questions, then I would read what was going on. And then it would be rather clarifying. That was actually one of the best functions of the Booklet for me.*" One participant reported preferring the Booklet rather than the educational videos because (s)he found the Booklet easier to access. Not all participants used the Booklet to write down their goals and experiences with the HAs. Those who did not, felt it was needless, because they were also able to orally discuss these with their dispenser. Others felt it was like going back to school: "*I think it is a piece of homework. I do have that thing [i.e., the HA] for myself and not for the HA dispenser. And if they want to know how I'm doing, they can ask me, right?...*" One participant explained to write down goals and experiences in the Booklet because then they would come to life more. Another participant said to just obey the request of the dispenser to write down experiences.

- Experiences with the online elements

Most participants indicated that they had watched only some of the educational videos, mainly because they had missed the emails, or felt they were already familiar with the information that would be shown. With regard to the instruction videos, most participants reported that the topic "cleaning of the HAs" was very relevant. Some of the participants who reported to have watched (one of) the videos on communication strategies and personal adjustment found that the situations shown were too exaggerated and too predictable. One participant reported: "*There was one situation that I remember of someone on a birthday party who failed so obviously [in coping with the situation], that you think: yes, I mean, if I'm talking to someone with earplugs in I will also fail. I mean, that was the atmosphere, it was so predictable [that the main character would not cope].*" Participants who watched (one of) the testimonial vides felt that these did not add anything extra and perceived them as being somewhat condescending. One participant explained: *"This may be a little sensitive, but I had the feeling that the target group was the elderly. The atmosphere was a little bit like, we need to speak to them very distinctly otherwise they will not follow. I found that a bit disturbing."*

- Suggestions for improvements of the SUPR elements

Some participants suggested making the Booklet more compact by, for instance, removing space to report goals and experiences. One participant recommended dividing the Booklet into two parts: One focusing on hearing loss and everything one can encounter during the HA journey, the second part focusing on maintenance and how to handle HAs. Some participants indicated they would have preferred a more personalized approach with regard to the online part of SUPR, for example by receiving videos that address the person's needs and only on-demand, or by providing access to an online library to allow clients to choose particular videos themselves. One participant proposed to decrease the number of emails and videos: "*The first video you watch with high interest. What is this? Oh this is useful. You watch the second video and then with the third and fourth you think: I think I can take it from here. And then with the fifth video I think: Now I don't want to watch anymore, this is an overkill.*" Another participant advised that the message of the video be transmitted in a shorter time, no longer than 1–2 min. Recommendations for new topics to be included in a future version of SUPR were "getting used to HAs" and "how to deal with background noise."

- Role of the CP

Most participants reported that their CP did not use the Booklet and/or watch the educational videos. Some participants did not want to involve their CP because they felt that their hearing loss was their own responsibility. To illustrate: "*I never would consider the idea to give her the Booklet. I did show that I received the Booklet, just like you share more things with each other, but not with the idea, this is interesting, you should take a look at it. I mean, her problem was that she noticed my hearing loss, but that has been restored and the other parts, fine, that is your own business.*"

Experiences With and Views on Hearing Care

Participants shared their views and experiences on (Dutch) hearing care. They reported on the commercial character of the hearing health care sector, on the dispenser's service level, and the professionalism and quality of the dispenser's supervision.

- Opinion on the hearing sector: commercial character

One participant felt that the mixture of medical and commercial care in the hearing sector was odd and unsatisfactory. (S)he explained that although hearing loss is a medical problem, HA dispensing is a commercial process and (advanced) HAs are expensive (note that in the Netherlands not all types of HAs are reimbursed): "*I can imagine that some people do not have a free choice and are led by their financial*

possibilities to what hearing care they opt for. I feel privileged that I am not restricted in that sense." One participant reported (s)he did not open 90% of the SUPR-emails because (s)he felt that all commercial companies were chasing him/her with emails after (s)he purchased a product: "*I throw away 90% of my email unread because it is all the same… If you buy something you are chased for the rest of your life [with commercial emails]. If I need information, I will look for it myself."* Another participant did not see the difference between the commercial videos of the HA dispensing practices company and the educational videos of SUPR.

- Opinion on the dispenser's service level

In general, participants were positive about the dispenser's level of service. They especially appreciated the "walk-in" consultation hour between 4 and 5 p.m. allowing them to walk in with any question relating to their HAs. They were also positive about the care offered after the purchase, for instance the provision of the SUPR videos: *"The best thing of the dispenser is the whole trajectory that you will pass through, the diligence, the proper education and also the after sale services, that is also great."*

- Supervision by the dispenser: professionalism and quality

Most participants were satisfied with the guidance of their dispenser and considered them to be working properly and professionally.

Dispensers

Of the six participating dispensers, four were female. Their mean age was 48 years (SD 8.8). On average, they had worked for the HAD company for 16 years. Two main themes related to the implementation of SUPR in clinical practice were identified in their data: (1) Barriers, (2) Facilitators.

Barriers to the Implementation of SUPR in Clinical Practice

The barriers dispensers reported on included: Policy changes, training issues, material issues, and clients' non-participation.

- Policy changes

The dispensers reported that policy changes within the company had had a negative impact on staff engagement in providing SUPR. They described several changes in the (national) dispensing system and reorganizations of personnel that had caused resistance and distrust toward providing SUPR in the HAD practice: *"For the past few years there have been enormous changes in this sector.… That has been very hectic and has evoked a lot of resistance… That same year [i.e., 2013] we've had our first real reorganization of personnel, so that caused resistance on resistance."*

- Lack of training/knowledge

Some dispensers could not remember if they had followed a training on how to implement SUPR, or what the content of the training was. Also, a lack of (recent) training caused the dispensers to forget what the SUPR videos were about. *"… but of course it is not exciting to watch videos of things you are doing [i.e., explaining how to use and clean HAs] every day, so I just looked at the structure so I could see what it was about, but that was a few years ago. Then I didn't think about it anymore and if I'm coming home at night I have other stuff to do, sorry!".*

- Material issues

Another barrier to discussing the educational videos with clients was the non-physical presence of the material: *"Dispenser 1: So I use it, but my focus is on the Booklet." Dispenser 2: "Yes, because that is physically available to us… because we see nothing of the online content as soon as they (the clients) sign up for it."*

- Non-participation of clients

Most dispensers felt that only half of the clients used the Booklet and that this was highly dependent on the motivation of the client. Moreover, they reported that a considerable number of their clients did not use the internet or had difficulties opening the emails and/or videos. Two dispensers reported that this was especially the case in the more rural areas. This had caused the dispensers to "select" the clients they could inform about the online elements: *"I do not explain the internet thing to all of my clients… Sometimes they (clients) will come and say: Yes, I couldn't open it or I couldn't get it sent.… So yeah I'm really looking to the type of client and then I will estimate if they will be able to handle it or not."*

Facilitators of the Implementation of SUPR in Clinical Practice

A range of facilitators to successfully implement SUPR in HAD practices were identified:

- Ease of use of program material

The dispensers believed that the Practical Support Booklet was easy to use, thereby referring to the option to note appointment dates and remarks. They also felt that using the Booklet facilitated the HA fitting process. One dispenser explained: "*If the clients use it [the intervention] well, it is very easy. Because then he will come to the appointments, he fills in the COSI [The Client Oriented Scale of Improvement], he knows what is going on with his hearing loss and what he is missing out on and he also knows what kind of assistive devices exist, so then it can be an enormous support."*

- Improved quality of care that the dispenser can provide

Dispensers were positive about the possibility to provide additional guidance to their clients. If, for example, the dispensers were running out of time during the appointments they could hand out the Practical Support Booklet: "*If you are really busy, then it is nice that they [the clients] can read it for a while, can let it sink in, and then when they return that you can continue to discuss it further."*

- Commercial advantage

Some dispensers believed that using SUPR had a commercial advantage to the company (sales-wise). For example, one dispenser explained that several clients had returned to the HAD practice because they had learned about an assistive listening

device while following SUPR, and they now wanted to try it out: *"I've had several clients [coming to my HAD practice] who came to purchase an assistive listening device because they had seen it in the videos."*

- Less returns to HAD practice

A commonly shared feeling among the dispensers was that SUPR led to fewer clients returning with questions about their HAs. They felt that SUPR increased clients ability to handle their HAs (by receiving information about settings, maintenance, and assistive listening devices). One dispenser described: *"A client who does not have to come back to me asking to replace the filter, but can do it by himself, and if that is the result of a video or a Booklet, great, because every little thing that a client can learn from the Booklet and that you don't have to do yourself… I think it is really good."* Fewer clients returning to the HAD practice after the fitting process was perceived as time-saving for both the dispenser and the clients.

The dispensers also believed there were some particular benefits of SUPR to their clients, and this motivated them to work with SUPR. A commonly shared view was that SUPR is highly useful for the clients on several levels, i.e., in the acceptance of hearing loss, and increase in HA use.

- Better acceptance of hearing loss

One dispenser described how the educational videos could increase clients' acceptance of hearing loss: *"And the other one [a testimonial video], I thought it was the one with the couple that talked about their experiences in difficult listening situations. To just hear it live from other HA users, then they [the clients] will watch it with some sort of acceptation."*

- Increase in HA use

Some believed SUPR would be a trigger and motivation for clients to use their HAs (more often) and that this in turn would lead to higher client satisfaction.

DISCUSSION

Findings from our cRCT showed that SUPR led to improvements in self-efficacy for advanced HA handling and HA satisfaction in the long term, i.e., 12 months, as well as greater HA use in the short term (directly after completion of SUPR) (22). However, SUPR did not enhance the use of communication strategies (primary outcome). Findings from the current PE study help to explain these outcomes and offer guidance as to how to further develop and implement SUPR, or similar AR interventions, especially those using web-based platforms in clinical practice.

Interpretation of Main Findings and Transferability to Other Clinical Fields

Booklet

The percentage of participants that had received the Booklet from their dispensers seemed reasonably high (78% according to the clients and at least 70% of the clients according to the large majority of the dispensers). However, the proportion of participants that had used the Booklet as intended, especially for the purpose to write down their goals and experiences, may be viewed as suboptimal (42% sometimes did this and 27% never). In general, setting specific goals and formulating expectations explicitly is viewed as a suitable approach for achieving client-centered care and is integral to self-management interventions. This is true for audiology (33–35), but also applies to other chronic conditions (36). For self-management interventions this seems an indispensable element to intervention success (36). With regard to SUPR, it is therefore important that the implementation of using the Booklet is improved, and all dispensers discuss and identify their clients' wishes and needs. Specific training for dispensers may improve this process further. It should be noted that administrating the Client-Oriented Scale of Improvement [COSI (37)] in every client was part of the Dutch HAD protocol at the time of the study. This protocol was enrolled for the whole hearing aid dispensing field in the Netherlands. Unfortunately, we did not collect data on the extent to which this part of the protocol was in fact followed by the clients included in the SUPR study. Thus, we are unsure if goal-setting *via* COSI did occur in parallel to (i.e., separate from) SUPR.

Viewing Rates of Online Intervention Elements

Despite the high percentage (92%) of intervention participants who confirmed their willingness to receive the SUPR emails (*reach*), relatively few clients actually engaged with the SUPR elements (*dose received*). The percentage of intervention participants starting the online educational videos ranged from 7 to 37% (emails 13 and 3, respectively), and clearly decreased over time. The videos about communication strategies were placed quite late in the intervention (first one in email 7). Placing key elements of an intervention early on in the program seems an important lesson for self-management programs in general. Regardless, decreasing and low intervention use in general are familiar phenomena for web-based platforms (38, 39): Participants do not take up a new e-intervention, stop using the e-intervention after a certain period, or do not use it according to how it was intended (40). In contrast, Ferguson et al. (19) found that at least 67% of their participants watched all the interactive videos in their multimedia educational program. Although the videos were not all offered *via* the internet (but also *via* DVD for PC and the internet) and participants were specifically requested to watch the videos, this is a much higher percentage than observed in the current study. It may be that using a real-life study design and using web-based elements only with limited motivation from a professional (as in the SUPR-study), resulted in a lower level of engagement.

The quantitative and qualitative data of this PE provided several other possible explanations as to why a relatively low number of participants watched the online educational videos. Many clients who did not watch (all) videos indicated that they had no interest in watching them, or believed they were already familiar with the information provided. This may indicate that not all clients had similar information needs and interests, and suggests that clients may have benefitted more from a personalized approach over the current "one-size-fits-all" approach. Tailoring intervention materials to clients' specific

needs is also broadly supported by literature evaluating elements of effective eHealth interventions (41, 42). For instance, as was also expressed by several focus group participants, offering access to an online library to allow selection of specific materials relevant for the person may increase implementation success. This also ties in with the importance of goal-setting: if particular goals were set for a person (e.g., relating to personal adjustment of hearing loss) the program could have been tailored to the person. Another reason for low intervention use might be related to the commercial character and setting in which the intervention was provided, as was suggested in the focus group and individual interviews. Several studies showed that users of an intervention typically believe that information is more trustworthy and reliable when given in an academic rather than in a commercial context (43, 44). This is supported by Preminger et al. (45) who reported that a commercialized approach typically results in low trust in hearing healthcare providers. A third reason for non-adherence may be dissatisfaction with the content of some videos. The quantitative data indicated that around two-thirds of the participants were satisfied with the usefulness of the videos (vs. around one-thirds being neutral, and 3–6% being dissatisfied). The focus group and individual interviews indicated that some participants were dissatisfied with some of the video content as they found the content sometimes too simplistic, which caused irritation. Others felt there were too many videos, or found them too long. An indirect sign that the duration of the videos may have been too long can be deduced from the online behavior data: especially the lengthier videos were not watched fully. In the current study, we did not assess design aspects such as entertainment value and message style (44). We suggest that further research and development should cover these aspects.

The cRCT showed that intervention effects were only found for outcomes related to the HA handling domain and not for outcomes in the psychosocial domain (22). This corresponds with the PE finding that relatively more participants engaged with the HA instruction videos (HA outcomes) than with the testimonial and communication strategies videos (psychosocial outcomes). See also **Figures 1**, **2**. Unfortunately, we were not able to evaluate whether engagement with the intervention elements correlated to the degree of behavior change (i.e., the primary and secondary outcomes of the cRCT), as we could not deduce the start percentages of *individual* study participants from Quadia. Alternatively, the absence of any effects on any of the psychosocial outcomes may indicate that outcomes such as personal adjustment and use of communication strategies require active, interpersonal contact and practice with an actual person (see under Involvement of CP).

Implementation Fidelity and Contextual Factors

Finally, we argue that low adherence may have been a consequence of the poor compliance of dispensers with the implementation instructions (i.e., low implementation *fidelity*). Only half of the dispensers complied with the instruction to explain the goals of the videos and recommended their clients to actually watch them (quantitative data). Note that this was despite the relatively high perceived benefit of SUPR for their clients (ranging from 3.7 to 4, on a scale from 1 to 5). The quantitative dispenser data showed that many dispensers expected their clients to watch the videos anyway, or they believed that particular clients would not be the right target group for SUPR (i.e., had no access to a device with an internet connection and/or were able to understand how to use the internet). Also several contextual factors (parameter *context*) such as policy changes, lack of (re-) training, and material issues were perceived by the dispensers as barriers. Across all fields that involve health behavior change, these are all factors typically associated with low implementation success (46–50), as they interfere with the likelihood to perform a new behavior (50, 51). For example, the focus group data indicated this quite explicitly for the forced cuts in personnel that was carried out by the HAD company at the time of the study: the staff felt resistance to the implementation process. Another barrier appeared to be a lack of training (focus group data and quantitative data). Although all dispensers attended the training, they expressed to feel not optimally equipped to carry out SUPR effectively. Sufficient skills, knowledge, and associated with this, motivation may have hampered the successful implementation of SUPR during the study (48, 50). Nevertheless, the large majority of the dispensers expressed that they were motivated to carry out SUPR (84%), and preferred to continue with the program in the future (93%) (quantitative data). These findings are positive and provide a good basis for optimizing the implementation context.

Involvement of CP

Twenty-four to thirty-six percent of the clients reported having watched the educational videos together with their CP and 9–22% reported that their CP watched the videos at another moment (quantitative results). As audiology research showed that engaging family members in AR has clear benefits (52, 53), it seems of importance that dispensers encourage their clients to involve their CPs during SUPR. It may be fruitful, for example, to inform them about the specific potential benefits, and explaining how this is supported by scientific research. For example, this could include the following benefits: a family member can assist in the use and operation of HAs (54), encourage an individual to use HAs (55, 56), and decrease hearing handicap by following support programs together, and providing emotional support mutually (57). Because of the low viewing rates by the HA users and the suboptimal CP involvement, we are uncertain if SUPR's communication strategy and testimonial videos could potentially have improved communication strategy use, personal adjustment to hearing loss, and hearing disability. Comparable hearing self-management e-interventions have found positive effects on such outcomes (17, 18), and suggest that interactions or practice with peers or a professional are indispensable and should be integrated in self-management programs. Further research is needed to examine if e-health interventions for chronic conditions like hearing loss can suffice with an individual approach or whether live- interactions with peers or a professional would be needed to increase success. In the latter case, it should be examined whether live involvement of others may be replaced by online, tailored alternatives, such as avatars or discussion fora. In any case, practicing communication and assertiveness skills with others is essential in case of hearing loss, as many skills relate to communication and thus require active and empathetic involvement of the CP. Moreover, involving and practicing

with others is important to overcome the social stigmas related to hearing loss, and this may also be important in other chronic conditions.

Strength and Limitations

A strength of this study is its comprehensiveness. Drawing on a solid research framework (28), eight process indicators were assessed. Self-reported and empirical client data and dispensers' perceptions were analyzed both quantitatively and qualitatively. Such triangulation of methods is known to generally improve quality of data analysis, and we believe that this has also strengthened the current PE. Another strength is the relatively large number of HAD practices ($n = 36$) spread across the Netherlands participating in this study. The practices were purposefully sampled for spread across all provinces, and for spread in the degree of rural/urban areas being represented. Including such a heterogeneous sample increased the likelihood of the results being externally valid for the chain's HAD practices in the Netherlands.

There are also some limitations that must be discussed. First, there was a chance of social desirability bias for dispensers who may have felt the need to provide a favorable image to the researchers or their colleagues of the HAD practices headquarters. We attempted to prevent this bias by guaranteeing the confidentiality of their answers. Moreover, given that certain outcomes were answered in a more negative way than we expected, social desirability does not seem to have played a significant role. Also, clients who responded to the questionnaires might have been positive about SUPR and study participation in general and might have reported above-average engagement. Again as certain outcomes turned out more negative than expected, the results do not point in this direction. Another limitation refers to the inability to quantify how dispensers perceived the usefulness of the specific SUPR materials because we only assessed how they rated the usefulness of the total SUPR intervention. Yet, the qualitative results did provide some insight into their opinions on this topic. A final limitation in the qualitative data collection for both clients and dispensers is that the sample size was small and data saturation could not be accomplished. The limited sample size was due to a low recruitment response. As a consequence, we cannot be certain that the samples represented the general group of clients and dispensers. It is possible that the full scope of factors that had an impact on engagement with the intervention and the implementation outcomes was not fully represented in this study. Nevertheless, the qualitative results provided useful insights into clients' and dispensers' positive experiences with SUPR, as well as the more negative ones.

CONCLUSIONS

We previously reported that adding SUPR to standard clinical HA dispensing care resulted in short-term and long-term improvements in HA outcomes (22). Combined with reasonably high satisfaction and benefit ratings of intervention materials from both clients and dispensers that resulted from the current study, we argue that these results indicate that SUPR can be considered an effective and useful addition to current care provided in HAD practices. Nonetheless, the educational videos were watched by fewer clients than was expected and may explain the absence of any effects found on psychosocial outcomes.

Insights from this PE suggest that tailoring of intervention elements to clients' specific needs, and investing in training facilities to increase clients' and dispensers' use of SUPR's educational videos are important to consider. A recent review on the state-of-the-art eHealth applied in the patient journey underlined the need for systematic analyses of these elements in order to optimize these eHealth services for adults with HAs (14). The lessons learned in this PE will help inform the further development and implementation of an improved version of SUPR, and possibly also help inform other, future eHealth services in the context of HA rehabilitation.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because this has not been applied for in the ethics application (and participants thus did not consent to use their data for that purpose). Requests to access the datasets should be directed to se.kramer@amsterdamumc.nl.

ETHICS STATEMENT

The study was approved by the Dutch Institutional Review Board of the VU University Medical Center.

AUTHOR CONTRIBUTIONS

SK and MP conceptualized and designed this PE study. JM collected the data, wrote the first draft of the manuscript, and analyzed the data. MP assisted in analyzing the qualitative data. BL-W provided statistical and methodological advice. All the authors were involved in data interpretation, commented on drafts of the paper, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.725388/full#supplementary-material

REFERENCES

1. Barker F, Mackenzie E, Elliott L, Jones S, de Lusignan S. Interventions to improve hearing aid use in adult auditory rehabilitation. *Cochrane Database Syst Rev.* (2016) 8:Cd010342. doi: 10.1002/14651858.CD010342.pub3
2. Chisolm TH, Johnson CE, Danhauer JL, Portz LJ, Abrams HB, Lesner S, et al. A systematic review of health-related quality of life and hearing aids: final report of the American Academy of Audiology Task Force On the Health-Related Quality of Life Benefits of Amplification in Adults. *J Am Acad Audiol.* (2007) 18:151–83. doi: 10.3766/jaaa.18.2.7
3. Wong LHL. *Evidence-Based Prachtice in Audiology: Evaluating Interventions for Children and Adults with Hearing Impairment*. San Diego, CA: Plural Publishing (2012).
4. Chisolm TH, Abrams HB, McArdle R. Short- and long-term outcomes of adult audiological rehabilitation. *Ear Hear.* (2004) 25:464–77. doi: 10.1097/01.aud.0000145114.24651.4e
5. Aazh H, Prasher D, Nanchahal K, Moore BC. Hearing-aid use and its determinants in the UK National Health Service: a cross-sectional study at the Royal Surrey County Hospital. *Int J Audiol.* (2015) 54:152–61. doi: 10.3109/14992027.2014.967367
6. Abrams HB, Kihm J. An introduction to markeTrak IX: A new baseline for the hearing aid market. *Hear Rev.* (2015) 22:16.
7. Bertoli S, Staehelin K, Zemp E, Schindler C, Bodmer D, Probst R. Survey on hearing aid use and satisfaction in Switzerland and their determinants. *Int J Audiol.* (2009) 48:183–95. doi: 10.1080/14992020802572627
8. Hartley D, Rochtchina E, Newall P, Golding M, Mitchell P. Use of hearing AIDS and assistive listening devices in an older Australian population. *J Am Acad Audiol.* (2010) 21:642–53. doi: 10.3766/jaaa.21.10.4
9. Kaplan-Neeman R, Muchnik C, Hildesheimer M, Henkin Y. Hearing aid satisfaction and use in the advanced digital era. *Laryngoscope.* (2012) 122:2029–36. doi: 10.1002/lary.23404
10. Solheim J, Hickson L. Hearing aid use in the elderly as measured by datalogging and self-report. *Int J Audiol.* (2017) 56:472–9. doi: 10.1080/14992027.2017.1303201
11. McCormack A, Fortnum H. Why do people fitted with hearing aids not wear them? *Int J Audiol.* (2013) 52:360–8. doi: 10.3109/14992027.2013.769066
12. Boothroyd A. Adult aural rehabilitation: what is it and does it work? *Trends Amplif.* (2007) 11:63–71. doi: 10.1177/1084713807301073
13. Laplante-Levesque A, Hickson L, Worrall L. Rehabilitation of older adults with hearing impairment: a critical review. *J Aging Health.* (2010) 22:143–53. doi: 10.1177/0898264309352731
14. Paglialonga A, Cleveland Nielsen A, Ingo E, Barr C, Laplante-Levesque A. eHealth and the hearing aid adult patient journey: a state-of-the-art review. *Biomed Eng Online.* (2018) 17:101. doi: 10.1186/s12938-018-0531-3
15. Saunders GH, Chisolm TH. Connected audiological rehabilitation: 21st century innovations. *J Am Acad Audiol.* (2015) 26:768–76. doi: 10.3766/jaaa.14062
16. Swanepoel de W, Clark JL, Koekemoer D, Hall JW, III, Krumm M, Ferrari DV, et al. Telehealth in audiology: the need and potential to reach underserved communities. *Int J Audiol.* (2010) 49:195–202. doi: 10.3109/14992020903470783
17. Thoren ES, Oberg M, Wanstrom G, Andersson G, Lunner T. A randomized controlled trial evaluating the effects of online rehabilitative intervention for adult hearing-aid users. *Int J Audiol.* (2014) 53:452–61. doi: 10.3109/14992027.2014.892643
18. Malmberg M, Lunner T, Kahari K, Andersson G. Evaluating the short-term and long-term effects of an internet-based aural rehabilitation programme for hearing aid users in general clinical practice: a randomised controlled trial. *BMJ Open.* (2017) 7:e013047. doi: 10.1136/bmjopen-2016-013047
19. Ferguson M, Brandreth M, Brassington W, Leighton P, Wharrad H. A randomized controlled trial to evaluate the benefits of a multimedia educational program for first-time hearing aid users. *Ear Hear.* (2016) 37:123–36. doi: 10.1097/AUD.0000000000000237
20. Kramer SE, Allessie GH, Dondorp AW, Zekveld AA, Kapteyn TS. A home education program for older adults with hearing impairment and their significant others: a randomized trial evaluating short- and long-term effects. *Int J Audiol.* (2005) 44:255–64. doi: 10.1080/14992020500060453
21. Meijerink JFJ, Pronk M, Kramer SE. Experiences with and lessons learned from developing, implementing, and evaluating a support program for older hearing aid users and their communication partners in the hearing aid dispensing setting. *Am J Audiol.* (2020) 29:638–47. doi: 10.1044/2020_AJA-19-00072
22. Meijerink JF, Pronk M, Lissenberg-Witte BI, Jansen V, Kramer SE. Effectiveness of a web-based SUpport PRogram (SUPR) for hearing aid users aged 50+: two-arm, cluster randomized controlled trial. *J Med Internet Res.* (2020) 22:e17927. doi: 10.2196/17927
23. Meijerink JF, Pronk M, Paulissen B, Witte BI, Wouden BV, Jansen V, et al. Effectiveness of an online SUpport PRogramme (SUPR) for older hearing aid users: study protocol for a cluster randomised controlled trial. *BMJ Open.* (2017) 7:e015012. doi: 10.1136/bmjopen-2016-015012
24. Grant A, Treweek S, Dreischulte T, Foy R, Guthrie B. Process evaluations for cluster-randomised trials of complex interventions: a proposed framework for design and reporting. *Trials.* (2013) 14:15. doi: 10.1186/1745-6215-14-15
25. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: medical Research Council guidance. *BMJ.* (2015) 350:h1258. doi: 10.1136/bmj.h1258
26. Oakley A, Strange V, Bonell C, Allen E, Stephenson J. Process evaluation in randomised controlled trials of complex interventions. *BMJ.* (2006) 332:413–6. doi: 10.1136/bmj.332.7538.413
27. Ratanjee-Vanmali H, Swanepoel W, Laplante-Lévesque A. Patient uptake, experience, and satisfaction using web-based and face-to-face hearing health services: process evaluation study. *J Med Internet Res.* (2020) 22:e15875. doi: 10.2196/15875
28. Linnan L, Steckler AB, Israel B. *Process Evaluation for Public Health Interventions and Research*. San Francisco, CA: Jossey-Bass (2002).
29. Dreschler WA, de Ronde-Brons I. A profiling system for the assessment of individual needs for rehabilitation with hearing aids. *Trends Hear.* (2016). 20:639. doi: 10.1177/2331216516673639
30. Noble W. Extending the IOI to significant others and to non-hearing-aid-based interventions. *Int J Audiol.* (2002) 41:27–9. doi: 10.3109/14992020209101308
31. Gussenhoven AH, Singh AS, Goverts ST, van Til M, Anema JR, Kramer SE, et al. process evaluation of implementing a vocational enablement protocol for employees with hearing difficulties in clinical practice. *Int J Audiol.* (2015) 54:507–17. doi: 10.3109/14992027.2015.1009642
32. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol.* (2006) 3:77–101. doi: 10.1191/1478088706qp063oa
33. Gagné J-P, Jennings MB. Incorporating a client-centered approach to audiologic rehabilitation. *The ASHA Leader.* (2011) 16:10–3. doi: 10.1044/leader.FTR1.16082011.10
34. Poost-Foroosh L, Jennings MB, Shaw L, Meston CN, Cheesman MF. Factors in client-clinician interaction that influence hearing aid adoption. *Trends Amplif.* (2011) 15:127–39. doi: 10.1177/1084713811430217
35. Laplante-Lévesque A, Hickson L, Worrall L. Promoting the participation of adults with acquired hearing impairment in their rehabilitation. *J Acad Rehabil Audiol.* (2010) 43:11–26.
36. Fredrix M, McSharry J, Flannery C, Dinneen S, Byrne M. Goal-setting in diabetes self-management: a systematic review and meta-analysis examining content and effectiveness of goal-setting interventions. *Psychol Health.* (2018) 33:955–77. doi: 10.1080/08870446.2018.1432760
37. Dillon H, James A, Ginis J. Client oriented scale of improvement (COSI) and its relationship to several other measures of benefit and satisfaction provided by hearing aids. *J Am Acad Audiol.* (1997) 8:27–43.
38. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JE. Persuasive system design does matter: a systematic review of adherence to web-based interventions. *J Med Internet Res.* (2012) 14:e152. doi: 10.2196/jmir.2104
39. Kohl LF, Crutzen R, de Vries NK. Online prevention aimed at lifestyle behaviors: a systematic review of reviews. *J Med Internet Res.* (2013) 15:e146. doi: 10.2196/jmir.2665
40. Eysenbach G. The law of attrition. *J Med Internet Res.* (2005) 7:e11. doi: 10.2196/jmir.7.1.e11
41. Yardley L, Spring BJ, Riper H, Morrison LG, Crane DH, Curtis K, et al. Understanding and promoting effective engagement with

digital behavior change interventions. *Am J Prev Med.* (2016) 51:833–42. doi: 10.1016/j.amepre.2016.06.015
42. Morrison LG, Yardley L, Powell J, Michie S. What design features are used in effective e-health interventions? A review using techniques from critical interpretive synthesis. *Telemed e-Health.* (2012) 18:137–44. doi: 10.1089/tmj.2011.0062
43. Hardiker NR, Grant MJ. Factors that influence public engagement with eHealth: a literature review. *Int J Med Inform.* (2011) 80:1–12. doi: 10.1016/j.ijmedinf.2010.10.017
44. Ritterband LM, Thorndike FP, Cox DJ, Kovatchev BP, Gonder-Frederick LA, A. behavior change model for internet interventions. *Ann Behav Med.* (2009) 38:18–27. doi: 10.1007/s12160-009-9133-4
45. Preminger JE, Oxenbøll M, Barnett MB, Jensen LD, Laplante-Lévesque A. Perceptions of adults with hearing impairment regarding the promotion of trust in hearing healthcare service delivery. *Int J Audiol.* (2015) 54:20–8. doi: 10.3109/14992027.2014.939776
46. Carroll C, Patterson M, Wood S, Booth A, Rick J, Balain S, et al. conceptual framework for implementation fidelity. *Implement Sci.* (2007) 2:40. doi: 10.1186/1748-5908-2-40
47. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci.* (2009) 4:50. doi: 10.1186/1748-5908-4-50
48. Durlak JA, DuPre EP. Implementation matters: a review of research on the influence of implementation on program outcomes and the factors affecting implementation. *Am J Community Psychol.* (2008) 41:327–50. doi: 10.1007/s10464-008-9165-0
49. Fixsen DL, Blase KA, Naoom SF, Wallace F. Core implementation components. *Res Soc Work Pract.* (2009) 19:531–40. doi: 10.1177/1049731509335549
50. Greenhalgh T, Robert G, Macfarlane F, Bate P, Kyriakidou O. Diffusion of innovations in service organizations: systematic review and recommendations. *Milbank Q.* (2004) 82:581–629. doi: 10.1111/j.0887-378X.2004.00325.x
51. Gustafson DH, Sainfort F, Eichler M, Adams L, Bisognano M, Steudel H. Developing and testing a model to predict outcomes of organizational change. *Health Serv Res.* (2003) 38:751–76. doi: 10.1111/1475-6773.00143
52. Meyer C, Scarinci N, Ryan B, Hickson L. "This is a partnership between all of us": audiologists' perceptions of family member involvement in hearing rehabilitation. *Am J Audiol.* (2015) 24:536–48. doi: 10.1044/2015_AJA-15-0026
53. Scarinci N, Meyer C, Ekberg K, Hickson L. Using a family-centered care approach in audiologic rehabilitation for adults with hearing impairment. *Persp Aural Rehabil Instrument.* (2013) 20:83–90. doi: 10.1044/arri20.3.83
54. Manchaiah VK, Stephens D, Lunner T. Communication partners' journey through their partner's hearing impairment. *Int J Otolaryngol.* (2013) 2013:707910. doi: 10.1155/2013/707910
55. Carson AJ. "What brings you here today?" The role of self-assessment in help-seeking for age-related hearing loss. *J Aging Stud.* (2005) 19:185–200. doi: 10.1016/j.jaging.2004.07.001
56. Lockey K, Jennings MB, Shaw L. Exploring hearing aid use in older women through narratives. *Int J Audiol.* (2010) 49:542–9. doi: 10.3109/14992021003685817
57. Preminger JE. Should significant others be encouraged to join adult group audiologic rehabilitation classes? *J Am Acad Audiol.* (2003) 14:545–55. doi: 10.3766/jaaa.14.10.3

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Process Evaluation of Internet-Based Cognitive Behavioral Therapy Intervention for Informal Caregivers

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Background: Informal caregivers are individuals who provide care for ill, frail, or otherwise dependent family members, siblings, or friends. Due to the caregiving demands, informal caregivers are known to experience negative mental health symptoms, such as stress or anxiety. Interventions based on Internet-based Cognitive Behavioral Therapy (ICBT) principles have been previously found to be effective for different populations and could also be considered as a plausible support option for informal caregivers. However, findings regarding effectiveness alone might not be sufficient for informing about the overall feasibility of the intervention.

Objective: The aim of this process evaluation study was to evaluate the feasibility of a previously developed ICBT intervention for informal caregivers in Lithuania. More specifically, we evaluated the suitability of the intervention in relation to its content and delivery mode.

Methods: Two studies were conducted. Study 1 consisted of participant evaluations of an 8-week, 8-module long therapist supported ICBT intervention. Evaluations for the Study 1 were retrieved from previously unused data, obtained from pilot testing of the intervention in which 63 informal caregivers took part. The evaluations contained of qualitative data (participant comments), as well as quantitative data (evaluations of each of the sessions). The Study 2 was an online stakeholder focus-group discussion conducted via Zoom. Eight stakeholders took part in the discussion, among whom there were social workers, medical professionals as well as individuals with caregiving experience themselves. Data were analyzed using descriptive statistics, thematic analysis, and data coding.

Results: Results of the Study 1 showed that most of the pilot randomized controlled trial participants evaluated content and format of the intervention positively. These results were complemented by the findings in the Study 2, in which stakeholders evaluated the intervention as suitable and promising. In addition, stakeholders made certain suggestions for improving the intervention's usability for the informal caregivers. This included improving the instructions, providing with more guidance, and considering personalization options.

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Conclusion: The process evaluation helped to evaluate the feasibility of the ICBT intervention for informal caregivers in Lithuania from the two perspectives: users and stakeholders. Our findings suggest that the intervention is suitable for the target population.

Keywords: process evaluation, ICBT, informal caregivers, feasibility, focus group

INTRODUCTION

Informal caregivers are individuals who provide care for family members, siblings, or close acquaintances who due to the chronic illness, frailty, or other reasons are not able to live fully independently. Informal caregiver involvement varies greatly from helping with general hygiene, medication intake, and up to 24 h per day support (1). Because of caregiving, many caregivers experience reduced well-being (2). Consequently, much of research efforts have focused on developing and testing possible support interventions for this population. Over the last decades, eHealth or internet interventions have been proposed as an alternative to traditional, face-to-face options. One of the benefits of internet interventions is that it can reach caregivers in remote geographical locations (3). It also provides an opportunity to reduce the treatment vs. demand gap (4), offers an alternative solution for individuals concerned with mental health stigma (5), and provides flexibility in accessing the material (6).

There are examples of internet interventions for informal caregivers. The focus has been on psychoeducation (7), information provision (8), and peer support (9). It is common to include multiple components in the interventions, such as education coupled with professional support (10). When it comes to the efficacy, the results have been described as promising (11). For example, multicomponent interventions have the potential to reduce symptoms of depression, anxiety, stress, and distress (12). Nevertheless, it is difficult to draw any firm conclusions about the existing interventions. As outlined by the Sherifali et al. (12), one of the reasons for this is the high heterogeneity of the interventions targeting various outcomes which are in turn assessed with different measures. In addition, findings of their meta-analysis found several included intervention trials to suffer from methodological limitations and hence be at high risk of bias in areas such as incomplete outcome data and blinding of participants among the other. This, therefore, leads to the conclusion that further, high quality research trials investigating internet intervention suitability for the informal caregivers are needed.

Due to its effectiveness in treating various psychiatric and somatic conditions (13) internet-delivered cognitive behavioral therapy (ICBT) could be outlined as a potentially beneficial way of psychological support for informal caregivers. Even though it is not uncommon for existing interventions to include certain Cognitive Behavioral Therapy (CBT) components, to the best of our knowledge, there were very few previous attempts to implement ICBT interventions for the informal caregivers. To give an example, in a recent review (14) three internet-based interventions including CBT components and targeted for dementia caregivers were reviewed (15–17). Despite including CBT components, these interventions differed in their approach regarding the guidance (guided vs. unguided) and delivery mode (computerized vs. computerized and bibliotherapy). One other example is the study by the Meichsner et al. (18) in which an existing CBT intervention was translated into the ICBT format. In this study informal caregivers were found to generally be very satisfied with the ICBT intervention which indicates its potential for this population. These findings, in combination with existing knowledge about the effectiveness of the CBT interventions, encourages further development and evaluation of the ICBT's suitability for informal caregivers.

Various frameworks exist for guiding the development, evaluation, and implementation of the internet interventions. The Medical Research Council (MRC) framework for complex interventions (interventions including several interacting components among other characteristics) (19–21) is a well-known and cited framework. It suggests that the intervention research consists of four phases: identification or development of an intervention, feasibility, evaluation, and implementation (21). There is also a set of common core elements outlined, relevant for all phases: consideration of the context, refinement of the theory, engagement of stakeholders, identification of uncertainties, refinement of the intervention and consideration of the economic factors. The phases do not necessarily follow a linear sequence meaning, that the intervention development, evaluation, and implementation process might require one to repeat some processes or move in between the phases back or forward (20). MRC framework also draws attention to the process evaluation of trials. Process evaluation has been defined as a process of exploring various aspects within research trials, such as receipt, setting, implementation and meaning of the results involving both, quantitative and qualitative methods (22). In their most recent update (21) MRC has reiterated that methods, such as process evaluations, can help researchers to move beyond evaluating the effectiveness of the interventions and answer other relevant questions, such as why the intervention does or does not work or how it could be optimized further.

When should a process evaluation be done? To start with, it could be useful following the development on an intervention, as the obtained knowledge could then be applied for investigating quality, feasibility, and prospects for implementation. At the same time, process evaluations could be conducted in other phases of development. For example, it could be useful after pilot testing of efficacy, to either help in interpreting the results or, to provide with additional evidence (23). Moreover, process evaluations could be conducted several times, at different stages of the intervention's development and analysis processes,

for monitoring the quality and the treatment throughout the development process. In terms of evaluation of fidelity, it is advisable to involve stakeholders, such as users, health professionals, or other relevant stakeholders (24). Consequently, depending on the process evaluation's aims, researchers can choose to collect either quantitative or qualitative data, or do both (22).

In this paper, we present the results of a process evaluation of an ICBT intervention for reducing informal caregiver burden. We recently conducted a pilot randomized controlled trial (RCT) (25) and a qualitative study (26) for evaluating the efficacy and acceptability of this intervention for Lithuanian informal caregivers. The ICBT intervention was an eight-week long, therapist-supported program aimed at adult informal caregivers. Following the pilot RCT with 63 informal caregivers we found that the intervention reduced caregiver burden as well as depression and anxiety symptoms (between group Cohen's d = −0.70, −0.69 and −0.74 respectively). Further, the intervention resulted in reductions of stress and improved quality of life (Cohen's d = −1.06 for stress and 0.8 and 0.85 for quality of life). The results of the qualitative study showed that the informal caregivers accepted the intervention, with its format and the contents overall were valued positively (26). At the same time some differing opinions were observed in relation to the therapist-support, content, and the format of the intervention with some participants preferring it more and others less. Based on the findings of these two studies we have concluded, that even though results are promising, some information is still lacking. Firstly, content evaluation data retrieved during the pilot RCT trial needed to be utilized to further evaluate interventions suitability in the light of the some of the controversies outlined following the qualitative study. Secondly, our findings were solely based on the participant experiences. Evaluation by health professionals, social workers, or other relevant parties was needed to evaluate sustainability and implementation of the intervention. Therefore, we decided to run an evaluation phase and further investigate feasibility before planning a larger RCT. For this purpose, process evaluation was deemed as the most appropriate approach for utilizing previously collected, but not used data in combination with data representing stakeholder perspectives.

The main objective of the present paper was to conduct a process evaluation study for examining feasibility of the ICBT intervention for reducing informal caregiver burden. More specifically, we focused on evaluating delivery, content, and suitability for the target population. For this purpose, two research studies were conducted and will further be presented separately. The findings in this study will hopefully guide further development and implementation of the intervention.

METHODS

This process evaluation study was performed following the efficacy and intervention acceptability studies. The study design was driven by recommendations provided by Moore et al. (23). To meet our goal, two separate research studies were conducted (**Figure 1**). The Study 1 was based on retrospective, but previously not used participant data collected during pilot RCT study (25). Study 2 was a stakeholder focus group discussion. We start by describing the intervention's development process. Representation of the two studies follows further.

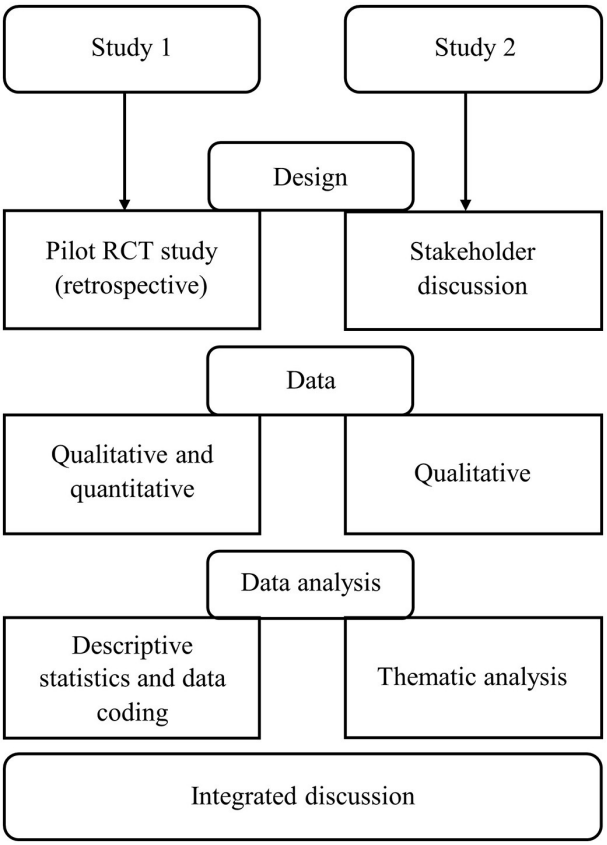

FIGURE 1 | Process flow of the studies procedures.

Development of the Intervention

The intervention was developed in three main steps: (1) concept development and considerations, (2) selection of the content, (3) revision of the content by a Lithuanian research group of clinical psychologists for cultural appropriateness and relevance.

Concept Development and Considerations

The idea to develop a guided internet-delivered self-help intervention for informal caregivers in Lithuania was initiated in association with an EU-project (ENTWINE) and was a collaboration between Linköping University in Sweden, Vilnius University in Lithuania, and the University of Groningen in the Netherlands. Few most important aspects were agreed upon on this stage. Firstly, the Iterapy online treatment platform (27) was chosen for running the intervention. Secondly, it was decided that the intervention should be therapist-guided as such interventions were found to be more effective and better adhered to than non-supported ones (28). Lastly, it was decided that the intervention should be transdiagnostic. That is, to cover several

topics that would suit a broad range of informal caregivers. The main motivation to choose this type of focus was that transdiagnostic interventions account for comorbidity, which is common in mental health disorders (29).

The intervention was named 'Slaugau artima' which translated from Lithuanian language means I take care of my close one. In the Lithuanian context this was decided to be the closest as well as culturally understandable approximation of the English term informal caregivers.

Selection of the Treatment Content

A CBT approach was chosen as theoretical framework. This decision was prompted by accumulating evidence in support of ICBT for adults experiencing psychiatric and somatic conditions (6). Following this, the literature was consulted for obtaining knowledge about the most faced challenges and psychological health outcomes for caregivers. Eight main themes were selected, resulting in eight treatment modules: Introduction, Thoughts, Stress and relaxation, Problem solving, Communication, Anxiety, Behavioral activation, and Maintenance. Content for the themes was then retrieved from existing ICBT intervention programs on anxiety and mood disorders at Linköping University. Detailed description of the content of the intervention is provided elsewhere (25).

The selected content was put together for each of the topics and then translated into Lithuanian language by Lithuanian speaking research group members. Initial checks for the comprehensiveness and appropriateness of the content for the target population were then conducted. Since the intervention targeted Lithuanian informal caregivers, much attention was dedicated for making the content culturally appropriate. From the initial stage throughout the development of the intervention, adjustments of intervention content to local cultural context were discussed in the Swedish and Lithuanian research teams. Also, a small convenience sample of stakeholders from the researchers' network were consulted when necessary.

Revision of the Content

In the first stage of the revisions, a Lithuanian fluent student assistant reviewed the content of the intervention for its suitability and comprehensiveness. Certain observations were noted regarding the use of language, case examples and the structure of the content which were communicated to the research team so that changes could be made where appropriate. Following this, several discussions in the research group, including experienced clinical psychologists and researchers from Lithuania, took place. Once again, the content was revised and adapted when needed. The intervention was finalized when there were no further revisions to be made regarding the content, cultural appropriateness, and the use of language. **Figure 2** represents the main page of the intervention after logging in. In the **Figure 3** a sample of the intervention's content is presented.

STUDY 1

Design

In Study 1 we retrieved previously unused intervention evaluation data obtained from the participants during the pilot RCT study (25). Participation in this research study was voluntary and all participants provided informed consent prior the start of the trial. Ethics approval for the study was granted by the Vilnius University Psychology Research Ethics Committee documented as 08-07-2019 No.26. No monetary compensation was provided.

FIGURE 2 | User screen after logging in. On the right-side of the screen users can click on *the Programos skyriai* to access different modules, click on *Užduotys* to access exercises or start a conversation with a psycholigst by clicking on *Pokalbiai*.

FIGURE 3 | Sample of the intervention's content. On the left side, users can move from tab to tab to access modules materials (Starting with *1. Sveiki!*).

Participants

A total of 63 informal caregivers were included in the pilot RCT. Most of the participants were female (90%) with an average age of 52 years (SD = 8.4). Participants displayed high burden (M = 53.92, SD = 12.66) as measured by the Caregiver Burden Inventory (30). A complete list of the characteristics is provided in the **Supplementary Material**.

Materials

Data retrieved from the pilot RCT participants consisted of module evaluation questions as well as an additional question about the content that participants were provided at the start of each module. Module evaluation questions consisted of four questions and one open box answer (**Table 1**). For this study, we did not incorporate the first question asking about the well-being of the participant. In addition, at the start of each week's module (session) participants were able to share their thoughts, ideas, or experiences in relation to the previous weeks content or their well-being (**Table 1**).

TABLE 1 | List of module evaluation questions for the pilot RCT participants.

Question	Rating
I Module evaluation questions	
What can your rate your current well-being?	1-very bad; 5-very good
Approximately what percentage of all the given information did you read?	0–100%
How do you overall rate this session?	1-very bad; 5-very good
How much time did you spend for reading the materials and conducting the exercises?	1 min—2 h
Here you can type in any thoughts, feelings, or insights that you have experienced during this session.	Open text answer
II Question at the start of the module	
Last week we have learnt about (), did you manage or have you tried to apply ()?* If you would like to share your feelings, thoughts, or experiences following (…) session, you can do so in the box below.	Open text answer

**At the start of the each week's module (session) participants were usually shortly reminded about the previous weeks topic and then shortly requested if they tried or managed to apply gained knowledge.*

Procedure

The pilot RCT study was conducted between October 2019 and March 2020. Participants in the study were able to choose to evaluate each of the eight modules as well as to share their experiences of applying the knowledge at the start of the each of the new modules. Answering intervention evaluation questions was on a voluntary basis and took only a few minutes.

Analysis

Quantitative data were analyzed using IBM SPSS Statistics (version 25). Descriptive statistics were used for summarizing quantitative responses. The qualitative data were coded after reading all the text responses provided by the participants (31). First, participant comments were open coded. Then, codes were reviewed, scrutinized, and integrated into categories.

Results

Quantitative Findings

Participant responses to multiple choice module evaluation questions are summarized in **Table 2**. The number of responses to module evaluation questions gradually decreased throughout the duration of the intervention: from 45 out of 63 (71.4%) at the start (Module 1) to 26 out of 63 (41.3%) at the end (Module 8). As the findings presented in the **Table 2** illustrate, the majority of the participants have read all the of the given information for each of the modules (from 77.1 to 93.5%). Consequently, the majority rated modules as good (24.3–46.2%) or very good (33.3–57.7%) with exception of module 5 (Communication), which was mostly rated as very good (51.4%) or neither good nor bad (31.4%). Lastly, most of participants spent between 30 min and 1 h for engaging with each week's material (35.6%-60%) except for Module 1 (51.1% spent 1–30 min).

Qualitative Findings

A summary of the results is presented in **Table 3**. A total of 323 comments were retrieved. These were either content specific experiences ($n = 176$) or participant reflections ($n = 147$). Latter comments were not coded further, as it represented individual's personal experiences and thoughts. Content specific comments were divided into three main categories: Content/format positive (72.2%), Content/format hesitant (20.4%) and Content/format negative (7.4%). Short definitions and examples of participant comments illustrating each of the categories and sub-categories are presented in **Table 4**.

Comments in the first, Content/format positive category represented aspects of the intervention that the participants appreciated. These comments were further sub-categorized into five smaller groups. The two biggest ones were Learning about

TABLE 3 | Summary of the open-ended module evaluation answers from pilot RCT participants.

Categories	Overall ($n = 323$)	At the end of module[a] ($n = 196$)	At the start of module[b] ($n = 127$)
I Reflections	147 (45.5%)	90 (45.9%)	57 (44.9%)
II Content specific comments	176 (54.5%)	106 (54.1%)	70 (55.1%)
. Content/format positive	127 (72.2%)	71 (67.0%)	56 (80.0%)
. Learning about thoughts	40 (31.5%)	20 (28.2%)	20 (35.7%)
. Overall applicability	30 (23.6%)	21 (29.6%)	9 (16.1%)
. Being able to relax	17 (13.4%)	12 (16.9%)	5 (8.9%)
. Dedicating time for own needs	16 (12.6%)	4 (5.6%)	12 (21.4%)
. Other (e.g., problem solving)	24 (18.9%)	14 (19.7%)	10 (17.9%)
Content/format hesitant	36 (20.4%)	27 (25.5%)	9 (12.9%)
Content/format negative	13 (7.4%)	8 (7.5%)	5 (7.1%)

[a] *Question at the end of the module: Here you can type in any thoughts, feelings, or insights that you have experienced during this session.*

[b] *Question at the start of the module (requesting about previous week's content): If you would like to share your feelings, thoughts, or experiences following (…) session, you can do so in the box below.*

TABLE 2 | Summary of the multiple-choice module evaluation answers from pilot RCT participants.

	List of modules							
	First	**Second**	**Third**	**Fourth**	**Fifth**	**Sixth**	**Seventh**	**Eight**
Total responses	45	39	38	38	35	37	31	26
Read info *n* (%)								
50%	1 (2.2)	0	0	1 (2.6)	0	0	0	1 (3.8)
75%	7 (15.6)	4 (10.3)	6 (15.8)	7 (18.4)	8 (22.9)	5 (13.5)	2 (6.5)	1 (3.8)
100%	37 (82.2)	35 (89.7)	32 (84.2)	30 (79.0)	27 (77.1)	32 (86.5)	29 (93.5)	24 (92.4)
Ratings *n* (%)								
Very bad	0	0	0	0	0	0	0	0
Bad	2 (4.4)	2 (5.1)	0	1 (2.6)	1 (2.9)	1 (2.7)	0	0
Neither good nor bad	11 (24.4)	6 (15.4)	6 (15.8)	8 (21.1)	11 (31.4)	7 (18.9)	9 (29.0)	2 (7.7)
Good	15 (33.4)	18 (46.2)	12 (31.6)	11 (28.9)	5 (14.3)	9 (24.3)	10 (32.3)	9 (34.6)
Very good	17 (37.8)	13 (33.3)	20 (52.6)	18 (47.4)	18 (51.4)	20 (54.1)	12 (38.7)	15 (57.7)
Time spent *n* (%)								
1–30 min	23 (51.1)	9 (23.1)	5 (13.2)	6 (15.8)	4 (11.4)	8 (21.6)	7 (22.6)	8 (30.8)
30 min−1 h	16 (35.6)	19 (48.7)	21 (55.2)	21 (55.3)	21 (60.0)	20 (54.1)	17 (54.8)	13 (50.0)
1–2 h	5 (11.1)	9 (23.1)	7 (18.4)	7 (18.4)	7 (20.0)	7 (18.9)	5 (16.1)	3 (11.5)
2>h	1 (2.2)	2 (5.1)	5 (13.2)	4(10.5)	3 (8.6)	2 (5.4)	2 (6.5)	2 (7.7)

List of modules: (1) Introduction, (2) Thoughts, (3) Stress and relaxation, (4) Problem solving, (5) Communication, (6) Anxiety, (7) Behavioral activation and (8) Maintenance.

TABLE 4 | Examples of participant comments categorized into Content specific category.

Category	Definition	Examples
Content /format positive	Comments representing participant appreciation of the intervention's content or format.	
Learning about thoughts	Benefit of better understanding thought processes.	*Alternative thoughts helps me to have a more positive outlook towards the future.* *Less chaos in thoughts and feelings.*
Overall applicability	Ability to apply intervention's content and *suitability of the format*.	*I have applied a lot of things.* *For me it was really useful; I was able to get to know myself better as well as my own feelings and disappointments.*
Being able to relax	Ability to relax and applicability of relaxation exercises.	*Provided meditation methods put me in a good mood.* *Exercises enable (me) to relax a little bit.*
Dedicating time for own needs	Learning about benefits of spending time for oneself.	*It is necessary to pay more attention to oneself.* *I am starting to manage to find time for myself and engage in pleasurable activities.*
Other	Comments in relation to problem solving, improving communication quality or sharing with the therapists	*I liked compiling a list of problem-solving solutions.* *It is easier for me to communicate with mum.* *I don't feel alone.*
Content/format hesitant	Comments representing participant uncertainty about the intervention's content, format, applicability of the information or their own ability to apply it.	*I have experienced a lack of faith in the usefulness of the exercises; or perhaps (the lack) of will conduct them.* *It is difficult to express thoughts via writing.*
Content/format negative	Comments representing participant dislike of the intervention's content or its applicability.	*The topic of this session was completely not in accordance with my situation.* *Taking part in this program has started to irritate me as it requires additional time.*

thoughts (31.5%) and Overall applicability (23.6%). Comments in the Learning about thoughts sub-category indicated participants to benefit from the knowledge about their own thought patterns. Also, to benefit from information about how to interpret their thoughts and how the negative automatic thoughts could be changed into the less-negative alternative ones. Consequently, participants comments in the Overall applicability sub-category indicated participants to be generally able to select and apply the provided information. Also, these comments indicated participants to find the content as well as the format of the intervention overall acceptable and suitable. The remaining three sub-categories in the Content/format positive category were Being able to relax (13.4%), Dedicating time for own needs (12.6%) and other (18.9%). Firstly, the comments in the first two sub-categories indicated participants to benefit from the relaxation techniques as well as the parts of the content, that encouraged to focus on own needs. By some, intervention itself was perceived as a means of distraction from daily routine and an opportunity to spend the time for one-self. In turn, the comments in the sub-category other were either in relation to learning to problem solve (5.5%), improving quality of communication with the close ones (5.5%), or ability to share own thoughts and experiences with the therapist (7.9%). That is, to very specific components of the intervention, namely, the problem solving and communication skill related content as well as the function allowing to communicate with the therapist.

The remaining two categories were the Content/format hesitant (20.4%) and Content/format negative (7.4%). It could be summarized, that the main difference between these two categories was that participant comments in the latter category expressed more direct dislike or lack of approval as opposed to hesitancy or reluctancy toward engaging with the intervention. To start with, comments in the Content/format hesitant category reflected participant reservations about either the content and format of the intervention or own abilities in applying the intervention's materials. That is, some of the comments expressed participant doubts regarding content's applicability to their own situation, with some of the topics or exercises being perceived as less relevant for individual caregivers. In addition, some participants expressed uncertainty or doubts about how some of the exercises should be conducted or, were not certain if they are able to conduct such exercises correctly. Also, there were comments that indicated some participants to experience difficulty in translating the knowledge from the intervention into the daily life situations. In turn, as indicated by the categories title, comments in the last category, Content/format negative, represented participant negative attitude toward intervention's format or applicability of the content. Most of the comments in this category could be summarized to illustrate participant critique toward the content or exercises as being not suited for their needs or circumstances. In addition, comments in this category also indicated some of the caregivers to be longing for more intensive contact with the therapists. Lastly, some comments indicated participants to be burdened with the fact that the intervention required time to engage with.

STUDY 2

Design

Study two was set up as a stakeholder discussion. Informed consent was obtained from all participants. Ethics approval for this study was not required according to the national ethical

regulations for research, as it was not a clinical trial, participants were not requested to share any sensitive information and no obvious risks could be identified. Participation in the focus group discussion was completely voluntary and no monetary compensation was offered.

Participants

We defined stakeholders as individuals who were connected to the informal caregiving either via personal experiences or professional capacity (21). As a consequence, we contacted several organizations, such as the Huntington's disease association or association of multiple sclerosis, with invitation to take part in the focus group discussion. In addition, researchers also reached out to the existing contacts, known to either have informal caregiving experience or acquaint with informal caregivers via their professional setting. As a result, a convenience sample of eight female participants was recruited (**Table 5**). Participants ages ranged from 39 to 58 years, with an average age of 47.71 years (SD = 7.66) One participant did not provide personal details. All participants had professional experience in healthcare or social services and had obtained higher education diploma. Three were involved in the social work, one was a medical doctor, one was changing career from economy to psychology, one was a state employee, and one was a teacher and an informal caregiver. Participants were residing in various parts of the country. After being included participants were able to view a short presentation introducing the intervention.

Materials

The discussion guide included the meeting's agenda, several broadly phrased questions, and several question probes. The discussion part was structured to cover three main aspects in relation to the intervention: (1) information provided in the public pages of the intervention, (2) format and the content of the intervention and (3) the communication function between the participants and the therapists. Some of the questions posed to the participants were: What is your first impression after viewing this? What are your thoughts after seeing this? and Now that you have seen it, what is your opinion about the structure of the content?

TABLE 5 | Focus group participant characteristics.

Name[a]	Age[b]	Residence[c]	Education	Occupational area
Sara	39–49	North	University degree	Social work
Iris	39–49	South-East	University degree	Transitioning
Ann	50–59	North	University degree	Social work
Rose	50–59	Middle	College degree	Social work
Mia	39–49	Middle	University degree	Medicine
Tess	50–59	West	University degree	Education
Lily	39–49	South-East	University degree	Governmental
Ida	Missing	Missing	Missing	Missing

[a] *The names in the table are pseudonyms.*
[b] *Age in years is presented in the approximate range.*
[c] *Area of residence in Lithuania.*

Procedure

In preparation for the discussion, the main author of the paper (IB) and a student assistant familiar with the intervention pilot tested the procedure using the discussion guide. The stakeholder focus group discussion took place in November 2020 online, via Zoom and was recorded following consent from all participants. IB chaired the discussion and the student assistant took the notes. The discussion started with a general introduction. Before recording, participants were once again asked for verbal consent. All three parts of the intervention relevant for the discussion (publicly available information, format and the content and communication function) were introduced and discussed separately. Following the focus group discussion, participants were provided with a short summary of the main discussion points. Participants were also encouraged to contact the researchers with suggestions or corrections regarding the discussion's summary.

Qualitative Data Analysis

Data analysis was performed using inductive reflexive Thematic Analysis (TA) (32, 33) conducted within realist paradigm framework. First, data were transcribed. After this, transcripts were manually coded. This resulted in a list of initial codes. These, in turn, where then collated to form themes. Themes were reviewed resulting in some of the codes being re-coded and re-grouped. This process was repeated until the themes were fully refined. Since our main goal was to explore stakeholder impressions and experiences, themes were identified on a semantic level, without putting too much focus on ideologies or underlying assumptions. Analysis process was conducted by the main author and the student assistant with the joint expertise of the remaining co-authors when necessary.

Results

The focus group discussion lasted for 1 h and 42 min. Following data analysis, one main theme titled *ICBT intervention's potential and considerations* and four sub-themes were generated. The sub-themes are: (1) feasible and needed, (2) need to clarify instructions and manage expectations, (3) need to provide with guidance after the intervention has ended, and (4) similar challenges, but need of flexibility. The first sub-theme (Feasible and needed) illustrates benefits of the current ICBT intervention. The remaining three present several suggestions that could be implemented for maximizing intervention's benefits for the caregivers. Illustration of the themes and sub-themes is presented in the **Figure 4**. Description of the findings is provided in the text as well as quotes in **Table 6**.

Discussion regarding the intervention's content was accompanied by the view, that informal caregivers, despite their unique circumstances, are often faced with similar psychological challenges. As described in the first sub-theme Feasible and needed, stakeholders overall expressed a positive attitude toward the intervention. More specifically, the intervention's format, selection of themes and ability to contact the therapists were

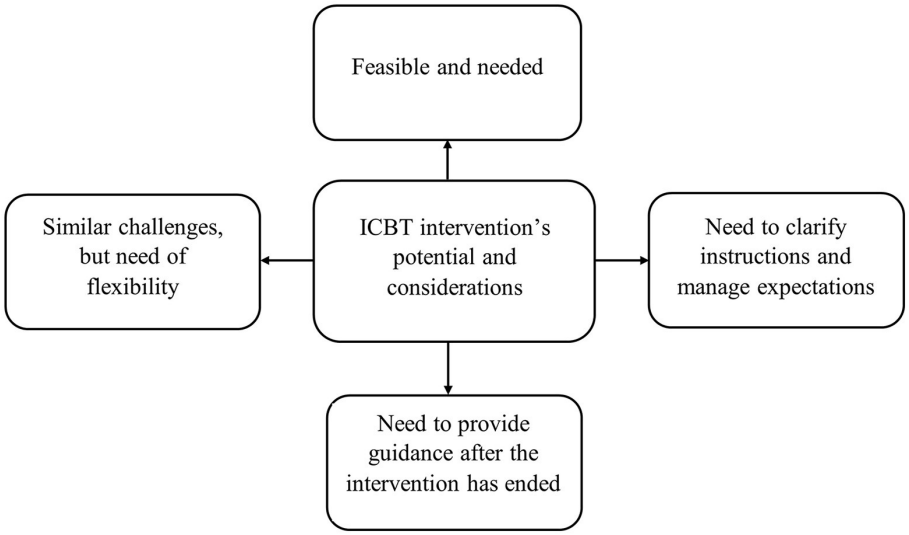

FIGURE 4 | Main theme and sub-themes generated following stakeholder focus group discussion.

TABLE 6 | Selected examples of focus group participant quotes.

Theme and sub-themes	Quote examples
. ICBT intervention's potential and considerations	
. Feasible and needed	*Everything is listed clearly, information is also comprehensible, structured.* *For the beginning, it's a very good platform, good basis and, I think, a good starting point.*
. Need to clarify instructions and manage expectations	*A person might even get a little frightened not knowing how much time (participation) will require.* *This is just like for everything: it is important that they (caregivers) know.*
. Need to provide guidance after the intervention has ended	*The continuation (of support) would be really necessary.* *In my opinion, such contacts would also be of a great help for these people.*
. Similar challenges, but need of flexibility	*For others it might be the other way round, there should be some kind of option to choose. The more options, the higher number of happy clients.*

appreciated. On the other hand, stakeholders emphasized that despite being faced with similar demands, each informal caregiver has a unique set of personal characteristics, has different caregiving experience, and is faced with unique challenges. Hence, the main overarching idea behind the remaining of the three sub-themes is that current version of the intervention could be developed further to offer valuable support for many, despite their different circumstances. That is, by providing options for personalization and by offering clearer instructions as well as options for the continuity of the support.

Feasible and Needed

Stakeholders reflected on how much psychological support is needed as well as the lack of resources for informal caregivers in Lithuania. The intervention was seen as an accessible and suitable support option that could bridge this existing gap. In addition, stakeholders appreciated that the intervention covered a range of different topics relevant for informal caregivers. Also, that the intervention was seen as well-structured.

> *One can see that a lot of work has been put into this; a lot of materials, systemised; included (information) is really useful and needed. (Ida)*

One other outlined aspect was the communication between the informal caregivers and therapists. Stakeholders positively reflected on the fact that informal caregivers were able to communicate with their assigned therapist throughout the duration of the intervention. This function was also found to be useful for encouraging caregivers to engage with the materials. Also, such function was deemed important for allowing them to share their personal experiences and challenges. Lastly, the fact that the intervention is delivered online was also perceived positively. This finding is especially valuable considering the ongoing COVID-19 pandemic at the time of data collection and the reduction in availability of face-to-face support.

> *At this moment, such support is more relevant than live support. (Ann)*

Need to Clarify Instructions and Manage Expectations

In addition to recommending including options for personalization stakeholders reflected upon certain aspects that could improve prior expectations and the ease of using

the intervention. To start with, two main aspects were outlined by the stakeholders regarding prospective user expectation management: time involvement and relationship with the therapist. Stakeholders emphasized the importance of informing informal caregivers about how much time would be required for engaging with the intervention. This was mentioned because caregivers often have a limited amount of time to spare. Including at least an approximate estimation of time could prepare them for scheduling the time around their duties. In addition, it was suggested that more information should be provided regarding the frequency of communication with the therapist. That is, how soon the participant will receive a response, how frequently communication will take place and what format it will take.

The more there is clarity, the easier everything is, the less questions arise. (Ann)

In terms of the ease of using the intervention, two main points were outlined. First, stakeholders suggested that more quick access options should be included in the intervention. That is, to provide certain shortcuts and a clear sequencing for accessing different topics and exercises. This was not only to make it more user friendly, but to also to save time for the caregivers. Second, stakeholders discussed including additional guidelines about using the intervention and especially, the technical parts of it, such as logging in, since not all the informal caregivers might be equally confident or affinitive in using online interventions.

. . . some instructions would help at least a bit for some. (Rose)

Need to Provide Guidance After the Intervention Has Ended

This subtheme reflects the need for continuation of support. Stakeholders discussed the importance of providing participants with different information sources about where one could reach out for support once the intervention had finished. For this, several suggestions were made. For example, to provide a list of helplines that offer mental health support, to provide with links to literature, useful web resources and possibly even online support communities. Such information regarding further support was stressed as an additional and essential tool for informal caregivers in allowing them to maintain their well-being and further apply the knowledge gained throughout the course of the intervention.

So not to leave (them) (. . .) in the hands of the fate, so that they could further reach out somewhere else in the future. (Ida)

Similar Challenges, but Need of Flexibility

Even though stakeholders described the topics of the intervention as useful, it was also commonly agreed upon that to reach and benefit informal caregivers in their differing circumstances, certain personalization options could be implemented. For example, to give participants an opportunity to choose the topics they want to start with instead of providing everyone with the same sequence of the topics.

My idea was that (. . .) a person could switch things around based on what theme is the most relevant for him at the moment. (Lily)

Other aspects that were mentioned were to include a wider range of selection options for either listening to information, or viewing it, since majority of the intervention's content is currently provided in text. Lastly, the opportunity for tailoring the communication with the therapist function was also discussed. Stakeholders suggested that due to individual differences, some of the participants might benefit for an opportunity to call or reach the therapist in other ways in addition or instead of currently implemented messaging function.

. . . hybrid way is good (. . .) meaning that it is possible to mix-it up, really. (Iris)

DISCUSSION

In this paper we aimed to conduct a process evaluation investigating the feasibility of ICBT intervention for informal caregivers in Lithuania. More specifically, we have aimed to evaluate the intervention by examining its delivery, content, and suitability for the target population. Two studies were conducted. In Study 1 we have analyzed evaluation data obtained from the informal caregivers who took part in a pilot RCT study for efficacy of the intervention (25). Study 2 was an online focus group discussion with eight stakeholders. Following data analysis, several aspects regarding intervention's feasibility were outlined. We further discuss these findings jointly.

Intervention's Feasibility

Feasibility of the Content

Most of the participants who filled in the module evaluations sheets spent between 30 min and 1 h for engaging with the module's materials, read all the provided information and rated modules as mostly good or very good. The latter is further evidenced by the finding that a majority of the coded pilot trial participant comments fell into the *Content/format positive* category. *Learning about thoughts (*the CBT explanation of relation between thought, emotions, and behavior) and *Overall applicability* were the two largest sub-categories in this group. This is in accordance with the *Feasible and needed* theme generated following focus group discussion in Study 2. Stakeholders found the intervention useful due to its clear structure and coverage of a range of topics. Clear structure, comprehensiveness and helpfulness of the content was previously outlined as beneficial in other ICBT studies (34). The opportunity to learn about relaxation methods, obtain knowledge about problem solving and communication were also found to be appreciated by the informal caregivers. As can be seen from the *Dedicating time for own needs* sub-category, the intervention also encouraged caregivers to focus on themselves. It is evident, that due to the caregiving demands and other responsibilities caregivers must often put their needs aside (1). As our findings illustrate, the intervention can help to bring this focus back.

Communication With the Therapist

Stakeholders viewed therapist support as beneficial for the caregivers. Specifically, for supporting them throughout the intervention period and allowing to share their experiences. On the other hand, only a fraction of the caregiver comments fell into this category (7.9% of the comments in *Content/format positive* category). It could be stated that the stakeholders were more expressive about the benefits of such support. As it is evident from our previous qualitative work in evaluating the acceptability of the ICBT intervention, not all informal caregivers appreciated the therapist support equally (26). This has been observed in previous research studies, with some of the users desiring for more support and contact with the therapist (35). Despite this, since this function was supported by at least a part of informal caregivers and by all stakeholders and considering previous findings suggesting ICBT interventions to be more effective than non-supported ones (28), we deem that this function should also be maintained in the further evaluation of the intervention.

In sum, we conclude that the joint results of the two studies indicate that the intervention is feasible. However, as it will be evident from the following sections, certain considerations must be accounted for further development of the ICBT intervention.

Further Development of the Intervention

Data from both informal caregivers and stakeholders outlined certain areas for intervention's improvement. In Study 1, comments in the *Content/format hesitant* category revealed that some of the informal caregivers experienced uncertainty about suitability of the material. Also, they questioned their own abilities to apply those materials. In turn, comments in the *Content/Format negative* category expressed informal caregiver dissatisfaction with the intervention or its components. Consequently, In Study 2, two of the themes reflected stakeholder suggestions about improving the intervention. That is: *Need to clarify instructions and manage expectations* and *Need to provide guidance after the intervention has ended*. The last theme, *Similar challenges, but need of flexibility* encourages us to think further about how to increase the flexibility of the intervention, so that it could be suitable for caregivers despite their differing circumstances. We discuss each of these points below.

Reducing the Hesitancy by Improving the Instructions

Not providing prospective users with enough information prior to the intervention might be one of the initial causes for participant non-engagement (36). In turn, providing clear instructions and information early on could help to build participant trust in the intervention and their confidence in using it (37). The latter could be important for informal caregivers, who might have negative prior experiences of using such interventions (38) or, consider themselves as less tech savvy (39). Including a 'search function' could also be another development allowing future users a quicker access for content related information as well as intervention use instructions (40). In addition to providing clear instructions, the stakeholders suggested providing information about the time needed for engaging with the intervention. Difficulty to integrate the use of the intervention into one's life due to the limited amount of time has been previously found to be a barrier for engagement with the intervention (38). Clarifying this early on could help to manage informal caregiver expectations and hence, engagement. The latter also applies for communication with the therapist. That is, informing about the type of communication (messaging) and the expected frequency. As a last point, stakeholders outlined a need to provide informal caregivers with guidance after the intervention. Even though it is out of the intervention's scope to provide with extensive list of informational resources, a list of useful websites, relevant literature, or support groups could be provided to be used for after the intervention ends.

Considering Informal Caregiver Differences and Similarities

The informal caregiver comments in the *Content/format negative* category represent their dissatisfaction with the intervention. Such experiences occurred either because the content or the format of the intervention did not meet their needs or did not suit their situation. Theme *Similar challenges, but need of flexibility*, generated a focus group discussion, and provides an explanation of such findings. Even though ICBT has been found to be effective in alleviating the symptoms of many psychological disorders (6), similarly as in traditional face-to-face CBT setting, effects are not equally successful for all the users. Hence, one aspect to consider is the transdiagnostic nature of the intervention. In the current version, all participants received access to the same intervention including eight themes, queued one after another. One benefit of such interventions is that they target comorbidity. Initially, a transdiagnostic approach seemed more appropriate as informal caregivers are known to experience various mental health symptoms such as for example, stress and depression (41). Also, based on the findings indicating both transdiagnostic and tailored treatments to be effective in depression and anxiety disorders (42). On the other hand, as suggested by the stakeholders, certain amount of tailoring could help to meet the needs of wider groups of caregivers. One of the solutions could be allowing caregivers to either choose the themes of the modules themselves, or request therapists to select and queue them individually, on a case-by-case basis. In such scenario, it would be possible to maintain a transdiagnostic approach and, at the same time, allow a degree of personalization.

Further development of the intervention could focus on clarifying the instructions for using the intervention, adding certain shortcuts to improve accessibility of the materials, and provide information on how to handle the situation when the intervention ends. In addition, implementation of personalization options, such as selecting and queuing themes based on each caregiver's needs, should be considered.

Limitations

Several limitations will be discussed. To start with, module evaluations in Study 1 were not filled in by all informal caregivers who took part in pilot RCT trial. For this reason, the collected data might not accurately represent all informal caregiver experiences. Similarly, a convenience sample of eight stakeholders in the Study 2 is relatively small and might not be representative. A more comprehensive recruitment

approach as well as higher sample size could have resulted in more representative findings. At the same time, stakeholders were individuals with various educational and occupational backgrounds residing in different locations spread throughout the country. Also, focus group discussions are often based on small samples. Another limitation stems from the fact that the process evaluation could have been conducted before the piloting of the ICBT intervention. Our decision was motivated by the knowledge that the basic structure of the intervention platform as well as the basic content, was researched in tens of trials (43). Therefore, this provided us with grounds for piloting the intervention first.

Relevance and Applicability of the Findings

First, this study describes a process evaluation of the ICBT intervention for the informal caregivers. Previously, there has only been few attempts to study the suitability of ICBT for informal caregivers, in spite of the established effects of ICBT for various psychological symptoms (13). Second, our findings provide information on how the intervention could be optimized further. We hope that this knowledge can also be beneficial for other researchers who are developing and adapting internet interventions. Third, the findings provide information about the possible future implementation and acceptability of ICBT as viewed by the stakeholders. Lastly, the study adds to the knowledge in relation to the specific cultural context for which internet intervention research still is scarce.

General Conclusion

A process evaluation was conducted for evaluating the feasibility of an ICBT intervention for informal caregivers. Most of the participant comments indicated the interventions format and content to be perceived positively. In addition, stakeholders described the intervention as needed and acceptable means of the support for the informal caregivers. Despite this, several developments could be made before further research investigating its effectiveness is conducted. To start with, clear instructions about the use of the intervention should be provided. Prospective participants should be informed about what to expect from the intervention and, what efforts will be required from them. In addition, by the end of the intervention, a concise list of further resources should be provided. Lastly, an opportunity to tailor the intervention's themes should be considered, based on informal caregiver circumstances. Once these are implemented, further evaluation of the intervention's effectiveness in a larger randomized controlled trial is warranted.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because it is not possible to fully anonymize the dataset without impacting the primary research. Requests to access the datasets should be directed to the primary investigator Prof. Gerhard Andersson, gerhard.andersson@liu.se.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Study 1: Vilnius University Psychology Research Ethics Committee documented as 08-07-2019 No. 26; Study 2: Ethics approval for this study was not required according to the national ethical regulations for research, as it was not a clinical trial, participants were not requested to share any sensitive information and no obvious risks could be identified. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IB and GA contributed to the study conception, coordination, design, and data collection and analysis. IB drafted the manuscript with input from GA. EK and RS contributed to the design of the study. All authors have contributed to revising the manuscript and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.725510/full#supplementary-material

REFERENCES

1. Revenson T, Griva K, Luszczynska A, Morrison V, Panagopoulou E, Vilchinsky N, et al. *Caregiving in the Illness Context*. London: Springer (2016). doi: 10.1057/9781137558985
2. Bom J, Bakx P, Schut F, van Doorslaer E. The impact of informal caregiving for older adults on the health of various types of caregivers: a systematic review. *Gerontologist*. (2019) 59:e629–42. doi: 10.1093/geront/gny137
3. Serafini JD, Damianakis T, Marziali E. Clinical practice standards and ethical issues applied to a virtual group intervention for spousal caregivers

of people with Alzheimer's. *Soc Work Health Care*. (2007) 44:225–43. doi: 10.1300/J010v44n03_07
4. Moock J. Support from the internet for individuals with mental disorders: advantages and disadvantages of e-mental health service delivery. *Front Public Health*. (2014) 2:65. doi: 10.3389/fpubh.2014.00065
5. Griffiths F, Lindenmeyer A, Powell J, Lowe P, Thorogood M. Why are health care interventions delivered over the internet? A systematic review of the published literature. *J Med Internet Res*. (2006) 8:e10. doi: 10.2196/jmir.8.2.e10
6. Andersson G, Titov N, Dear BF, Rozental A, Carlbring P. Internet-delivered psychological treatments: from innovation to implementation. *World Psychiatry*. (2019) 18:20–8. doi: 10.1002/wps.20610
7. Cristancho-Lacroix V, Wrobel J, Cantegreil-Kallen I, Dub T, Rouquette A, Rigaud A-S. A web-based psychoeducational program for informal caregivers of patients with Alzheimer's disease: a pilot randomized controlled trial. *J Med Internet Res*. (2015) 17:e117. doi: 10.2196/jmir.3717
8. Núñez-Naveira L, Alonso-Búa B, de Labra C, Gregersen R, Maibom K, Mojs E, et al. UnderstAID, an ICT platform to help informal caregivers of people with dementia: a pilot randomized controlled study. *Biomed Res Int*. (2016) 2016:5726465. doi: 10.1155/2016/5726465
9. Wallace SJ, Kothari J, Jayasekera A, Tointon J, Baiyewun T, Shrubsole K. Do caregivers who connect online have better outcomes? A systematic review of online peer-support interventions for caregivers of people with stroke, dementia, traumatic brain injury, Parkinson's disease and multiple sclerosis. *Brain Impairment*. (2021) 1–27. doi: 10.1017/BrImp.2021.5
10. Wasilewski MB, Stinson JN, Cameron JI. Web-based health interventions for family caregivers of elderly individuals: a scoping review. *Int J Med Inform*. (2017) 103:109–38. doi: 10.1016/j.ijmedinf.2017.04.009
11. Spencer L, Potterton R, Allen K, Musiat P, Schmidt U. Internet-based interventions for carers of individuals with psychiatric disorders, neurological disorders, or brain injuries: systematic review. *J Med Internet Res*. (2019) 21:e10876. doi: 10.2196/10876
12. Sherifali D, Ali MU, Ploeg J, Markle-Reid M, Valaitis R, Bartholomew A, et al. Impact of internet-based interventions on caregiver mental health: systematic review and meta-analysis. *J Med Internet Res*. (2018) 20:e10668. doi: 10.2196/10668
13. Carlbring P, Andersson G, Cuijpers P, Riper H, Hedman-Lagerlöf E. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. *Cogn Behav Ther*. (2018) 47:1–18. doi: 10.1080/16506073.2017.1401115
14. Kaddour L, Kishita N, Schaller A. A meta-analysis of low-intensity cognitive behavioral therapy-based interventions for dementia caregivers. *Int Psychogeriatr*. (2019) 31:961–76. doi: 10.1017/S1041610218001436
15. Beauchamp N, Irvine AB, Seeley J, Johnson B. Worksite-based internet multimedia program for family caregivers of persons with dementia. *Gerontologist*. (2005) 45:793–801. doi: 10.1093/geront/45.6.793
16. Blom MM, Zarit SH, Groot Zwaaftink RB, Cuijpers P, Pot AM. Effectiveness of an Internet intervention for family caregivers of people with dementia: results of a randomized controlled trial. *PLoS ONE*. (2015) 10:e0116622. doi: 10.1371/journal.pone.0116622
17. Kajiyama B, Thompson LW, Eto-Iwase T, Yamashita M, Di Mario J, Marian Tzuang Y, et al. Exploring the effectiveness of an internet-based program for reducing caregiver distress using the iCare Stress Management e-Training Program. *Aging Mental Health*. (2013) 17:544–54. doi: 10.1080/13607863.2013.775641
18. Meichsner F, Theurer C, Wilz G. Acceptance and treatment effects of an internet-delivered cognitive-behavioral intervention for family caregivers of people with dementia: a randomized-controlled trial. *J Clin Psychol*. (2019) 75:594–613. doi: 10.1002/jclp.22739
19. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. *BMJ*. (2000) 321:694–6. doi: 10.1136/bmj.321.7262.694
20. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. (2008) 337:a1655. doi: 10.1136/bmj.a1655
21. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ*. (2021) 374:n2061. doi: 10.1136/bmj.n2061
22. Oakley A, Strange V, Bonell C, Allen E, Stephenson J. Process evaluation in randomised controlled trials of complex interventions. *BMJ*. (2006) 332:413–6. doi: 10.1136/bmj.332.7538.413
23. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: medical research council guidance. *BMJ*. (2015) 350:h1258. doi: 10.1136/bmj.h1258
24. van Gemert-Pijnen L, Kelders SM, Kip H, Sanderman R. *eHealth Research, Theory and Development: a Multi-Disciplinary Approach*. Abingdon: Routledge (2018). doi: 10.4324/9781315385907
25. Biliunaite I, Kazlauskas E, Sanderman R, Truskauskaite-Kuneviciene I, Dumarkaite A, Andersson G. Internet-based cognitive behavioral therapy for informal caregivers: randomized controlled pilot trial. *J Med Internet Res*. (2021) 23:e21466. doi: 10.2196/21466
26. Biliunaite I, Dumarkaite A, Kazlauskas E, Sanderman R, Andersson G. ICBT program for improving informal caregiver well-being: a qualitative study. *Internet Interv*. (2021) 23:100361. doi: 10.1016/j.invent.2021.100361
27. Vlaescu G, Alasjö A, Miloff A, Carlbring P, Andersson G. Features and functionality of the Iterapi platform for internet-based psychological treatment. *Internet Interv*. (2016) 6:107–14. doi: 10.1016/j.invent.2016.09.006
28. Baumeister H, Reichler L, Munzinger M, Lin J. The impact of guidance on Internet-based mental health interventions—a systematic review. *Internet Interv*. (2014) 1:205–15. doi: 10.1016/j.invent.2014.08.003
29. Roca M, Gili M, Garcia-Garcia M, Salva J, Vives M, Campayo JG, et al. Prevalence and comorbidity of common mental disorders in primary care. *J Affect Disord*. (2009) 119:52–8. doi: 10.1016/j.jad.2009.03.014
30. Novak M, Guest C. Application of a multidimensional caregiver burden inventory. *Gerontologist*. (1989) 29:798–803. doi: 10.1093/geront/29.6.798
31. Blair E. A reflexive exploration of two qualitative data coding techniques. *J Methods Measur Soc Sci*. (2015) 6:14–29. doi: 10.2458/v6i1.18772
32. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol*. (2006) 3:77–101. doi: 10.1191/1478088706qp063oa
33. Braun V, Clarke V. One size fits all? What counts as quality practice in (reflexive) thematic analysis? *Qual Res Psychol*. (2020) 18:328–52. doi: 10.1080/14780887.2020.1769238
34. Beukes EW, Manchaiah V, Davies AS, Allen PM, Baguley DM, Andersson G. Participants' experiences of an Internet-based cognitive behavioural therapy intervention for tinnitus. *Int J Audiol*. (2018) 57:947–54. doi: 10.1080/14992027.2018.1514538
35. Rozental A, Kothari R, Wade T, Egan S, Andersson G, Carlbring P, et al. Reconsidering perfect: a qualitative study of the experiences of internet-based cognitive behaviour therapy for perfectionism. *Behav Cogn Psychother*. (2020) 48:432–41. doi: 10.1017/S1352465820000090
36. Johansson O, Michel T, Andersson G, Paxling B. Experiences of non-adherence to Internet-delivered cognitive behavior therapy: a qualitative study. *Internet Interv*. (2015) 2:137–42. doi: 10.1016/j.invent.2015.02.006
37. Pywell J, Vijaykumar S, Dodd A, Coventry L. Barriers to older adults' uptake of mobile-based mental health interventions. *Digit Health*. (2020) 6:2055207620905422. doi: 10.1177/2055207620905422
38. Borghouts J, Eikey E, Mark G, De Leon C, Schueller SM, Schneider M, et al. Barriers to and facilitators of user engagement with digital mental health interventions: systematic review. *J Med Internet Res*. (2021) 23:e24387. doi: 10.2196/24387
39. Beatty L, Binnion C. A systematic review of predictors of, and reasons for, adherence to online psychological interventions. *Int J Behav Med*. (2016) 23:776–94. doi: 10.1007/s12529-016-9556-9

40. Christie HL, Bartels SL, Boots LM, Tange HJ, Verhey FR, de Vugt ME. A systematic review on the implementation of eHealth interventions for informal caregivers of people with dementia. *Internet Interv*. (2018) 13:51–9. doi: 10.1016/j.invent.2018.07.002
41. Pinquart M, Sörensen S. Differences between caregivers and noncaregivers in psychological health and physical health: a meta-analysis. *Psychol Aging*. (2003) 18:250. doi: 10.1037/0882-7974.18.2.250
42. Păsărelu CR, Andersson G, Bergman Nordgren L, Dobrean A. Internet-delivered transdiagnostic and tailored cognitive behavioral therapy for anxiety and depression: a systematic review and meta-analysis of randomized controlled trials. *Cogn Behav Ther*. (2017) 46:1–28. doi: 10.1080/16506073.2016.1231219
43. Andersson G, Carlbring P, Lindefors N. *History and Current Status of ICBT. Guided Internet-Based Treatments in Psychiatry*. Springer (2016). p. 1–16. doi: 10.1007/978-3-319-06083-5_1

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Patient Uptake, Experiences, and Process Evaluation of a Randomized Controlled Trial of Internet-Based Cognitive Behavioral Therapy for Tinnitus in the United States

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Introduction: An internet-based cognitive behavioral therapy (ICBT) offers a way to increase access to evidence-based tinnitus care. To increase the accessibility of this intervention, the materials were translated into Spanish to reach Spanish as well as English speakers. A clinical trial indicated favorable outcomes of ICBT for tinnitus for the population of the United States. In view of later dissemination, a way to increase the applicability of this intervention is required. Such understanding is best obtained by considering the perspectives and experiences of participants of an intervention. This study aimed to identify the processes that could facilitate or hinder the clinical implementation of ICBT in the United States.

Methods: This study evaluated the processes regarding enrolment, allocation, intervention delivery, the outcomes obtained, and the trial implementation. The study sample consisted of 158 participants who were randomly assigned to the experimental and control group.

Results: Although the recruitment was sufficient for English speakers, recruiting the Spanish participants and participants belonging to ethnic minority groups was difficult despite using a wide range of recruitment strategies. The allocation processes were effective in successfully randomizing the groups. The intervention was delivered as planned, but not all the participants chose to engage with the materials provided. Compliance for completing the outcome measures was low. The personal and intervention factors were identified as barriers for the implementation whereas the facilitators included the support received, being empowering, the accessibility of the intervention, and its structure.

Conclusion: An understanding regarding the factors contributing to the outcomes obtained, the barriers and facilitators of the results, engagement, and compliance were obtained. These insights will be helpful in preparing for the future dissemination of such interventions.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT04004260. Registered on 2 July 2019.

Keywords: process evaluation, clinical trial, internet-interventions, tinnitus, cognitive behavioral therapy, digital therapeutics, experiences, patient uptake

INTRODUCTION

Tinnitus is a chronic symptom, characterized by the perception of sounds in the ears or head of an individual without any external sound source, is a highly prevalent symptom affecting at least 10–15% of the adult population (1). Although not everyone is bothered by tinnitus, a proportion of those experiencing tinnitus finds it very distressing and it may affect many aspects of daily life, such as sleeping and concentrating. As experiencing tinnitus is associated with an increased risk of psychological difficulties, such as anxiety, depression, those distressed require interventions to help them cope with the tinnitus (2, 3). Managing tinnitus can be, notoriously challenging as there is often no medical cure (4). Management thus focuses on the address associated hearing loss, educating the patients, and provide tools and strategies to manage the tinnitus and associated problems. The intervention with the strongest research evidence according to tinnitus practice guidelines (5–7) and several systematic reviews (8, 9) is cognitive behavioral therapy (CBT).

A CBT is a psychological treatment addressing the unhelpful behaviors, thought patterns, and emotional reactions caused by tinnitus (10). To increase access to the CBT for tinnitus, an internet-based CBT for tinnitus (ICBT) was developed in Sweden (11) in a self-help format with psychological guidance. This program was later translated to German (12) and English (13). To further increase the accessibility, the ICBT for tinnitus is adapted to be delivered by the audiologists (14) with some training to handle the CBT elements without compromising the outcomes (15–18). To further increase the availability of CBT, the intervention was adapted for the population of the United States (19) and also translated into Spanish to reach the Spanish and English speakers (20). As a pilot study indicated the feasibility of the intervention (21, 22), a randomized clinical trial (RCT) was undertaken (21, 23). The studies in the United Kingdom were the first in which the ICBT was delivered by an audiologist (16–18). When delivered by an audiologist, this RCT in the United Kingdom indicated that ICBT led to a greater reduction in tinntius distress compared with weekly monitoring with an effective size of $d = 0.46$ [0.14–0.77]. The results were in line with the outcomes obtained in the studies in which psychologists had provided the guidance. In addition, there was a greater reduction in the negative tinnitus cognitions and insomnia. The results remained stable over the 2 month follow-up period. Although the favorable outcomes were obtained, there were some difficulties encountered during the running of the trial, largely surrounding low engagement, and the poor compliance rates for the questionnaire completion. To increase the applicability of the intervention and to prepare for later dissemination, an understanding is needed regarding the factors contributing to the outcomes, engagement, and compliance. Such understanding is best obtained by considering the perspectives and experiences of the participants of an intervention.

The process evaluations are a means of providing a framework for analyzing the key components in the healthcare interventions. Such evaluations are important as various external factors can affect the health conditions and intervention uptake (24–26). The different process evaluation models for healthcare interventions have thus been developed, such as the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework [RE-AIM (27, 28)] and the components suggested by Baranowski and Stables (29) and Linnan and Steckler (30). Although each model is unique, the overlapping component includes investigating the recruitment procedures, the context of the research, the intervention delivery and how it was received, the outcomes obtained, and the implementation of the intervention. Despite the relevance of process evaluations, they are not widely used within audiology with only a few process evaluations related to hearing difficulties (31–33) and one related to the ICBT for the population of the United Kingdom (34).

The research objective of the present study was to identify the processes that could facilitate or hinder the clinical implementation of ICBT for tinnitus in the United State (23). This was done by considering the full trial implication from the recruitment to post-intervention follow-up. This was in view of gaining insights into the applicability of ICBT for the population in the United States and identify the factors that could help optimize dissemination. The specific objectives were to evaluate the processes regarding the enrollment, allocation, intervention delivery, the outcomes obtained, and the trial implementation.

MATERIALS AND METHODS

Research Design

This study was a process evaluation of an RCT of ICBT for tinnitus conducted between March 2020 and July 2020. The process evaluation was conducted in parallel to a clinical trial that investigated the efficacy of ICBT for tinnitus in the United States (23). The participants were randomized with a 1:1 allocation ratio to the *experimental group* to receive ICBT for 8 weeks,

or the *control group* who received the intervention after a delay of 8 weeks during which time they were monitored weekly. The outcome measures were completed at baseline, T1 (post-intervention for the experimental group), T2 (post-intervention for the control group), T3 at 2 month follow-up post-intervention for each group, T4 at 1 year follow-up.

The RCT and its protocol were pre-registered at the Clinical Trials.gov: NCT04004260 on July 2, 2019. Ethical approval was obtained from the Institutional Review Board at Lamar University, Beaumont, Texas, United States (IRB-FY17-209). The study was conducted and reported according to the Consolidated Standards of Reporting Trials (CONSORT) EHealth guidelines (35). An independent data monitoring committee monitored the running of the trial.

Participants

Target Recruitment

Following the sample size calculations, the goal was to enroll 152 participants. To ensure inclusivity, the aim was to recruit 48 Hispanic or Latino participants and 94 non-Hispanic or Latino. The racial categories targeted were American Indian/Alaskan Native (2), Asian (6), Black or African American (18), more than one race (20), and White (106).

Eligibility Criteria

Eligibility was determined in a two-stage process. The inclusion criteria were that the participants needed to be aged 18 years or over and living in Texas, United States. Computer and internet access were required. The participants had to have experienced tinnitus for a minimum duration of 3 months and have a score of 25 or above on the Tinnitus Functional Index (TFI), suggesting a need for tinnitus care (36). The exclusion criteria were indications of significant depression ($\geq$15 scores) on the Patient Health Questionnaire [PHQ-9 (37)]. Other aspects that resulted in the exclusion are: indications of self-harm thoughts or intent (i.e., answering affirming on Question 10 of the PHQ-9 questionnaire), reporting any major medical, psychiatric, or mental disorder which may hamper commitment to the program or tinnitus as a consequence of a medical disorder still under investigation.

Eligibility Screening

Initially, the participants completed the baseline measurements online (T0). Following completion, a telephonic screening was arranged, to ensure participants fulfilled the study requirements. For any participant indicating possible self-harm thoughts or significant depression on the PHQ-9, a psychologist would phone them within 24 h. A clear protocol was set up for these participants. The scores were discussed, and the participants were questioned as to whether they had additional help and support for these problems. If there were any concerns, a stabilization plan was set up. If this was not possible, the crisis team would be contacted. The person would be kept on the phone until the crisis team arrived, although no such cases were reported in the current study. Everyone who called on the phone was provided with the emergency contact details. The psychology or other appointments were arranged as appropriate, or referrals made were indicated.

Intervention

The ICBT content was based on a Swedish CBT self-help program (38), transformed into an 8 week interactive e-learning version (39) and then, adapted linguistically, culturally, and functionally to ensure the suitability for the population of the United States (19, 20). The ICBT platform consisted of 22 modules with worksheets and quizzes (14). The participants were asked to read the modules weekly and ideally spend at least 10 min each day practicing the suggested strategies. The intervention specifically targeted reducing the activity limitations and participation restrictions and included applied relaxation due to the importance of this aspect in tinnitus managment (40). Both the groups received the same intervention, only the timings regarding receiving the intervention varied.

The guidance was provided to support the participants while undertaking the intervention. This included monitoring progress, monitoring the weekly scores, providing feedback on the worksheets completed, outlining the content of new modules, and answering questions. The participants who did not engage were contacted to support participation and to discuss the possible barriers. An encrypted 2-way messaging system within the ePlatform was used to communicate (39). The intervention was provided free of charge and the participants could continue to access it after the intervention was completed.

Parameters Used for the Process Evaluation of the Clinical Trial

The overlapping and relevant elements from the healthcare process evaluation models were used to identify the process to evaluate for this clinical trial from the RE-AIM model (27, 28), from Baranowski and Stables (29) and Linnan and Steckler (30). Five processes were selected, namely, enrollment, allocation, intervention delivery, the outcomes obtained, and the trial implementation as illustrated in **Table 1**. A demographic questionnaire was used to establish the health-related and tinnitus-specific information at baseline (T0). The standardized outcome measures were completed at baseline (T0), after the experimental group completed the intervention (T1) after the control group completed the intervention (T2), at 2 month follow-up (T3), and 1 year follow-up (T4). The primary outcome measure was tinnitus severity as measured by the TFI (36). The secondary outcomes were:

- The Generalized Anxiety Disorder−7 [GAD-7 (41)] to assess the symptoms of generalized anxiety disorder.
- The PHQ-9 (37) (38) indicated the symptoms of depression.
- The Insomnia Severity Index [ISI (42)] assessed the presence of insomnia.
- The Tinnitus Cognitions Questionnaire [TCQ (43)] was used to measure the negative tinnitus cognitions.
- The EQ-5D-5L (44) measured general health-related quality of life.

TABLE 1 | The processes in the clinical trial.

Process	Sub-process	Description	Data Collection
Enrolment	Recruitment	Processes involved in approaching and attracting participants	• Evaluation of the recruitment formats used • Use of Google analytics to examine recruitment trends
	Participant screening	Processes involved in selecting the participants for the study	• Scrutiny of the inclusion criteria • Motivation ratings on a Likert scale of 1–10 • Expectations ratings on a Likert scale of 1–10 • Two-step process • Protocols
Allocation	Reach: Number recruited	Whether the target number of participants were obtained for the study and whether they represented the target population of those with distressing tinnitus	• Comparison of the recruitment targets set and achieved
	Context: Participant characteristics	The social, demographic, and socio-economic characteristics of the participants that may affect generalizability of the outcomes	• Considering participant demographical profiles (gender, age, tinnitus duration, previous tinnitus treatments) • Internet proficiency
	Randomization	The effectiveness of the randomization process selected	
Intervention delivery	Dose delivered	The amount and content of the intervention	• Number of modules • Number of videos • Guidance received
	Dose received	Participants engagement with the intervention	• Number of logins • Modules that were opened • Module ratings • Worksheets completed • Messages sent • Time spent on the modules
Outcomes	Adherence	Participants completing the outcome measures	• Percentage completing the outcome measures at each time point
	Primary outcome results	Whether tinnitus severity decreased	• The effect of the intervention on tinnitus severity
	Secondary outcomes	Whether tinnitus comorbidities improved	• Data monitoring • The effect of the intervention on anxiety, depression, insomnia, quality of life and hearing-related outcomes
Trial implementation	Implementation Fidelity	The degree to which the protocol was carried out as intended	• Comparison of the actual programme to the protocols described
	Barriers to implementation	Processes that were barriers to the implementation	• Satisfaction questionnaire • Qualitative data from participant interview • Qualitative data from open ended questions • Qualitative data from *ad hoc* messages
	Facilitation of effectiveness	Processes that facilitated effectiveness from the participants perspectives	• Satisfaction questionnaire • Qualitative data from participant interview • Qualitative data from open ended questions • Qualitative data from *ad hoc* messages

- The Tinnitus and Hearing Survey [THS (45)] was used as a short measure to identify the tinnitus severity, hearing disability, and hyperacusis of the participants.
- A short questionnaire was administered to try to determine the effect of coronavirus disease 2019 (COVID-19) on the study asking whether the participants had COVID-19 and how this was affecting them. This questionnaire was added during the middle of the study due to the study being administered during the height of the first wave of the pandemic.
- A satisfaction questionnaire was designed to assess the suitability, content, usability, presentation, and exercises from the intervention consisting of 15 five-point Likert-type scaled questions (39).
- The open-ended questions to find out more about the experiences from the intervention such as which modules were helpful, what barriers were found, and suggestions for improvements. This was done by both asking open-ended questions in a survey as well during the phone calls made to the participants post-intervention.

Data Analysis

Data analysis incorporated a mixed approach, including both quantitative and qualitative analyses. The Statistical Package for Social Sciences (IMB SPSS for Windows V.26.0, NY, USA) was used for the statistical analyses (46).

Descriptive statistics were used to describe the sample characteristics. The continuous variables were summarized with

means and SDs. The categorical variables were described using frequencies and percentages. The effect sizes were used to determine the outcome effectiveness. The outcomes related to the satisfaction of the intervention and the specific components were rated on a 5-point Likert scale and were analyzed using descriptive statistics.

The open-ended questions were analyzed using a qualitative content analysis described by Graneheim and Lundman (47). The content analysis enables the systematic interpretation of the participant statements to identify the central aspects (a set of condensed categories) that emerge from careful examination of the raw data using a bottom-up approach. Various steps were involved in the process. Initially, the responses were read repeatedly and coded for "meaning units," which are statements that relate to the same central category. These meaning units formed the units of analysis for coding. The next process was identifying the categories that were repeatedly mentioned. The responses that related to the same category were grouped together. The repeated patterns were further grouped until the clear condensed categories and subcategories were identified. The codes were then gradually merged into the broader categories and subcategories by grouping thematically similar codes together. The categories were subsequently condensed by combining the categories with similarities, ensuring that the categories were mutually exclusive. The category labels were assigned. After selecting the codes and categories, the original responses were checked to ensure they were in line with the assigned categories and to identify if any additional categories emerged. The dataset was rechecked for consistency. The data coding was performed independently by the two researchers. The coding was compared and in case of inconsistencies, these were discussed.

RESULTS

Processes Related to the Enrollment

The recruitment and participant screening processes are discussed in this section.

Processes Related to Recruitment

The multidimensional recruitment strategies were employed to obtain a varied sample. **Table 2** outlines the different recruitment strategies used and how successful each was. A comprehensive study website was designed to provide information for those who were interested in the study. This included how to register, the aims of the program, the time commitment, and the nature of the intervention. All the recruitment strategies guided individuals to the study website (www.tacklingtinnitus.org). Google analytics indicated that 3,720 users viewed the website as outlined in **Table 2**. This indicates that the recruitment strategies drew sufficient interest to the website.

All the recruitment materials were translated from English into Spanish, adding an extra layer of complexity. Both the English and Spanish team members were required for this study. Recruiting the Spanish participants required additional thought and it was difficult to target these participants. Direct contact was included during the recruitment, using a public patient initiative (PPI).

Processes Related to Participant Screening

There were 157 participants who registered on the study website and showed interest prior to the recruitment opening. Further recruitment means drew a total of 315 participants who showed interest in the study and were screened (263 English and 52 Spanish). Of these, 158 were eligible (as shown in **Figure 1**). The exclusion reasons included having high depression scores or a positive answer regarding self-harm intent (46 English and 3 Spanish), low tinnitus severity (36 English and 1 Spanish), living outside the recruitment area in the State of Texas, United States (5 English and 40 Spanish). According to the protocol set for this trial, a psychologist was required in the team to make phone calls to the 49 participants (three using translation) who had high depression scores. Having a psychologist was helpful, as tinnitus is best approached from a multidisciplinary perspective (4–10) but involving more experts may be an expense, not all the teams can accommodate. As all the participants contacted were those with known depression that was being treated and there were no cases that raised concern, this particular study did not specifically require the expertise of the psychologist to deal with any serious depression or self-harm intent.

Processes Related to Allocation

Reach

The target numbers according to sample size calculations were $n = 152$. A total of 158 participants were enrolled as shown in **Figure 1**, which indicated that the required participants were reached. There were fewer Spanish speaking participants than aimed for.

Context

The social, demographical, and socio-economic characteristics of the participants were identified. Equal gender ratios were recruited with $n = 80$ (51%) being female and $n = 78$ (49%) being male. A wide age range was represented (19–84 years) with a mean of 57 (SD: 12) years, which correspond to the expected range due to the incidence of tinnitus being most prevalent in the 40–70 years age range (1). A wide range of tinnitus duration was found (3 months−70 years) with the average tinnitus duration being 14 years (SD: 14).

The majority had obtained a university degree ($n = 84$; 53%) or other training vocationally or from a college ($n = 53$; 34%). Only a minority had only a high school qualification ($n = 21$; 13%). The majority were skilled workers or professionals ($n = 95$, 61%) with only 10 (6%) not working, and 52 (33%) being retired. To ensure the participants were representative of those living in the United States, different ethnic categories were targeted. In addition, the planned ethnic enrollment was less than expected as shown in **Table 3**. Most of the participants indicated that they were frequent computer and internet users ($n = 144$, 91%) with only 9% ($n = 14$) having only basic computer skills.

The clinical presentation of the participants indicated tinnitus severity at a level requiring the need for a tinnitus intervention with a mean TFI score of 53.98 (SD: 17.54). The mean anxiety score on the GAD-7 was 5.6/21 (SD: 4.26) and the mean PHQ-9 was 5.48/27 (4.12) indicating mild anxiety and depression. This reflects the inclusion criteria requiring no participants with

TABLE 2 | The various recruitment strategies used.

Recruitment Means	Reach	Facilitators	Barriers
Intervention website (www.tacklingtinnitus.org)	• 3,720 users • Average pages viewed: 11 • Average session duration: 10 min • 24% returned; 76% were new • Peak in views were during March 2020 during the recruitment period • 71% found the website directly, 19% via social media, 8% *via* a search engine, 2% via referral	• Information in English and Spanish • Cost-effective • Informative, all the information in one place • Gives a feel of the intervention as the same website pages are used	• Difficult to attract only participants meeting the inclusion criteria • Recruitment pages were long. They may be too long and put people off
Location of website views	United States $n = 3,720$; 82% Spain $n = 141$, 4% Mexico $n = 88$; 3% Argentina $n = 48$, 1%	Attracted mostly from the United States as required	• Difficult to target only those in Texas (attracted 18% from other countries countries)
Story board YouTube video	Premiered before the pilot study on September 21, 2019 and had 549 views at the time investigation	Attractive, information presented in an auditory and visual format in English and Spanish	• Very costly
Professional recruitment agency (i.e., Trial Facts)	Number recruited: 92 (44 English, 38 Spanish) Online screening: 25 not suitable Phone screening by study team for: 67 Phone screening indicated unsuitability: 18 not suitable/ not interested/ or not answering calls Passed screening: 49 Of those passing, 23 enrolled in the program (25% enrolled)	• Clear outline provided of the reasons people did not meet the inclusion criteria • Clear processes to follow	• Very costly • Additional screening processes requiring additional time resources from the study team required for these participants • Recruitment materials needed to be provided and formatted by study team for this company requiring additional time • Feedback had to be provided to the company using their software • Additional time with meetings for the agency • Recruitment of Spanish and ethnic minorities numbers still low
Direct contact	Leaflet/ posters to churches, old age homes, community centers to target Spanish participants and ethnic minorities in particular	Reaching people who may not find out via the internet or social media	• Poor understanding of the Spanish publics' perspective of recruitment • Costly • Needed a lot of time from the study team
Targeting those patients seeking help	Emails/ posters/ leaflets provided to professionals who may see patients with tinnitus asking them to pass on • Audiologists • Psychologists • Physicians/ doctors • Ear, Nose and Throat (ENT) specialists • Student clinics at Lamar University	Reaching people with probably bothersome tinnitus Building networks with the professional community	• Costly • Needed a lot of time from the study team
Public Patient Initiative (PPI)	• Used to gain ideas for recruitment • The contacted their local professionals	• Participant perspectives helpful • Video of experiences	Could have involved more in all processes during recruitment
Media	• Press release • Television advertisement • Radio advertisement • Newspapers (Beaumont enterprise)	Many readers with potential for a good reach	• Very costly • Difficult to find contacts
Social Media	• Twitter • Instagram • YouTube • Facebook	Potential for a good reach	Needed additional resources from the study team to set up and manage
Patient organizations	• American Tinnitus Association (ATA) • Sertoma, Spanish organization helping people with hearing loss	Building networks with these organizations	Could not control how much/ little the distributed the information
Tinnitus support groups	• The researchers, audiologists and member from the public patient involvement group attended tinnitus support groups to share information about the intervention and encourage recruitment	• The face-to-face contact was appreciated • Recruitment strategy was effective	• Costly • Time consuming • Many of these people are already helped and don't need the intensity of such a program

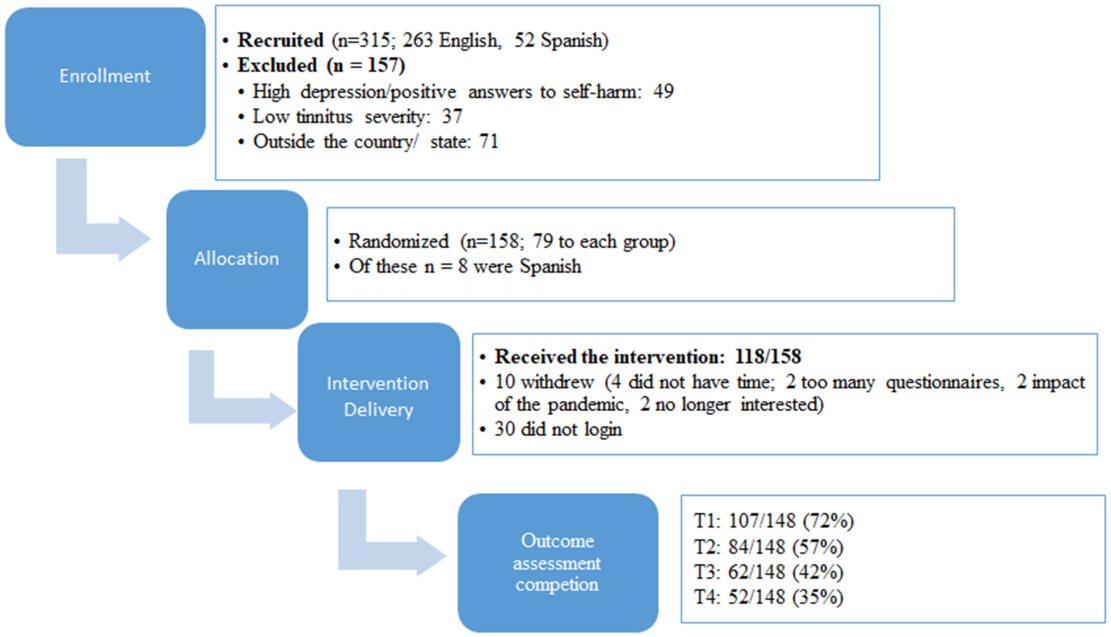

FIGURE 1 | Flowchart of enrollment, allocation, intervention delivery, and outcome assessment completion. T1 is after the experimental group received the treatment, T2 after the control group received the treatment, T3 is at 2 month follow-up, and T4 is at 1 year follow-up.

significant levels of depression (15 or more on the PHQ-9). The ISI indicated that this group had subthreshold insomnia with a score of 10.05 (SD: 5.84). The context of the research thus showed that the participants with troublesome tinnitus and a wide range of demographic backgrounds were drawn to the study.

Randomization

As an unbiased randomization process is required in a clinical trial, the randomization process was considered. Randomization was not done by the team directly involved with the participants to avoid any possible bias. The team statistician provided computer-generated randomization scheduled and an independent research assistant randomized the participants in a 1:1 allocation in the blocks of varying sizes after the participants were pre-stratified for language (English and Spanish). Following randomization, no group differences were evident as there was no estimated difference in the baseline tinnitus severity between the groups ($p = 0.92$). The demographic profiles of the groups were similar in the terms of variables, such as gender and age. The participants and investigators could not be blinded to the group allocation due to the nature of the intervention. To minimize bias, the participants were informed when the intervention would commence but not explicitly to which group they were assigned.

Processes Involved in Intervention Delivery

Dose Delivered

The intervention materials were released weekly over and 8 week period. Each week, the participants received 2–3 modules, a practice diary, and videos of the techniques as shown in **Table 4**. The dose was delivered as planned and according to the protocol.

TABLE 3 | The ethnic and racial characteristics of the participants.

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	7 (29)	13 (29)	20 (58)
Not Hispanic or Latino	73 (47)	65 (47)	138 (94)
Ethnic Category: Total of All Subjects	80 (76)	78 (76)	158 (152)
Racial Categories			
American Indian/Alaska Native	0 (1)	0 (1)	0 (2)
Asian	0 (3)	1 (3)	1 (6)
Black or African American	2 (9)	2 (9)	4 (18)
White	78 (53)	70 (53)	148 (106)
More than One Race	0 (10)	5 (10)	5 (20)
Racial Categories: Total of All Subjects	80 (76)	78 (76)	158 (152)

Numbers in the parenthesis are the planned enrollment numbers.

It outlines that a comprehensive intervention was delivered consisting of 22 modules and a variety of other elements. This included videos in most of the modules. In addition, the participants received weekly guidance in the form of messages to provide feedback on the work done and to try to encourage the participants who were not engaging during the intervention.

Dose Received

Only 54% of the participants were able to complete the 8 week CBT course as 10 withdrew and 38 never accessed the intervention materials. **Table 4** shows the extent to which participants actively engaged and interacted with the resources

TABLE 4 | Dose delivered and received for 118 participants undertaking the internet-based cognitive behavioral therapy (ICBT) intervention.

	Dose delivered	Dose received
Logged into the platform	158 = Login information, with reminders, phone calls and text messages to encourage login	118 of the 158 participants with an average of 8.1 logins (SD: 11.3)
Number of modules	22 (17 recommended and 5 optional) releasing 2–3 weekly	Average 6.4 (SD: 7.9)
Number of videos	16	*Positive feedback:* Expert opinions helped me give more trust to the material; very informative *Negative feedback*: Some were a little too long
Guidance received	5,660 messages (36 per average for the 158 participants)	163 messages sent (Mean 1.0, SD: 2.8)
Time spent on the modules	Materials for ∼20–40 min per module depending on the content and tasks	20 min: 45/118 participants 20–45 min: 51/118 participants Longer than 45 min: 18/118 participants
Program completion		Yes: 64/118 (54%) No: 54/118 (46%)

provided. **Table 5** shows how many users opened each module. There was a steady decline from 104 opening the initial module to 30 doing the final module. The engagement for the optional modules was also low ranging between 55 and 19 openings of each module. The number of worksheets completed was reduced from 86 for the initial worksheet to 14 for the later worksheets.

To identify whether the engagement was related to satisfaction with the modules, the satisfaction for each module is shown in **Table 5**. The overall ratings were high for being able to understand the modules at 9.4/10 (SD: 1.2), the usefulness of the information 9.1/10 (SD: 1.6), and applicability of the information was 9.0/10 (SD: 1.6). These ratings are high, indicating those that did the modules found them helpful and usable as indicated by the example of the open-ended responses about what they gained from the information.

Processes Involved in the Outcomes Obtained

Adherence

Overall, the compliance for completing the outcome measures was low as shown in **Figure 1**. The completion rates at T1 were 72%. This decreased to 57% at T2, 42% at T3, and 35% at T4.

Primary Outcome Results

The main outcome was a reduction in tinnitus distress. This was achieved as indicated by an effect size of $d = 0.46$ (*CI*: 0.14–0.77) after the experimental group received the treatment (23). After the control group received the treatment, their tinnitus severity reduced. These improvements were maintained during the 2 and 12 month follow-up periods. These results were clinically significant for 51% of the participants from both the groups after completing the intervention ($n = 75/148$) indicating that their tinnitus severity reduced by more than 22.74 points. Hence, although the engagement was not optimal, the improvements in tinnitus distress were evident.

Secondary Outcome Results

Furthermore, the intervention led to the experimental group having a significantly greater reduction in insomnia, negative tinnitus cognitions, and hearing disability. Significant differences were not found for anxiety, depression, and quality of life, although the reductions were maintained during the follow-up periods (23).

The study reported minimal or no adverse effects. During the intervention period, only 1 (0.6%) participant had an increase of more than 10 points on the THI-S questionnaire. On finding out more, this was related to a particularly stressful deadline for work under difficult circumstances during the COVID-19 pandemic. There was only 1 (0.6%) participant who reported an adverse effect on the outcome questionnaire, explaining that initially, their tinnitus was more bothersome due to all the focus on tinnitus at the start of the intervention. There were no serious adverse events such as privacy breaches or major technical problems.

The involvement of a data monitoring committee added transparency and accountability to the results. The quarterly reports were prepared for the committee to monitor the enrollment, recruitment, results, adverse effects, and trial running.

Processes Involved in the Trial Implementation

Implementation Fidelity

Various protocols were set up before commencing and a pilot trial was initially run to identify the shortcomings to aid the effective implementation of the clinical trial (21, 22). The materials were adapted to ensure they were accessible without high linguistic demands (20) and the platform was functionally acceptable (19) before running the clinical trial. The intervention was delivered between the end of March 2020 and July 2020. This was during the peak of the first wave of the COVID-19 pandemic. The intervention ran as planned, although it was started 2 weeks earlier than planned when it became apparent that the pandemic was causing disruptions to everyday life.

A questionnaire was administered to try to determine the effect of COVID-19 on the study. Only a few responses were received. Of those responses, 5/43 (12%) said that they had had the COVID-19 virus. Of those answering, 12/43 (28%) reported that the situation was affecting their tinnitus. The reasons provided included increased anxiety, stress, being

TABLE 5 | The engagement and satisfaction with the intervention.

Module	Number of users opening the modules	Number of participants completing the worksheets	Intervention satisfaction: Scale of 1–10. Mean (SD)			Examples of the usability of the information
			Understand-ability was the module	Usefulness of the information	Applicability of the information	
Recommended modules						
Introduction	104 (88%)	No 1: 86 (73%) No 2: 72 (61%)	NA	NA	NA	NA
Tinnitus overview	84 (71%)	No 1: 79 (60%) No 2: 77 (65%) No 3: 74 (63%) No 4: 72 (61%)	9.5 (1.0)	9.1 (1.2)	9.3 (1.1)	I now understand that I am somewhat in control of my tinnitus, in that I can change the way I think about it, which will change my feelings, which will change my reaction to it. Thereby taking the importance off of it, and ultimately accepting it as a part of me.
Deep relaxation	83 (70%)	No 1: 79 (60%) No 2: 76 (64%) No 3: 74 (63%)	9.4 (1.0)	9.1 (1.5)	9.0 (1.8)	Seems like a good way to stop the feedback loop of anxiety by interrupting some of the physiological practices that reinforce anxiety. The connection between anxiety and tinnitus is noticeable. I can see where this practice can help to interrupt that connection
Positive imagery	59 (50%)	No 1: 49 (42%) No 2: 47 (40%)	9.2 (1.7)	9.0 (1.7)	8.6 (2.1)	I was honestly amazed by how much I let my mind take me on a journey. I completely forgot about my tinnitus for a good chunk of it
Deep breathing	51 (43%)	No 1: 49 (42%) No 2: 43 (36%)	9.3 (1.2)	9.1 (1.5)	9.3 (1.5)	What stood out was that we typically don't get enough air with shallow breathing, and especially when we're tense. Also placing 1 hand on chest and the other on belly helps me feel the difference between chest and belly breathing
Changing views	48 (41%)	No 1: 43 (36%) No 2: 43 (36%) No 3: 39 (33%) No 4: 37 (31%) No 5: 38 (32%)	9.0 (1.4)	8.4 (2.0)	8.4 (2.1)	I thought the sounds you hear all the time you just never pay attention to, but they are there like the ceiling fan, or Ice Box. I like the idea suggested of listening to the waves but then diving in the water to make the waves less noticeable is a way of helping me to think about it all
Entire body relaxation	47 (40%)	No 1: 24 (20%)	9.7 (0.6)	9.2 (1.4)	9.3 (1.4)	I like the idea of whole body relaxation done quickly. I feel it is as or more effective than the slower way
Shifting focus	42 (36%)	No 1: 40 (34%)	9.4 (0.9)	9.0 (1.5)	9.0 (1.8)	The technique itself, shifting focus between two things and shifting focus between one object and tinnitus, is new to me. The explanation in the video about how tinnitus is not worthy of attention is quite helpful too. I think I'll start answering my tinnitus with that thought
Frequent relaxation	38 (32%)	No 1: 22 (19%)	9.8 (0.8)	9.0 (2.0)	9.0 (2.0)	I am struggling this week, just lost a good friend and it seems like the whole country is in chaos right now. But relaxation techniques are really valuable right now, not just for coping with tinnitus
Thinking patterns	39 (33%)	No 1: 30 (25%) No 2: 31 (26%) No 3: 17 (14%)	9.2 (1.0)	9.0 (1.4)	8.7 (1.5)	I am amazed that my thinking pattern is making such a havoc physical mentally and emotionally my body and nervous system is worn out from fighting myself Thankful getting some understanding and help in CBT I can see there is a light in the end of the tunnel. I have so far benefited from this program tremendously
Quick relaxation	39 (33%)	No 1: 20 (16%)	9.6 (0.7)	9.4 (1.2)	9.4 (1.1)	I didn't really consider before of doing rapid relaxation. It seems like less pressure to do rather than spending a lot of time trying to relax. I like that it is quick and easy

(Continued)

TABLE 5 | Continued

Module	Number of users opening the modules	Number of participants completing the worksheets	Intervention satisfaction: Scale of 1–10. Mean (SD)			Examples of the usability of the information
			Understand-ability was the module	Usefulness of the information	Applicability of the information	
Challenging thoughts	38 (32%)	No 1: 14 (11%)	7.9 (2.0)	8.6 (1.9)	8.8 (1.7)	I never thought about challenging my negative thoughts, nor did I realize how different mindsets can interfere with our thinking. I recognize all of the mindsets (except for Blaming) as ones that I do a lot. My plan is to determine which mindset I'm in at the time of a negative thought and then try to switch to an opposite mindset
Relaxation routine	37 (31%)	No 1: 16 (13%)	9.7 (0.9)	9.3 (1.3)	9.3 (1.3)	Making time to enjoy things is important and is part of relaxation. The routine specified actually sounds a lot more doable than I had imagined
Being mindful	33 (28%)	No 1: 20 (16%)	9.9 (0.6)	9.1 (1.5)	9.0 (1.5)	Slowing down to focus and enjoy the moment in time helps in relaxation, my breathing, I can feel my body responding in an overall calmness
Listening to tinnitus	36 (31%)	No 1: 25 (21%)	9.9 (0.3)	9.3 (1.3)	9.2 (1.6)	This module is one of the best, only behind relaxation! I am not anxious about my tinnitus anymore. It's just a minor annoyance
Key point summary	31 (26%)	Reported elsewhere	NA	NA	NA	NA
Future planning	30 (25%)	No 1: 22 (18%) No 2: 27 (22%) No 3: 21 (17%)	NA	NA	NA	NA
Sound enrichment	55 (47%)	No 1: 17 (14%)	9.0 (0.7)	9.1 (1.9)	9.4 (1.0)	I have been trying to cover up my Tinnitus sound so I did not hear it. Now I understand that my brain has to get use to the tinnitus sound and have the masking sound just below the Tinnitus sound
Sleep guidelines	38 (32%)	No 1: 29 (24%) No 2: 28 (23%) No 3: 26 (22%) No 4: 22 (18%) No 5: 24 (20%) No 6: 16(13%)	9.7 (0.7)	9.1 (1.6)	8.6 (2.0)	Learned that our sleep cycles during the night go up/down. I also plan to implement the 20 min rule about getting up if unable to sleep after 20 min
Improving focus	28 (24%)	No 1: 11 (9%)	9.5 (0.8)	9.2 (1.4)	9.3 (1.2)	Take breaks to allow for better concentration, tinnitus is not always the reason for lack of concentration
Sound tolerance	26 (22%)	No 1: 14 (11%) No 2: 17 (14%)	9.6 (0.7)	9.8 (0.7)	9.5 (0.9)	This module was incredible. I finally feel understood and like I have been given advice I can truly implement in my life instead of just hearing "you can't do anything about tinnitus or hyperacusis"
Listening tips	19 (16%)	No 1: 5 (4%) No 2: 7 (5%)	9.9 (0.3)	9.9 (0.3)	9.8 (0.6)	I must pay better attention to the environment to modify the things I can for better hearing perception
Goals	NA	Initial: 72 (61%) Mid-program: 27 (22%) End: 22 (18%)	NA	NA	NA	NA
Practice worksheet		Completed 364 times	NA	NA	NA	NA

more depressed, and social isolation. Almost half (21/43; 49%) indicated that the pandemic had negatively impacted their emotional state and 12/ 43 (28%) felt lonely due to the social restrictions. During the intervention, some people became ill and could not complete the program. Others were given additional time as they did not have enough energy to complete the program after recovering. Thus, the pandemic did influence the intervention fidelity for some participants.

Barriers to Implementation

To identify the barriers to intervention usage, an intervention satisfaction questionnaire (39) was completed to identify how satisfied participants were with the intervention. The mean overall score for the satisfaction questionnaire was 46/75 (61% satisfaction) which was lower than expected due to higher satisfaction during the feasibility and pilot phase (19–21). To further investigate this, the ratings for the individual questions were investigated as shown in **Figure 2**. The highest rating was for the readability of the materials that the navigation was clear and it was straightforward to use. The lowest ratings were for having the motivation to complete the program, the worksheets, and how interesting the information was. These intervention aspects were the barriers to the intervention engagement.

The open-ended questions were furthermore analyzed to identify the additional barriers to implementation. These included both the personal and intervention factors as shown in **Table 6**. The personal factors identified were time barriers, the impact of the COVID-19 pandemic, lack of self-discipline, and other health problems. The intervention factors making completion difficult included the length and number of tasks on the intervention, that tinnitus was heightened due to the focus on tinnitus during the intervention, and that some people sought a cure and not strategies to help them cope with the tinnitus.

Facilitation of Effectiveness

Prior to starting the intervention, the participants were asked to commit to the intervention and indicate the level of commitment on a 1–10 points scale. Those committing indicated this by a score of 10. Some found they were not able to commit as intended although this commitment motivated others as indicated by the statements, such as "I have a family and full-time job. I couldn't keep up at some point. But I made a huge commitment to the first modules (because I felt the improvement on my tinnitus) so I did my sessions every day." This commitment by some contributed to them noticing the improvements in their tinnitus.

The open-ended responses were analyzed to identify the facilitators of effectiveness. The facilitators identified were that the intervention was empowering, accessible, well-structured, and they were adequately supported while undertaking it, as shown in **Table 7**.

DISCUSSION

This process evaluation was undertaken to determine which aspects of the implementation of a clinical trial delivering ICBT to the population of the United States hampered and facilitated the outcomes obtained. The process explored included the enrollment of participants, the intervention delivery, the outcomes obtained, and trial implementation as explored in this discussion.

Processes Involved in the Enrollment

A lot of preparation and planning was involved to ensure a range of recruitment strategies was incorporated. As this was the first tinnitus ICBT trial with Spanish participants, much research was done to investigate how to improve reaching this population [e.g., (48–52)]. The Spanish speakers were furthermore involved in the research team and during the intervention adaptation (20). Despite costly and varied recruitment strategies, it was very difficult to recruit Spanish speakers for this trial. A subsequent pilot trial with a wider recruitment area indicated that there is interest from the Spanish speakers, but ways of reaching and encouraging them to participate are still difficult (22). Moreover, although the trial targeted different ethnic and racial groups, this was not achieved and the strategies to reach a greater variety of ethnic and racial groups need to be sought.

This process evaluation highlighted various factors that could help with future trials to aid recruitment and enrollment. More hands-on involvement from a public patient group involving the individuals with bothersome tinnitus would be helpful to reach those with tinnitus (53). Such a group would advise on the strategies that the research team may not consider. Although the group members were involved in generating the recruitment ideas, directly contacting those with tinnitus at support groups, more involvement in future trials is encouraged. Hearing about the intervention effects from those with tinnitus may carry more weight than the professional contact. It was identified that a better understanding of the current public views on tinnitus and tinnitus interventions is required. Having a clear picture of what is being said in social media, public statements, on websites, on social media, blogs, and forums, advertising, policy documents, or reports provides a starting point regarding what perceptions need to be managed. Many people with tinnitus desire a treatment to completely cure tinnitus (54). Although explicitly stated that this intervention involved tinnitus management, some people still expected a cure and hence were disappointed.

It was evident that careful thought needs to be given to the inclusion criteria in the clinical trials. Excluding those with mild depression made the screening process very complicated as a psychologist had to be involved in the trial and screening process which increase the resources required. The subsequent trials indicated that including the participants with depression did not hamper the trial outcomes and their tinnitus severity decreased more than those without significant depression (23). Narrowing the recruitment to only the State of Texas was a further barrier. As this was an internet trial, using a wider pool across the country may be more helpful to reach the targeted numbers. The participants reached were those with higher socioeconomic status due to the higher levels of education. This may reflect the recruitment strategies used. An alternative way of reaching the different socio-economic groups needs to be sought which is likely to involve the alternative treatment approaches, such as less intense versions of this intervention.

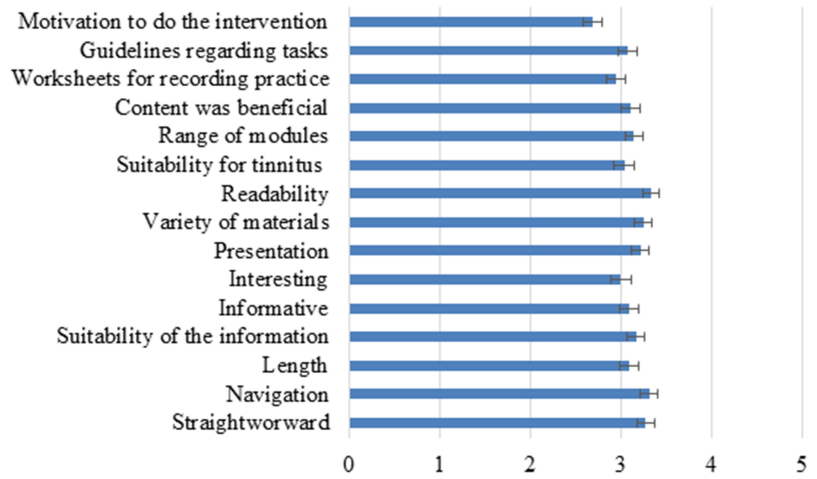

FIGURE 2 | The ratings of different aspects of the intervention on a scale of 1–5. The error bars represent SEM.

TABLE 6 | The barriers to the intervention implementation.

Category	Sub-category	Number of meaning units	Example of a meaning unit
Personal factors	Time barriers	88	"I know I must have missed some. I have been dealing with my own and my families health issues and dropped everything. including my job to deal with that, but I'm slowly going back to work"
	COVID-19 pandemic	15	"...the surge in Corona Virus cases in my area have distracted me and just make getting safely though the day challenging for the last month"
	Not using sound therapy	14	"I've been through tinnitus retraining therapy and focus on this by using sound masking for 8-12 hours a day. It is hard to fit in this time and doing the suggestions in the program without sound on"
	Health factors	9	"The fatigue and other side effects from being ill have made focusing on the program difficult"
	Lack of self-discipline	8	"Lack of self discipline…"
	Trying new techniques	6	"I'm just afraid to let go of my current method and try some new techniques in the module"
Intervention factors	Length	20	"To many modules in a very short time. I would either extent the study time or reduce the amount of modules."
	Too many activities	2	"Too many questionnaires and worksheets for my busy schedule as a full time employee and full time caregiver."
	Heightened awareness of tinnitus	4	"I feel like I'm focusing too much on the Demon T and I know that's not what a person is supposed to do."
	Approach	6	"This program seemed to be more about how to cope with the tinnitus than how to get rid of it. I thought the purpose of this was to lessen the tinnitus sound more than how to cope with it"

Processes Involved in the Allocation

The aim of the screening process prior to the participant allocation was to ensure that those involved were suitable for the trial, motivated to complete the intervention, and committed to completing the outcome measures for the trial. Although the participants confirmed this in the online and telephone screening, many never started the intervention. A clear need was identified to have better means of identifying who may be more engaged and motivated to do the intervention. To try to identify if this intervention is more suitable for certain tinnitus subgroups, a further trial was undertaken, dividing the participants into subgroups based on the level of their tinnitus severity (23). This indicated that the effectiveness of the intervention increased with the greater initial levels of tinnitus distress a baseline. The reductions in tinnitus distress were greater for those with significant levels of depression at the bassline. Rodrigo et al. (55) identified that the greater baseline tinnitus severity and those with greater educational levels were more likely to have a greater reduction in tinnitus distress after undertaking an ICBT intervention. The participants in this

TABLE 7 | The facilitators of effectiveness to the intervention.

Category	Sub-category	Number of meaning units	Example of a meaning unit
Empowering	Gaining knowledge	51	The real insight into the condition. The knowledge base and the interplay of condition with thoughts emotions and perception. I really understood how to bring positivity into my attitude and response to my condition. Understanding the purpose/meaning behind things is helpful
	Coping techniques	13	Discovering ways to help deal with my tinnitus with actual helpful tools to cope Realizing there are techniques to reduce the impact of tinnitus and having a variety of techniques to try
	Ways of managing anxiety	18	It has helped me be less distracted and irritated with my tinnitus but I've also been able to use the technique to manage my general anxiety disorder in a more positive way
	Learning to relax	21	The techniques for calming myself in order to lessen my attention to the tinnitus were so helpful
Accessible	Flexibility	6	The convenience of being online and doing in my own schedule It can be done anywhere by yourself
Well-structured	Content	12	The modules were very well put together between the slides and the videos. The content was very relevant and made me feel like the researchers understood how patients feel about their tinnitus
	Variety	23	I appreciated how thorough and well-explained the program was presenting a wide variety of techniques as well as good solid information. There were a number of techniques shown. If one was difficult it didn't work for me i could try something else
	Well-organized	13	I have really struggled with finding good material for tinnitus. This is the most organized and helpful material that I have found. I most enjoyed the expert opinion videos and FAQs at the ends of the modules. It kept it interesting and informative with clearly defined activities and good explanations Very clear instructions and tips for practicing the different techniques and downloadable content
Support	Guidance	17	Great to have a contact at anytime when needed. My therapist was very positive and helpful throughout this experience. I appreciated the emails and calls. I could tell that my contact really cared about my condition and wanted to help

current trial represented those with higher levels of education as the majority had a university degree, college, or vocational training. When subgrouping those with tinnitus, Beukes et al. (56) suggested that the unique management pathways may be more suited for some tinnitus subgroups. Further work is required to identify which individuals with tinnitus are more suited for ICBT.

Processes Involved in Intervention Delivery

All the participants who were assigned to the treatment were provided with access to the treatment program. However, several did not take the opportunity to engage with the material as 10 participants withdrew, and 30 participants never logged into the platform to access the intervention. Although attrition is similar to that of prior ICBT studies [mean of 14% (57)], engagement is lower than that previously reported in the trials in the United Kingdom [e.g., (16, 17)].

In addition, the initial modules were opened more than the final modules. The worksheet completion decreased during the later weeks of the intervention. Some participants indicated that they thought the intervention was too long which could be a contributing factor. Other participants found it helpful to have a comprehensive intervention. The intervention length and range of materials may, however, be a barrier for some. For those reading the modules, they rated the intervention highly in the terms of usefulness, applicability, and being able to understand the modules. The intervention dose was similar in the terms of guidance and delivery. The US intervention, however, had one additional module and more worksheets. Despite modifying it for ease of reading, the modules were opened by fewer participants compared with the participants of the United Kingdom who opened 74% of the recommended modules and 50% of the optional modules (34). When comparing these results with engagement by the population of the United Kingdom (16), stark differences are found. This earlier clinical trial indicated that the participants logged into the program on average 27 times compared with 8 times for the participants of the United States (23).

Processes Involved in the Outcomes Obtained

Undertaking ICBT led to a significant reduction in tinnitus distress which was the primary aim of the intervention. The overall reduction with an effect size of $d = 0.46$ (*CI*: 0.14–0.77) was slightly lower than that compared with the pooled result of previous European ICBT trials of $d = 0.50$ (*CI*: 0.37–0.63) in the recent systematic review (57). These studies found a medium effect for ICBT reducing insomnia and a small effect for reducing anxiety and depression. The present study results varied as significant reductions being evident for

the secondary outcomes for insomnia, tinnitus cognitions, and hearing disability but not for anxiety and depression. This may be related to those with significant levels of depression being excluded.

The compliance for completing the outcome measures was low, with 72% completion at the first time point, and dropping to 35% at the 1 year follow-up. This is lower than the previous ICBT in Europe, for example, the completing levels of 92 and 78% at post-intervention and 2 month follow-up for the participants from the United Kingdom (18). It may indicate that the population of the United States has other intervention needs or require additional motivation or incentives to complete the outcome measures. Satisfaction was lowest for motivation to complete, doing the worksheets, and how interesting the information was. Interestingly, the participants from the United Kingdom also rated these aspects the lowest (16, 34). The ways of increasing the motivation to do the intervention and worksheets are required. Overall satisfaction was lower than the ratings from the population of the United Kingdom where the majority of the scores were above 3/5 (16, 34). This may indicate the cultural differences or expectations from the interventions that may differ.

The facilitators identified were that the intervention was empowering, accessible, well-structured, and they were adequately supported while undertaking. Those thus undertaking the intervention found it very helpful and ways of getting more people to undertake the intervention are required.

Processes Involved in the Trial Implementation

Adequate trial preparations were undertaken, such as assessing the intervention materials (20), the functionality of the platform (19), and doing a pilot study before commencing (21, 22). Although the implementation fidelity was high, the trial was run during the first wave of the COVID-19 pandemic. Due to the intervention being online the trial could, however, continue. It was apparent that some of the participants were unwell with COVID-19 and thus unable to engage as planned. Even after recovering, they found it difficult to do the program due to less energy. They were given more time to complete the program which impacted the intervention fidelity. Both the COVID-19 pandemic and virus have been shown to impact the tinnitus severity for some individuals (58). A subsection of participants (12%) in this study indicated that they had COVID-19 and 49% reported that the pandemic had negatively impacted their emotional state. It is likely that the pandemic and COVID-19 had a negative impact on the engagement in the intervention, but the extent of the impact is difficult to untangle. The participants in the control group had a weekly questionnaire to complete during the active intervention period without receiving the intervention. Some participants expressed a dislike of these questionnaires which may have impacted their subsequent engagement in the trial.

This process evaluation provides an opportunity for the participants to highlight the factors that made undertaking the intervention difficult. Personal parries, such as time barriers, the impact of the COVID-19 pandemic, lack of self-discipline, and other health problems were identified as barriers. The ways of increasing support to do the intervention should be sought. One idea may be involving significant others in the intervention process (59). This support may be motivational and help the intervention seem less burdensome. The intervention factors making the completion difficult included the length and number of tasks on the intervention, that tinnitus was heightened due to the focus on tinnitus during the intervention, and that some people sought a cure and not strategies to help them cope with the tinnitus. Such barriers can be reduced by ensuring the potential participants have a good understanding of exactly what the intervention entails. Modifying the intervention to ensure it is less time consuming but still comprehensive is required. The facilitators to the intervention's effectiveness were that it is empowering, accessible, and well-structured. The participants greatly valued the support they received from the guidance provided.

Study Limitations and Future Directions

This evaluation was based on the barriers and facilitators identified by the participants completing the outcome measures. Although those not engaging were contacted by email, text, and phone, it was not always possible to reach them. This process evaluation would have benefited from including the views of those who did not engage or complete the outcome measures to truly reflect the barriers to participation. More effective ways of measuring engagement are required. Although it is possible to see if someone has opened a module, it is not possible to determine how much they have read, or how long they spent on the chapter. The outcomes measures used were all based on the clinical outcomes. For tinnitus, there may be more important or relevant outcomes not included that could have provided more insights. Future studies should investigate these, such as the intervention effectiveness on participation in the activities, impact on work, and relationships.

CONCLUSIONS

This process evaluation has provided a broader understanding of the factors affecting recruitment and the research context. The impact of factors, such as social and family support should be considered (24–26). The aspects that contributed to the effectiveness of the intervention, such as the participants finding it empowering, accessible, and well-structured were identified. The barriers restricting engagement, such as the intervention length, time limitations, and low self-discipline levels need addressing. The results of this process evaluation should be implemented into further clinical trials to improve the reach, engagement, and outcomes obtained.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and

accession number(s) can be found at: http://doi.org/10.6084/m9.figshare.13646012.

ETHICS STATEMENT

Ethical approval was obtained from the Institutional Review Board at Lamar University, Beaumont, Texas, US (IRB-FY17-209). The patients/participants provided their written informed consent online to participate in this study.

AUTHOR CONTRIBUTIONS

The study was conceived by VM, GA, and EB. The study platform was provided by GA. The data collection and analysis were done by EB. EB drafted the manuscript. All the authors critically analyzed the full manuscript and approved the final version.

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REFERENCES

1. McCormack A, Edmondson-Jones M, Somerset S, Hall D. A systematic review of the reporting of tinnitus prevalence and severity. *Hear Res.* (2016) 337:70–9. doi: 10.1016/j.heares.2016.05.009
2. Trevis KJ, McLachlan NM, Wilson SJ. A systematic review and meta-analysis of psychological functioning in chronic tinnitus. *Clin Psychol Rev.* (2018) 60:62–86. doi: 10.1016/j.cpr.2017.12.006
3. Salazar JW, Meisel K, Smith ER, Quiggle A, McCoy DB, Amans MR. Depression in patients with tinnitus: a systematic review. *Otolaryngol Head Neck Surg.* (2019) 161:28–35. doi: 10.1177/0194599819835178
4. Zenner HP, Delb W, Kröner-Herwig B, Jäger B, Peroz I, Hesse G, et al. A multidisciplinary systematic review of the treatment for chronic idiopathic tinnitus. *Eur Arch Otorhinol.* (2017) 274:2079–91. doi: 10.1007/s00405-016-4401-y
5. Cima RF, Mazurek B, Haider H, Kikidis D, Lapira A, Noreña A, et al. A multidisciplinary European guideline for tinnitus: diagnostics, assessment, and treatment. *HNO.* (2019) 67:10–42. doi: 10.1007/s00106-019-0633-7
6. Fuller TE, Haider HF, Kikidis D, Lapira A, Mazurek B, Norena A, et al. Different teams, same conclusions? A systematic review of existing clinical guidelines for the assessment and treatment of tinnitus in adults. *Front Psychol.* (2017) 8:206. doi: 10.3389/fpsyg.2017.00206
7. Tunkel DE, Bauer CA, Sun GH, Rosenfeld RM, Chandrasekhar SS, Cunningham ER Jr, et al. Clinical practice guideline: tinnitus. *JAMA Otolaryngol Head Neck Surg.* (2014) 15:S1–40. doi: 10.1177/0194599814545325
8. Fuller TE, Cima R, Langguth B, Mazurek B, Vlaeyen JW, Hoare DJ. Cognitive behavioural therapy for tinnitus. *Cochrane Database Syst Rev.* (2020) 1:CD012614. doi: 10.1002/14651858.CD012614.pub2
9. Landry EC, Sandoval XC, Simeone CN, Tidball G, Lea J, Westerberg BD. Systematic review and network meta-analysis of cognitive and/or behavioral therapies (CBT) for tinnitus. *Otol Neurotol.* (2020) 41:153–66. doi: 10.1097/MAO.0000000000002472
10. Andersson G. Psychological aspects of tinnitus and the application of cognitive–behavioral therapy. *Clin Psychol Rev.* (2002) 22:977–90. doi: 10.1016/S0272-7358(01)00124-6
11. Andersson G, Strömgren T, Ström L, Lyttkens L. Randomized controlled trial of internet-based cognitive behavior therapy for distress associated with tinnitus. *Psychosom Med.* (2002) 64:810–6. doi: 10.1097/00006842-200209000-00014
12. Jasper K, Weise C, Conrad I, Andersson G, Hiller W, Kleinstaeuber M. Internet-based guided self-help versus group cognitive behavioural therapy for chronic tinnitus: a randomized controlled trial. *Psychother Psychosom.* (2014) 83:234–46. doi: 10.1159/000360705
13. Abbott JA, Kaldo V, Klein B, Austin D, Hamilton C, Piterman L, et al. A cluster randomized trial of an internet-based intervention program for tinnitus distress in an industrial setting. *Cogn Behav Ther.* (2009) 38:162–73. doi: 10.1080/16506070902763174
14. Beukes EW, Andersson G, Manchaiah V, Kaldo V. *Cognitive Behavioral Therapy for Tinnitus*. San Diego, CA: Plural Publishing (2021).
15. Beukes EW, Allen PM, Manchaiah V, Baguley DM, Andersson G. Internet-based intervention for tinnitus: outcome of a single-group open trial. *J AM Acad Audiol.* (2017) 28:340–51. doi: 10.3766/jaaa.16055
16. Beukes EW, Baguley DM, Allen PM, Manchaiah V, Andersson G. Audiologist-guided Internet-based cognitive behaviour therapy for adults with tinnitus in the United Kingdom: a randomized controlled trial. *Ear Hear.* (2018) 39:423–33. doi: 10.1097/AUD.0000000000000505
17. Beukes EW, Andersson G, Allen PM, Manchaiah V, Baguley DM. Effectiveness of guided internet-based cognitive behavioural therapy vs face-to-face clinical care for treatment of tinnitus: a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg.* (2018) 144:1126–33. doi: 10.1001/jamaoto.2018.2238
18. Beukes EW, Allen PM, Baguley DM, Manchaiah V, Andersson G. Long-term efficacy of audiologist-guided Internet-based cognitive behaviour therapy for tinnitus. *Am J Audiol.* (2018) 27:431–47. doi: 10.1044/2018_AJA-IMIA3-18-0004
19. Manchaiah V, Vlaescu G, Varadaraj S, Aronson EP, Fagelson MA, Munoz MF, et al. Features, functionality, and acceptability of internet-based cognitive behavioral therapy for tinnitus in the United States. *Am J Audiol.* (2020) 29:476–90. doi: 10.1044/2020_AJA-20-00002
20. Beukes EW, Fagelson M, Aronson EP, Munoz MF, Andersson G, Manchaiah V. Readability following cultural and linguistic adaptations of an Internet-based intervention for tinnitus for use in the United States. *Am J Audiol.* (2020) 29:97–109. doi: 10.1044/2019_AJA-19-00014
21. Beukes EW, Andersson G, Fagelson M, Manchaiah, V. Audiologist-supported Internet-based cognitive behavioural therapy for tinnitus in the United States: a pilot trial. *Am J Audiol.* (2021) 30: 717–29. doi: 10.1044/2021_AJA-20-00222
22. Beukes EW, Munoz MF, Andersson G, Manchaiah V. Internet-based cognitive behavioral therapy for tinnitus in Spanish: a global feasibility trial. *Int J Audiol.* (2021). doi: 10.1080/14992027.2021.1971780
23. Beukes E, Andersson G, Fagelson M, Manchaiah V. Internet-based audiologist-guided cognitive behavioral therapy for tinnitus in the United States: A randomized controlled trial. *J Med Int Res.* (2021)
24. Guilaran J, de Terte I, Kaniasty K, Stephens C. Psychological outcomes in disaster responders: a systematic review and meta-analysis on the effect of social support. *Inter J Disaster Risk Sci.* (2018) 9:344–58. doi: 10.1007/s13753-018-0184-7
25. Hou D, Chen YX, He D, Zhang X, Fan X. The relationship between caregiver reactions and psychological distress in family caregivers of patients with heart failure. *J Cardiovasc Nurs.* (2020) 35:234–42. doi: 10.1097/JCN.0000000000000636
26. Wang J, Mann F, Lloyd-Evans B, Ma R, Johnson S. Associations between loneliness and perceived social support and outcomes of mental health problems: a systematic review. *BMC Psychiatry.* (2018) 18:156. doi: 10.1186/s12888-018-1736-5

27. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health.* (1999) 89:1322–7. doi: 10.2105/AJPH.89.9.1322
28. Dzewaltowski DA, Glasgow RE, Kelsges, LM, Estabrooks PA, Brock E. RE-AIM: evidence-based standards and a Web resource to improve translation of research into practice. *Ann Behav Med.* (2004) 28:75–80. doi: 10.1207/s15324796abm2802_1
29. Baranowski T, Stables G. Process evaluations of the 5-a-day projects. *Health Educ Behav.* (2000) 27:157–66. doi: 10.1177/109019810002700202
30. Linnan L, Steckler A., editors. *Process Evaluation for Public Health Interventions and Research*. San Francisco, CA: Jossey-Bass/Wiley (2002).
31. Gussenhoven AH, Singh AS, Goverts ST, van Til M, Anema JR, Kramer SE. A process evaluation of implementing a vocational enablement protocol for employees with hearing difficulties in clinical practice. *Int J Audiol.* (2015) 54:507–17. doi: 10.3109/14992027.2015.1009642
32. Meijerink JFJ, Pronk M, Kramer SE. Experiences with and lessons learned from developing, implementing, and evaluating a support program for older hearing aid users and their communication partners in the hearing aid dispensing setting. *Am J Audiol.* (2020) 29:638–47. doi: 10.1044/2020_AJA-19-00072
33. Ratanjee-Vanmali H, Swanepoel DW, Laplante-Lévesque A. Patient uptake, experience, and satisfaction using web-based and face-to-face hearing health services: process evaluation study. *J Med Internet Res.* (2020) 22:e15875. doi: 10.2196/15875
34. Beukes EW, Manchaiah V, Baguley DM, Allen PM, Andersson G. Process evaluation of Internet-based cognitive behavioural therapy for adults with tinnitus in the context of a randomised control trial. *Int J Audiol.* (2018) 57:98–09. doi: 10.1080/14992027.2017.1384858
35. Eysenbach G, Consort-EHEALTH Group. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. *J Med Internet Res.* (2011) 13:e126. doi: 10.2196/jmir.1923
36. Meikle MB, Henry JA, Griest SE, Stewart BJ, Abrams HB, McArdle R, et al. The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear Hear.* (2012) 33:153–76. doi: 10.1097/AUD.0b013e31822f67c0
37. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *JAMA.* (1999) 282:1737–44. doi: 10.1001/jama.282.18.1737
38. Andersson G, Kaldo V. Internet-based cognitive behavioral therapy for tinnitus. *J Clin Psychol.* (2004) 60:171–8. doi: 10.1002/jclp.10243
39. Beukes EW, Vlaescu G., Manchaiah V, Baguley, DM, Allen PM, et al. Development and technical functionality of an Internet-based intervention for tinnitus in the UK. *Internet Interv.* (2016) 6:6–15. doi: 10.1016/j.invent.2016.08.002
40. Beukes E, Andersson G, Fagelson M, Manchaiah V. Dismantling internet based cognitive behavioral therapy for tinnitus. The contribution of applied relaxation: a randomized controlled trial. *Internet Interv.* (2021) 25:100402. doi: 10.1016/j.invent.2021.100402
41. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* (2006) 166:1092–7. doi: 10.1001/archinte.166.10.1092
42. Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Med.* (2001) 2:297–307. doi: 10.1016/S1389-9457(00)00065-4
43. Wilson P, Henry J. Tinnitus cognitions questionnaire: development and psychometric properties of a measure of dysfunctional cognitions associated with tinnitus. *Int Tinnitus J.* (1998) 4:23–30.
44. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* (2011) 22:1727–36. doi: 10.1007/s11136-011-9903-x
45. Henry J, Griest S, Zaugg TL, Thielman E, Kaelin C, Galvez G, et al. Tinnitus and hearing survey: a screening tool to differentiate bothersome tinnitus from hearing difficulties. *Am J Audiol.* (2015) 24:66–77. doi: 10.1044/2014_AJA-14-0042
46. IBM Corp. *IBM SPSS Statistics for Windows, Version 26.0*. Armonk, NY: IBM Corp (2019).
47. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today.* (2004) 24:105–12. doi: 10.1016/j.nedt.2003.10.001
48. Barrera AZ, Kelman AR, Muñoz RF. Keywords to recruit Spanish- and English-speaking participants: evidence from an online postpartum depression randomized controlled trial. *J Med Internet Res.* (2014) 16:e6. doi: 10.2196/jmir.2999
49. Bunge EL, Taylor LA, Bond M, Stephens TN, Nishimuta K, Barrera AZ, et al. Facebook for recruiting Spanish- and English-speaking smokers. *Internet Interv.* (2019) 17:100238. doi: 10.1016/j.invent.2019.02.002
50. García AA, Zuñiga JA, Lagon C. A personal touch: the most important strategy for recruiting Latino research participants. *J Transcult Nurs.* (2017) 28:342–7. doi: 10.1177/1043659616644958
51. Hammer CS. Strategies for recruiting African American and Hispanic women as participants in research. *Contemp Issues Commun Sci Dis.* (2000) 27:127–34. doi: 10.1044/cicsd_27_F_127
52. Sha M, McAvinchey G, Quiroz R, Moncada J. Successful techniques to recruit Hispanic and Latino research participants. *Survey Pract.* (2017) 10:1–9. doi: 10.29115/SP-2017-0014
53. Grier S, Evans D, Gibson A, Chin TL, Stoddart M, Kok M, et al. Finding and engaging patients and the public to work collaboratively on an acute infection microbiology research public panel. *Res Involv Engagem.* (2018) 4:1–9. doi: 10.1186/s40900-018-0083-5
54. Beukes EW, Onozuka J, Brazell TP, Manchaiah V. Coping with tinnitus during the COVID-19 pandemic. *Am J Audiol.* (2021) 30:385–93. doi: 10.1044/2021_AJA-20-00188
55. Rodrigo H, Beukes EW, Andersson G, Manchaiah V. Internet-based cognitive-behavioural therapy for tinnitus: secondary analysis to examine predictors of outcomes. *BMJ Open.* (2021) 11:e049384. doi: 10.1136/bmjopen-2021-049384
56. Beukes EW, Baguley DM, Manchaiah V, Andersson G, Allen PM, Kaldo V, et al. Investigating tinnitus subgroups based on hearing-related difficulties. *Int J Clin Pract.* (2021) 75:e14684. doi: 10.1111/ijcp.14684
57. Beukes EW, Manchaiah V, Allen PM, Baguley DM, Andersson G. Internet-based interventions for adults with hearing loss, tinnitus, and vestibular disorders: a systematic review and meta-analysis. *Trends Hear.* (2019) 23:233121651985174. doi: 10.1177/2331216519851749
58. Beukes E, Ulep AJ, Eubank T, Manchaiah, V. The Impact of COVID-19 and the pandemic on tinnitus: a systematic review. *J Clin Med.* (2021) 10:2763. doi: 10.3390/jcm10132763
59. Beukes EW, Andersson G, Manchaiah V. Third party disability for significant others of individuals with tinnitus: A cross-sectional survey design. *Authorea.* (2021). doi: 10.22541/au.163045338.85276524/v1

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ASHA-Led Community-Based Groups to Support Control of Hypertension in Rural India Are Feasible and Potentially Scalable

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Background: To improve the control of hypertension in low- and middle-income countries, we trialed a community-based group program co-designed with local policy makers to fit within the framework of India's health system. Trained accredited social health activists (ASHAs), delivered the program, in three economically and developmentally diverse settings in rural India. We evaluated the program's implementation and scalability.

Methods: Our mixed methods process evaluation was guided by the United Kingdom Medical Research Council guidelines for complex interventions. Meeting attendance reports, as well as blood pressure and weight measures of attendees and adherence to meeting content and use of meeting tools were used to evaluate the implementation process. Thematic analysis of separate focus group discussions with participants and ASHAs as well as meeting reports and participant evaluation were used to investigate the mechanisms of impact.

Results: Fifteen ASHAs led 32 community-based groups in three rural settings in the states of Kerala and Andhra Pradesh, Southern India. Overall, the fidelity of intervention delivery was high. Six meetings were delivered over a 3-month period to each of the intervention groups. The mean number of meetings attended by participants at each

site varied significantly, with participants in Rishi Valley attending fewer meetings [mean (SD) = 2.83 (1.68)] than participants in West Godavari (Tukeys test, $p = 0.009$) and Trivandrum (Tukeys test, $p < 0.001$) and participants in West Godavari [mean (SD) = 3.48 (1.72)] attending significantly fewer meetings than participants in Trivandrum [mean (SD) = 4.29 (1.76), Tukeys test, $p < 0.001$]. Culturally appropriate intervention resources and the training of ASHAs, and supportive supervision of them during the program were critical enablers to program implementation. Although highly motivated during the implementation of the program ASHA reported historical issues with timely remuneration and lack of supportive supervision.

Conclusions: Culturally appropriate community-based group programs run by trained and supported ASHAs are a successful and potentially scalable model for improving the control of hypertension in rural India. However, consideration of issues related to unreliable/insufficient remuneration for ASHAs, supportive supervision and their formal role in the wider health workforce in India will be important to address in future program scale up.

Trial Registration: Clinical Trial Registry of India [CTRI/2016/02/006678, Registered prospectively].

Keywords: hypertension control, self-management, community-based, task-shifting, implementation evaluation, accredited social health activist, rural, India

INTRODUCTION

Hypertension is a major modifiable risk factor for cardiovascular disease. In 2019, high systolic blood pressure (SBP) was the leading global risk factor for attributable death and was responsible for 10–20% of Disability Adjusted Life Years (1).

In India, rural regions, while having similar prevalence of hypertension to urban regions, have poorer awareness and control of hypertension. In their large systematic review, Anchala and colleagues found that the prevalence of hypertension in rural areas was ∼25% compared to 33% in urban areas, while awareness was less in rural (25%) than in urban areas (42%) (2). Furthermore, only 10% of the rural population with hypertension and 20% of the urban population with hypertension have their blood pressure (BP) under control (2).

Poor control of hypertension in rural India, similar to findings from elsewhere in the world, may be attributable to poor knowledge and awareness of hypertension (3), as well as a shortage of health care providers, non-availability of medications, and the relative high cost of treatment when treatment is available (4). Poor control may also be affected by physician inertia, especially the lack of knowledge of the latest guidelines for the management of hypertension and the concept of prehypertension (5).

Community health workers (CHWs)/non-physician health workers (NPHWs), lay health workers, lay health advisors, peers, and others may be an important avenue for improving the control of hypertension. Indeed, there have been positive effects of employing these workers/volunteers in assisting and maintaining health behavior changes in programs for maternal and child health, HIV/AIDS, diabetes, and cardiovascular disease (6, 7). Furthermore, in an analysis of task sharing in eight projects funded by the Global Alliance for Chronic Diseases, task-sharing between CHWs/NPHWs and doctors was shown to be feasible and potentially scalable to deliver care in hard-to-reach and poorly resourced settings in low-and middle-income countries (LMICs) (8, 9).

In India, CHWs, called Accredited Social Health Activists (ASHAs), are an important component of the 2005 National Rural Health Mission, to improve access of rural people to effective primary healthcare (10, 11). ASHAs are predominantly female, non-physician, community-based volunteers, whose work complements that of Auxiliary Nurse Midwives (ANMs) and act as a bridge between the community and the healthcare system. ASHA have existing relationships with their communities and thus may be suitably placed to provide a community-based program to rural communities. Accountability for the work of the ASHAs primarily lies within the purview of the Village Health Sanitation and Nutrition Committee which is a committee formed at the revenue village level and acts as a subcommittee of the village council. A 2011 evaluation of the ASHA program identified the challenges of integrating a largely volunteer and incentivized workforce into the country's health and human resource strategy (12).

During 2014–16, we conducted a cluster randomized controlled trial (cRCT) to test the effectiveness of an ASHA-led, community-based group program for improving the control of hypertension in rural India (CHIRI) in three settings, each at a different stage of economic and epidemiological transition (13, 14). Within the three settings, 637 participants from five intervention clusters and 1,097 participants from 10 control clusters were recruited between November 2015 and April 2016,

with follow-up occurring in 459 participants in the intervention group and 1,012 participants in the control arm.

We found that reduction in both SBP and diastolic BP (DBP) was more in the intervention group than in the control group in all the three study areas. The proportion of participants with control of hypertension was greater in the intervention group than in the control group in two of the three study sites (13).

We conducted an evaluation of the CHIRI program implementation (intervention arm only) with the aim of determining its fidelity, the barriers to and enablers of the program, possible mechanisms of impact and the potential for future scalability of ASHA-led community-based group programs to improve the control of hypertension in rural India.

METHODS

Setting and Sample

Details of the protocol and main outcomes have been published earlier (13, 14). Briefly, the CHIRI study was done in two phases, the first of which included (1) a baseline survey to identify people with hypertension; (2) focus group discussions (FGDs) and in-depth interviews (IDIs) to identify individual- and system-level barriers to diagnosis and control of hypertension; and (3) a cross-sectional survey to determine the availability, affordability, and accessibility of medicines essential for treatment of hypertension, type 2 diabetes, and secondary prevention of cardiovascular disease.

Informed by the knowledge and data gained during phase 1, phase 2 tested the feasibility and effectiveness of community-based group meetings to support individuals in the self-management of hypertension. Within the three settings, 637 participants from five intervention clusters and 1,097 participants from 10 control clusters were recruited between November 2015 and April 2016, with follow-up occurring in 459 participants in the intervention group and 1,012 participants in the control arm.

Eligible participants for phase 2 were adult women and men aged at least 18 years with hypertension (defined as SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg and/or taking anti-hypertensive medication), identified in the phase 1 baseline survey and residing in the study settings randomized to receive the intervention.

Intervention Theory

The intervention was based on the CHW peer support model described by Heisler (15). The principles of the Chronic Disease Self-Management Program and behavior change guided the mechanism of impact (16). Program content, known to significantly contribute to improved self-management, included knowledge, and understanding of the disease, promotion of uptake of healthy behavior and clinical interaction through goal setting and active engagement in monitoring and treatment (7, 15, 17).

Implementation Framework

We used the Intervention Evaluation Process Model developed by the United Kingdom Medical Research Council guidelines for complex interventions, which focuses on three components: context, implementation process, and mechanisms of impact (see **Figure 1**) (18). Phase 1 of the study was used to understand the context and to inform the development of the intervention with respect to the prevalence of hypertension, current awareness of hypertension, knowledge about hypertension and use of health services, and availability of medicines (14).

We used an evaluation of the ASHA training (19) to provide details about the future feasibility of using ASHAs as the workforce to deliver the program. The fidelity of the program and its dose were assessed through (1) meeting reports completed by ASHAs with support from Research Officers (ROs), during and after the community meetings; (2) monitoring and evaluation sheets completed by the ROs, and; (3) meeting attendance and BP/adherence monitoring sheets that were recorded by the ASHAs in the meeting resources manual (available from Figshare https://figshare.com/s/b94c7af22ae220540c45).

At their final visit, participants provided feedback on the program, including details about the support they received from family and friends, their perception about their relationships with health care providers, and their perceived support from the ASHAs who conducted the meetings. Post-intervention FGDs, held separately with ASHAs and participants, provided additional information regarding feasibility and potential scalability of the intervention. The mechanisms of impact were assessed through the same meeting reports completed by ASHAs and ROs during and after the community meetings, as outlined in point (1) above.

CHIRI Intervention

Details of the intervention protocol and its impact evaluation have been described previously (13, 14). As outlined (13), during the development of the program we met with stakeholders/policy makers, including experts from the Ministry of Health, Indian Council of Medical Research, and independent researchers to obtain input about how best to tailor our approach to fit within the Indian Health system. ASHAs were financially remunerated to conduct the group meetings in accordance with the existing schedule for Village Health Sanitation and Nutrition Committee Activities (20) and Village Health and Nutrition Days (21). At the local administrative level, the study was conducted with permission from the local community leaders in each region.

ASHA Training

We conducted a pilot of the ASHA training program with ASHAs, who were not involved in delivering the program, and local clinicians, which enabled refinement of the training and program resources, as well as the delivery of the training program.

ASHAs were trained over 5 days to lead community groups and support control of hypertension through improving participants' knowledge of hypertension, using goal setting to adopt healthier lifestyles, and monitoring of blood pressure and weight (14, 19).

The ASHAs and ROs were provided with a training manual which included details of each education session, the requirements for working within a research project (particularly with respect to completing reports and meeting details that were used to evaluate the implementation as outlined above),

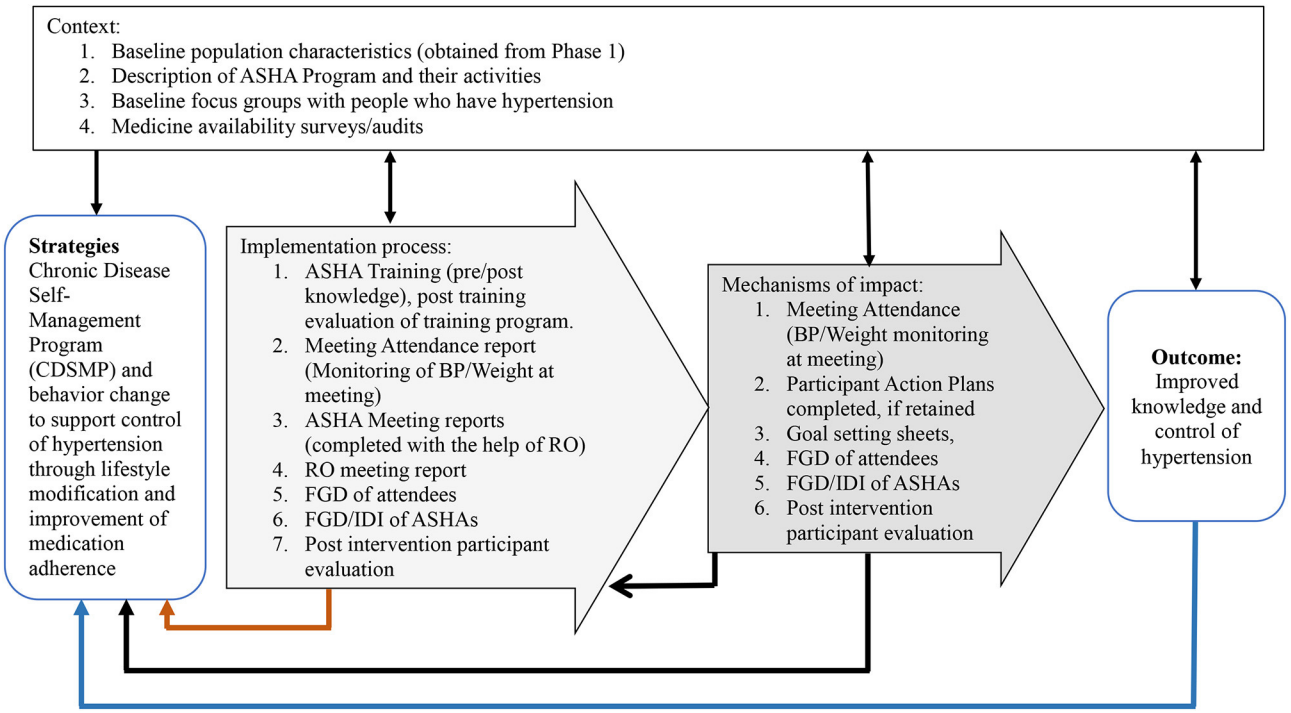

FIGURE 1 | Description of intervention activities/data tools to inform process evaluation using the United Kingdom Medical Research Council framework (17). ASHA, Accredited Social Health Activist; BP, Blood Pressure; RO, Research Officer; FGD, Focus Group Discussion; IDI, In Depth Interviews.

group facilitation skills, ethics, and self-care. ASHA were supported during each meeting by an RO from the study team. The RO was available to assist the ASHA to answer questions and clarify meeting messages if required. At the end of each meeting the ROs reviewed, with ASHAs, the content of the meeting and all activities undertaken in each meeting (available from Figshare https://figshare.com/s/7bbfcc22e0c9c91a5ca0?file=11780321).

CHIRI Program

The program consisted of six fortnightly sessions, each of ∼90 min, during which ASHAs recorded the attendance of participants, weight and blood pressure, adherence to BP medication, and any visit to a health care provider (HCP) for hypertension-related illness in the previous 2 weeks. The content of the meetings included knowledge of hypertension, encompassing risk factors, control of hypertension, physical activity, diet, practical self-management, and strategies to continue control of hypertension after the final meeting (14). Participants also received handouts to take home to remind them of the ideas and messages discussed at the meetings and to assist them with self-management actions between meetings. For example, at each meeting participants received a pictorial monitoring chart to record foods eaten, exercise undertaken, and salt, tobacco, and alcohol reduction in between meetings.

At the beginning of each meeting, participants were encouraged to share their experiences from the previous 2 weeks, achievements in self-management, and any difficulties encountered. Then, ASHAs delivered the meeting content using flipcharts, provided by the study team. These flipcharts (and handouts) were mostly pictorial and were delivered in the local language (Malayalam in Trivandrum and Telugu in West Godavari and Rishi Valley) (Meeting flip charts and handouts are available at: Figshare https://figshare.com/s/7bbfcc22e0c9c91a5ca0).

SMART (Specific, Measurable, Actionable, Realistic, Time limited) goal setting was practiced during each meeting. Participant goals were recorded by the ASHAs for review at the following meeting. When reviewing goals, during the meetings, participants were encouraged to share difficulties they may have experienced in achieving their set goals and group members were invited to share potential solutions and experiences when facing similar difficulties in achieving goals.

Data Collection for Evaluation of Implementation

ASHAs were provided with a handbook of meeting resources (Figshare- https://figshare.com/s/b94c7af22ae220540c45), to be used at and after each meeting. Each of the following, which were located within the handbook, were completed by the ASHAs, and subsequently used to assess the fidelity, intervention dose, and adherence to the protocol, as part of this evaluation:

1. The "Meeting Attendance and BP/Adherence Monitoring Sheet" was used to record the meeting date and theme, participant attendance, number of additional support

persons/family attendees, BP and heart rate, weight of each participant, each participant's use of medication or visits to an HCP for BP-related issues in the past 2 weeks. This sheet was part of the program as it provided a record of each participant's attendance and previous BP/weight for the ASHA to monitor at each meeting. This sheet also provided a means to assess fidelity to the program, including the dose of intervention received by each participant.

2. The "Goal Setting Sheet" was used to track individual participant's goals set during the meeting to enable review at the next meeting. These sheets comprised part of the program and were reviewed to assess the fidelity to the program and to confirm goal setting activities at each meeting.
3. Post-meeting reports:
   a. "Meeting Report:" This report was completed by ASHAs with support from ROs, during and after the community meetings, and included specific details of the content and management of each meeting, the number of participants and support persons/family attendees and use of supplied resources and support from RO assessed using a 5-point Likert scale "none/little—0–20%" to "a lot of information—81–100%." Motivation of participants was rated by ASHAs on a 5-point Likert scale from "not at all motivated" to "very motivated." The following were also collected by the ASHAs: (i) The time taken by ASHAs to prepare for the meeting, (ii) meeting activities, (iii) challenges faced by ASHAs in conducting the meetings, (iv) assessment by ASHAs of the positive and negative aspects of the meetings, (v) any additional activities undertaken in their community related to hypertension and chronic disease management, and time spent on those activities, and (vi) additional engagement by ASHAs with village leaders or other health care professionals.
   b. "Monitoring and Evaluation Sheet for Research Officers:" This sheet was completed by the RO attending the meeting, to provide an objective assessment of the fidelity and dose of the intervention at each meeting. The report included details of the topics covered during the meeting, timing of meeting activities, and a checklist of ASHAs activities during meetings (BP/weight measurement of attending participants, goal revision from previous meeting, use of the flip chart for the meeting, goal setting, use of the action plan tool). Additional space was available to record any issues raised by the participants with respect to (i) barriers or difficulties the participants had in achieving their goals, and (ii) difficulties, barriers and potential solutions raised by the participants during the meeting for controlling hypertension.

At the final assessment, the participants randomized to receive the intervention completed an evaluation survey (see **Appendix 1**) seeking the participant's perspective of attendance, support, and assistance to manage BP received from the ASHA, HCPs, members of the family, friends/support persons, and other members of the community. This information contributed to our understanding of the mechanisms of impact. A Likert scale was used for some questions in this evaluation survey. Each participant evaluated "how well do you think the ASHA helped you manage your high BP on a day-to-day basis?" using a 3-point Likert scale ("Not at all," "Some of the time," "All of the time"). The question about "how useful" various people had been in assisting their management of hypertension was graded on a 7-point Likert scale from "A little useful" through to "Extremely useful." The question about how much the group meetings helped with day-to-day management of hypertension was measured using a 3-point Likert scale ("Not at all," "A little bit," "A great deal"). Another question about "how much support/encouragement did the (various) meeting activities give you to manage your BP on a daily basis?", was measured on a 4-point Likert scale ("No support," "Little support," Moderate support," "A lot of support," "Not applicable;" the latter was selected if the participant did not receive or complete the activity).

Focus Group Discussions were conducted with ASHAs after completion of the program. The interview guide is available on Figshare (https://figshare.com/s/b94c7af22ae220540c45). Among those randomized to participate in the program, we conducted FGDs with those who chose to attend the program group meetings (see **Appendix 2**: Interview guide 1a), and IDIs with those who chose not to attend any of the group meetings (see **Appendix 2**: Interview guide 1b). These were conducted ∼2 months after the program was completed and were done to separately determine the perceptions of these two distinct groups. These discussions were audio-recorded, transcribed verbatim and general themes investigated as described below.

Data Analysis

Data from the "Meeting Reports" and "Monitoring and Evaluation Sheet for Research Officers" were entered into a Microsoft Access 2007–2016 database and the tabulated data were analyzed using Stata IC/14.0 (StataCorp, College Station TX, USA). Basic descriptive data are presented as means (standard deviation), medians (quartile 1–quartile 3) and number (%). Differences in means between sites were assessed using analysis of variance followed by Tukey's test. For categorical variables, Pearson's χ^2-test was used, and Bonferroni correction was used to account for the three comparisons. Two-tailed $P \leq 0.05$ was considered statistically significant.

Qualitative data were analyzed by deductive coding using a simple framework matrix derived from questions/discussion points from the discussion guides. An excel spreadsheet was developed using the questions/discussion points from the discussion guides (see **Appendix 2**). Codes included motivation to attend meetings, barriers and enablers to meeting attendance, new knowledge gained during the program, use of the resources provided for the program, support from family/friends, other group members and ASHAs, BP monitoring, and access to medication after the meetings ended.

RESULTS

Context

Context was assessed using the framework developed by Daivadanam et al. (22). The CHIRI study was conducted in three rural settings in Southern India, each at a different stage of economic and epidemiological transition. The population in

the Trivandrum district in the State of Kerala have a higher life expectancy and more than 93% literacy (late transition region). The population in the Rishi Valley (early transition region) in Chittoor District in the southern part of AP consists mainly of subsistence farmers and ∼50% have no formal schooling. West Godavari district in coastal Andhra Pradesh (AP) is economically between the two other regions and literacy in 2011 was 74.6% (23). At the individual/family level, in the context of BP, baseline mean SBP was greater in participants in the Rishi Valley than in the other two settings. Mean baseline DBP differed across all settings with the Rishi Valley participants having the highest and participants in Trivandrum the lowest (13). Participants in the Rishi Valley generally were less literate, had lower educational attainment, and a greater proportion were below the poverty line, than those in either West Godavari or Trivandrum. At the community level, 11 of the villages selected for the program had existing ASHAs while four villages did not have ASHAs, so we specifically recruited one woman from each of those four villages to fulfill the role of ASHA for the purposes of this study. Training of the ASHAs successfully led to increased knowledge of hypertension, skills, and motivation which has previously been evaluated and described (19).

At the healthcare setting, access to services was variable, with participants in the Rishi Valley reporting greater difficulty in accessing health care services than those at the other two sites. Seventeen pharmacies (51%; 10 public, 5 private, 2 other) had at least one drug from each class of the recommended cardiovascular disease preventive therapy combination of antiplatelet, statin, ACE/ARB, plus beta blocker or other BP lowering drugs. One private pharmacy did not carry any essential medicines for cardiovascular disease, BP, or type 2 diabetes mellitus, while the remaining 32 (97%) carried at least one glucose lowering agent and one BP lowering agent at the time the survey on the availability of medicines was undertaken.

Program Fidelity

A total of 15 ASHAs delivered the program in 15 villages. Four ASHAs in Rishi Valley led six community groups, seven ASHAs in West Godavari led 14 community groups and four ASHAs in Trivandrum led 12 community groups. A total of 192 meetings (36 Rishi Valley, 84 Godavari, and 72 Trivandrum) were conducted. Two groups in the Rishi Valley were combined for meetings four to six, but attendance data and other meeting data were analyzed per group. Each group completed six community-based meetings over a 3-month period, and all delivered the meeting content as planned, using the flip charts provided as recorded by the RO in the "Monitoring and Evaluation Sheet for Research Officers." At the beginning of each group meeting all attending participants had their BP, weight, heart rate, medication adherence and any hypertension-related health care visits since the last meeting recorded by ASHAs into the "Meeting Attendance and BP/Adherence Monitoring Sheet" in the ASHA resource manual. At each of the meetings goal setting was undertaken by the participants and goals were recorded by ASHAs in the "Goal Setting Sheet" for each participant in the ASHA resource manual.

On average, ASHAs reported spending 73.7 (SD 42.2) min preparing for each meeting. ASHAs in West Godavari reported spending significantly more time preparing for meetings [mean 86.7 (SD 42.4) min] than ASHAs in Trivandrum [60.7 (SD 43.7) min; Tukeys test, $p < 0.001$]. Meeting preparation time for ASHAs in Rishi Valley [69.6 (SD 29.0) min] was not significantly different to that for ASHAs in Trivandrum (Tukeys test, $p = 0.53$) or West Godavari (Tukeys test, $p = 0.09$). ASHAs accessed "some," (defined as 51–80%) or "a lot," (defined as 81–100%) of information from the training resources during meeting preparation for 181/192 (94.3%) of the meetings and "some" or "a lot" of information from the RO for 181/192 (94.3%) of the meetings. Fidelity in delivering the program in accordance with the protocol was high.

Program Exposure

A total of 637 participants consented to participate in the community group meetings. The average age of participants was 56.6 years (SD 14.3) and 58.7% were female (13). Overall, 416 (65.3%) of participants attended at least one meeting. The participation rate varied by site with West Godavari having the greatest participation rate and Trivandrum the least (**Table 1**).

Overall, approximately eight participants attended each of the meetings. Significantly fewer participants, on average, attended meetings in West Godavari compared with attendance by participants in Rishi Valley (Tukeys test, $p = 0.04$) or Trivandrum (Tukeys test, $p < 0.001$). Overall, each participant attended approximately four meetings. Program exposure based on the mean number of meetings attended by participants at each site varied significantly, with participants in Rishi Valley attending fewer meetings [mean (SD) = 2.83 (1.68)] than participants in West Godavari (Tukeys test, $p = 0.009$) and Trivandrum (Tukeys test, $p < 0.001$) and participants in West Godavari [mean (SD) = 3.48 (1.72)] attending significantly fewer meetings than participants in Trivandrum [mean (SD) = 4.29 (1.76), Tukeys test, $p < 0.001$]. Overall, 87/416 participants (20.9%) attended only one meeting, with the greatest proportion in the Rishi Valley. Approximately one in five (81/416; 19.5%) attended all six meetings, the greatest proportion being in Trivandrum. Lack of time (47.3%) and health issues (17.3%) were the main reasons cited by participants for not attending meetings. Attendance at meetings by a support person of the participant was significantly greater in West Godavari than Rishi Valley (Tukeys test, $p < 0.001$) and Trivandrum (Tukeys test, $p < 0.001$; **Table 1**), with no detectable difference between Trivandrum and Rishi Valley. According to the protocol, meetings were scheduled to last 90 min, including the time taken to measure BP and weight. Overall, the average duration of meetings was 78.1 min (SD 28.0; **Table 2**). The meetings were longest in Trivandrum, this being the region with the greatest number of participants attending per session, so having the longest duration for recording of BP.

Mechanisms of Impact

Motivation of participants was rated by ASHAs as "very motivated" for 89.1% (171/192) and "motivated" for the remaining 10.9% (21/192) of meetings. ASHAs in West Godavari tended to rate participants as "very motivated" (96.4%) more

TABLE 1 | Meeting attendance by study site.

Study site	Total recruited	Number participants (% participation*)	Number participants attending per meeting Mean (SD)	Number participants attending per meeting Median (IQR)	Total meetings attended per participant [Mean (SD)]	Total meetings attended per participant Median (IQR)	Number (%) attending only 1 meeting	Number (%) attending all 6 meetings	Community member attendance Mean (SD)
Rishi Valley	135	103 (76.3)	8.1 (4.2)	7 (5–11)	2.83 (1.68)^{A‡,B§}	3 (1–4)	33 (32)	9 (8.7)	0.28 (0.57)
West Godavari	198	162 (81.8)	6.7 (2.4)$^{A\dagger C\S}$	6 (5–8)	3.48 (1.72)^{C§}	4 (2–5)	31 (19.7)	24 (14.8)	3.4 (3.37)$^{A\S C\S}$
Trivandrum	304	151 (49.7)	9.1 (2.3)	9 (7–11)	4.29 (1.76)	5 (3–6)	23 (15.2)	48 (31.8)	1.3 (1.6)
Total	637	416 (65.3)	7.8 (3.0)	7 (5–10)	3.61 (1.81)	4 (2–5)	87 (20.9)	81 (19.5)	

*SD, standard deviation; IQR, interquartile range. *Participation defined as attending at least one community meeting. For continuous variables, if $P_{Region} \leq 0.05$, Tukey's test was used to determine which regions differed at $P \leq 0.05$. This is shown by superscript (A = RV vs. WG, B = RV vs. T, C = WG vs. T, and $^{\dagger}P \leq 0.05$, $^{\ddagger}P < 0.01$, $^{\S}P < 0.001$).*

TABLE 2 | Meeting duration by study site.

Study site	Mean (SD) meeting duration minutes	Mean (SD) duration for measurement of BP/Weight minutes
Rishi Valley	61.8 (19.0)	23.8 (9.2)
West Godavari	65.7 (16.4)	17.1 (7.0)$^{A\S C\S}$
Trivandrum	100 (28.3)$^{B\S C\S}$	33.9 (9.4)^{B§}
Total	78.1 (28.0)	24.7 (11.3)

SD Standard deviation, For continuous variables, if $P_{Region} \leq 0.05$, Tukey's test was used to determine which regions differed at $P \leq 0.05$. This is shown by superscript (A = RV vs. WG, B = RV vs. T, C = WG vs. T, and $^{\S}P < 0.001$).

often than ASHAs from Rishi Valley (80.6%) or Trivandrum (84.7%) ($p = 0.04$, Pearson χ^2 with Bonferroni correction).

To understand possible mechanisms of impact of the program outside of the meeting sessions, ASHAs were asked to report any additional support they provided to participants outside the meetings as well as any additional information they provided to their communities, other than program participants, about hypertension, other chronic diseases, or information about the CHIRI program. ASHAs in West Godavari reported providing additional support to participants, in the 2 weeks between every meeting (**Table 3**). ASHAs provided between-meeting support to participants after most of the group meetings in Trivandrum (69/72) and after each group meeting in West Godavari (84/84) while ASHAs in Rishi Valley provided between-meeting support after three group meetings (3/36). ASHAs in West Godavari were in general significantly more likely to provide between-meeting support to participants than ASHAs in Rishi Valley, although all ASHAs provided some support to participants between meetings for management of hypertension, medication adherence, alcohol cessation/reduction and assistance with visiting HCPs. ASHAs in West Godavari and Trivandrum discussed aspects of the program with community leaders or health service providers while ASHAs in Rishi Valley did not report any discussions with community leaders or health services staff (data not shown).

Nearly three quarters (467/637, 73.3%) of participants invited to participate in the group meetings responded to the participant evaluation survey. Three hundred and fifty-six of those responding (76.2%) attended at least one meeting and provided a response about attending the meetings with a support person or family member. Of these, 79 (22.2%) attended with a support person (**Table 4**). Support from family and friends to implement information gained at the meetings to improve blood pressure control was reported "very often" by ∼45.8% (163/356) of participants. Participants reported receiving support "very often" more frequently in Rishi Valley (50.9%) and Trivandrum (63.5%) than West Godavari (27.3%). Overall, 85.0% of participants reported that attending group meetings did not change their relationship with their HCP. A greater proportion in Rishi Valley stated an unchanged relationship with their HCP (96.5 vs. 81.8% in West Godavari, 83.5% in Trivandrum), but these apparent differences by site were not statistically significant.

Generally, participants in West Godavari rated the extent of help and support received from ASHAs in daily management of

TABLE 3 | Mean duration (minutes) of between-meeting support given by ASHAs to participants.

Type of support	Rishi Valley	West Godavari	Trivandrum	Total	*p*-value
	Mean duration in minutes (SD) (Min–Max)	Mean duration in minutes (SD) (Min–Max)	Mean duration in minutes (SD) (Min–Max)	Mean duration in minutes (SD) (Min–Max)	
Hypertension management	0.28 (1.7) (0–10)	13.6 (9.8) (0–60)	13.3 (11.65) (0–60)	11.0 (10.9) (0–60)	$<0.001^{A,B}$
Goal setting and review	0	10.2 (5.1) (0–30)	8.1 (8.3) (0–30)	7.5 (7.2) (0–30)	$<0.001^{A,B}$
Medication adherence strategies	1.8 (10.0) (0–60)	8.2 (5.1) (0–20)	4.8 (6.1) (0–20)	5.7 (7.0) (0–60)	$<0.001^{A}$ 0.006^{C}
Tobacco cessation	0	9.6 (4.7) (0–30)	1.3 (4.4) (0–30)	4.7 (6.0) (0–30)	$<0.001^{A,C}$
Alcohol cessation/reduction	0.14 (0.8) (0–5)	8.8 (7.5) (0–30)	1.4 (3.8) (0–20)	4.4 (6.7) (0–30)	$<0.001^{A,C}$
Need for clinical advice	0	8.4 (6.2) (0–20)	4.8 (8.3) (0–40)	6.8 (7.4) (0–40)	$<0.001^{A}$ 0.001^{B} 0.002^{C}
BP monitoring	0	10.3 (7.8) (0–30)	9.5 (14.7) (0–90)	8.1 (11.1) (0–90)	$<0.001^{A,B}$
Assistance with visiting health care provider/facility	2.5 (11.1) (0–60)	5.1 (9.0) (0–60)	1.9 (6.6) (0–50)	3.4 (8.7) (0–60)	$>0.05^{A, B,}$ $= 0.05^{C}$
Assistance with family negotiation	0	8.3 (7.0) (0–30)	0.4 (1.8) (0–10)	4.7 (6.6) (0–30)	$<0.001^{A,C}$

ASHAs, Accredited Social Health Activist; SD, Standard deviation; BP, Blood Pressure; Min, Minimum; Max, Maximum. For continuous variables, if $P_{Region} \leq 0.05$, Tukey's test was used to determine which regions differed at $P \leq 0.05$. This is shown by superscript (A = RV vs. WG, B = RV vs. T, C = WG vs. T).

TABLE 4 | Number of participants who attended group meetings with a support person and assessment of the frequency of support, received by participants to use meeting information to improve BP, from support person who attended meetings with the participant and from family/friends who did not attend the group meetings, by study site.

Study site	Number of participants who attended meeting with support person *n* (%/site)	Frequency of between meeting support received from support person *n* (%)†			Frequency of between meeting support received from family/friends *n* (%)‡		
		Not often	Sometimes	Very often	Not often	Sometimes	Very often
Rishi Valley ($n = 57$)*	10 (17.5)	0	5 (50.0)	5 (50.0)	7 (12.3)	21 (36.8)	29 (50.9)
West Godavari ($n = 154$)*	43 (27.9)	9 (20.9)	13 (30.2)	21 (48.8)	65 (42.2)	47 (30.5)	42 (27.3)
Trivandrum ($n = 145$)*	26 (17.9)	0	8 (32.0)	17 (68.0)	12 (8.3)	41 (28.3)	92 (63.5)
Total ($N = 356$)*	79 (22.2)	9 (11.5)	26 (33.3)	43 (55.1)	84 (23.6)	109 (30.6)	163 (45.8)

*BP, Blood Pressure, *111 missing data (12 Rishi Valley, 22 West Godavari, 77 Trivandrum). †Pearson χ^2 with Bonferroni correction for multiple comparisons (3 regions) $p = 0.23$, ‡Pearson χ^2 with Bonferroni correction for multiple comparisons (3 regions), $p = 0.003$.*

high BP more supportively than participants in Trivandrum and Rishi Valley, particularly with respect to behaviors relating to diet and medications (**Table 5**).

Overall, 57.1% of participants thought that the community group meetings helped "A great deal" to manage their high BP on a day-to-day basis. Fewer participants (43.9%) in Rishi Valley reported group meetings helped "A great deal" than in West Godavari (54.6%) and Trivandrum (65.1%) (Pearson χ^2 with Bonferroni correction, $p < 0.001$). More than two thirds of participants in Rishi Valley (71.9%) and West Godavari (68.0%) believed other factors, in addition to the group meetings, were helpful to them for day-to-day management of BP while in Trivandrum less than three percent of participants stated other factors were helpful (Pearson χ^2 with Bonferroni correction, $p < 0.001$). Other factors, including reduction of salt in their diet and taking medicine as directed, were identified by participants of Rishi Valley and West Godavari as additionally being of major importance for managing their BP, despite these two messages being part of the group meeting content (**Table 6**). Participants in West Godavari reported that family support was important for monitoring BP, while participants in Rishi Valley reported that frequent monitoring of BP was helpful.

TABLE 5 | Participant evaluation of help from ASHAs during the group meetings to manage high BP on a day-to-day basis.

To what extent did the ASHA	Rishi Valley* $n = 57$			West Godavari† $n = 154$			Trivandrum‡ $n = 145$			Total $N = 356$		
	Not at all	Some of the time	All of the time	Not at all	Some of the time	All of the time	Not at all	Some of the time	All of the time	Not at all	Some of the time	All of the time
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Help you to remember to take your medication	54 (94.7)	3 (5.3)	0 (0)	6 (3.9)	85 (55.2)	63 (40.9)	109 (75.2)	36 (24.8)	0 (0)	169 (47.5)	124 (34.8)	63 (17.7)
Help you to get your medications	56 (98.3)	1 (1.8)	0 (0)	15 (9.7)	85 (55.2)	54 (35.1)	110 (75.9)	35 (24.1)	0 (0)	181 (50.8)	121 (34.0)	54 (15.2)
Ask you about problems with medications/effects	57 (100)	0 (0)	0 (0)	80 (52.0)	63 (40.9)	11 (7.1)	116 (80.0)	29 (20.0)	0 (0)	253 (71.1)	92 (25.8)	11 (3.1)
Help you with monitoring your BP	57 (100)	0 (0)	0 (0)	12 (7.8)	84 (54.6)	58 (37.7)	104 (71.7)	41 (28.3)	0 (0)	173 (48.6)	125 (35.1)	58 (16.3)
Remind you to see HCP regularly even when well	56 (98.3)	1 (1.8)	0 (0)	60 (39.0)	60 (39.0)	34 (22.1)	129 (89.0)	16 (11.0)	0 (0)	245 (68.8)	77 (21.6)	34 (9.6)
Help you to build better communication with HCP	57 (100)	0 (0)	0 (0)	84 (54.6)	59 (38.3)	11 (7.1)	128 (88.3)	17 (11.7)	0 (0)	269 (75.6)	76 (21.4)	11 (3.1)
Remind and help you to put your needs first	56 (98.3)	1 (1.8)	0 (0)	89 (58.6)	53 (34.9)	10 (6.6)	119 (82.1)	26 (17.9)	0 (0)	264 (74.6)	80 (22.6)	10 (2.8)
Reminding and helping you to eat more fruit/veg	55 (96.5)	2 (3.5)	0 (0)	5 (3.3)	44 (28.6)	105 (68.2)	128 (88.3)	17 (11.7)	0 (0)	188 (52.8)	63 (17.7)	105 (29.5)
Remind and help you to reduce portion size	56 (98.3)	1 (1.8)	0 (0)	11 (7.1)	70 (45.5)	73 (47.4)	125 (86.8)	19 (13.2)	0 (0)	192 (54.1)	90 (25.4)	73 (20.6)
Remind and help you to do 30 min. daily physical activity	56 (98.3)	1 (1.8)	0 (0)	5 (3.3)	61 (39.6)	88 (57.1)	119 (82.1)	26 (17.9)	0 (0)	180 (50.6)	88 (24.7)	88 (24.7)
Remind and help you to reduce oily foods/salt/sugar in your diet	56 (98.3)	1 (1.8)	0 (0)	1 (0.7)	48 (31.2)	105 (68.2)	112 (77.2)	32 (22.1)	1 (0.7)	169 (47.5)	81 (22.8)	106 (29.8)

*ASHAs, Accredited Social Health Activist; BP, Blood pressure; HCP, Health care practitioner, * 12 missing data, † 22 missing data, ‡ 77 missing data.*

TABLE 6 | Factors/activities other than the group meetings that may have helped participants manage BP on a day-to-day basis.

Other factors assisting day to day management of high BP	Rishi Valley *n* = 69 (%)	West Godavari*n* = 176 (%)	Trivandrum *n* = 222 (%)	Total *N* = 467 (%)
Reducing salt in diet	41 (59.4)	76 (43.2)	3 (1.4)	120 (25.7)
Family support	18 (26.1)	89 (50.6)	2 (0.9)	109 (23.3)
More frequent BP monitoring	36 (52.2)	48 (27.3)	2 (0.9)	86 (18.4)
Taking medicine as directed by HCP	19 (27.5)	53 (30.1)	1 (0.5)	73 (15.6)
Information from data collector	0	69 (39.2)	0	69 (14.8)
Increasing green vegetables	15 (21.7)	46 (26.1)	1 (0.5)	62 (13.2)
Support from HCP	3 (4.4)	31 (17.6)	1 (0.5)	35 (7.5)
Regular exercise	3 (4.4)	14 (8.0)	1 (0.5)	18 (3.9)
Attend 104 mobile clinic	0	8 (4.6)	0	8 (1.7)
Other community members	0	5 (2.8)	0	5 (1.1)

Focus Group Discussions

Nine FGDs were conducted with participants who attended the group meetings. In Trivandrum, two FGDs were held with 15 participants in each of them. In West Godavari, six meetings were held with an average of nine participants per meeting. In Rishi Valley one FGD was done with six participants. Overall, ∼54% of participants attending FGDs were female, and age of participants ranged from 25 to 78 years. Focus group discussions reinforced the findings of the post-program participant evaluation surveys (see **Supplementary Table 1**). The overwhelming motivation for participants to attend the meetings was to obtain information about hypertension and how to manage it. Participants stated the information about how to control hypertension that they received from their HCPs was basic and consisted mostly of prescriptions for medication and basic dietary advice about salt reduction.

Participants stated the meetings provided them with knowledge about hypertension and how to improve their management of it, by adopting simple and practical lifestyle changes with respect to diet (e.g., demonstration of portion size), exercise (e.g., suggestion to get off the bus one stop earlier than their destination bus stop) and adherence to medication (e.g., using simple medication reminders and monitoring sheets).

Program resources were helpful and were still being used by participants after cessation of the program. The pictorial exercise handout was frequently mentioned as a resource still being used. Participants stated the pictures in the resources were well-understood by educated and illiterate participants alike.

Participants reported that family support was important for ongoing BP control and that dietary changes, such as reduction of salt during meal preparation, was the most frequent form of support.

Not all participants agreed that ASHAs or other group members provided support after the program had ceased, although those who lived near other participants or ASHAs in the villages reported that ASHAs and group members maintained contact with them and enquired about their BP.

Simple goals such as taking tablets as directed may be sustainable over time, but participants expressed some lack of motivation or accountability if their goals were not being reviewed or monitored regularly. Participants in FGD found it useful to get their BP checked at each meeting and felt accomplished when efforts were successful. However, ongoing access to BP monitoring after the program ceased was difficult and participants reported checking their BP only if they felt unwell.

Lack of medication distribution during the meetings was a prominent discussion point by the participants and by the ASHAs. Participants had some expectations that medications might be distributed and, at each FGD, participants and ASHAs expressed views that provision of medications would increase attendance at the meetings. ASHAs reported that lack of provision of medications was a frequent complaint from the participants. Cost of medications was seen as a potential barrier to continued control of BP. Participants considered the BP medication available through the mobile 104 service (mobile services providing scheduled primary health care services to villages of India) to be sub-standard or different from those prescribed by their HCP, driving participants to purchase medications from private suppliers.

Suggestions, from the participants who attended meetings, to improve the program included provision of medications during the meetings, inclusion of free blood sugar monitoring and medication (for diabetes) in addition to BP monitoring, home visits, electronic reminders to attend meetings, assistance with transportation to meetings, ensuring convenient meeting locations and meeting schedules for all residents.

In FGDs conducted with ASHAs after the program was completed, ASHAs expressed views supporting the meetings and the need for their continuation in their communities. Inclusion of past participants, provision of medications and incorporation of home visits were suggested as improvements to future meetings.

> *"If we include our participants who are self-managing their BP after participating in our program in the next program and make them share their experience, then it would be useful."—ASHA West Godavari*

> *"Visit people's homes and check their BP at least once in a month. If we do like that, they will concentrate on diet control and exercise."—ASHA Trivandrum*

"They will definitely come if we give them injections or tablets."—ASHA Rishi Valley

Twelve IDIs in West Godavari and two FGD in Trivandrum were conducted with invitees to the program who declined to attend any group meetings. Those who did not attend the group meetings reported work commitments (at home, agriculture, or workplace), physical disabilities, and carer responsibilities as barriers to attendance. Group meeting participants expressed their willingness to share the knowledge gained in the meetings with their family and community members. Those who did not attend the meetings reported that those who had attended the group meetings had shared information from the group meetings with them.

DISCUSSION

This process evaluation has shown that the CHIRI study was implemented with good fidelity to all the components of the CHIRI program, as outlined in the original study protocol (14). The ASHA-led training component of the program was implemented with high fidelity (19). All six group meetings were delivered using the program materials (flip charts and meeting handouts) at each study site and during each meeting, and all participants were weighed and had their BP measured at each meeting. Participants attended a median of four of the six meetings and the meetings lasted an average of 78 min. However, there was some variation across study sites. Response rates and participation in the program varied across study sites and the percentage of eligible participants who participated in at least one of these sessions, and who attended all six meetings, varied across study sites. Some of this variation might be explained by the differences in educational attainment, literacy, and main employment types in each setting. Support provided to participants by the ASHAs between meetings, to help manage high BP on a day-to-day basis, varied between study sites as did support received by family and friends of the participants. Even though there were some variations in the implementation of the program model in each of the three CHIRI sites, the effect size and primary outcome (control of hypertension) did not vary significantly across the three sites (13).

ASHAs utilized the training, program resources and support from ROs nearly 95% of the time to prepare for the meetings. During the post program FGDs, ASHAs reported that they felt empowered and motivated to perform the tasks they were trained to do.

Qualitative data obtained from FGDs and IDIs with participants and ASHAs may enhance understanding of the factors that influence the causal relationship between implementation and outcome in a real-world setting (24). Focus Group Discussions helped to understand community perspectives on health care seeking behaviors in general and regarding hypertension and were useful to understand the individual- and system-level barriers to control of hypertension in the three settings.

Dietary changes, specifically salt reduction, and frequent blood pressure monitoring were seen as beneficial by participants in this study. These aspects of the program are evidence-based components of improving control of hypertension (25, 26).

Incorporating support from family and friends into future iterations of the program, by supporting flexibility and willingness of supporters to adapt, may enhance outcomes (27) and was acknowledged as important by participants in this study.

In India, ASHAs are already very important within the National Health Mission (10). Indeed, input from ASHAs and from local stakeholders, including health care professionals and policy makers, contributed to the design and delivery of a program which has a good fit with India's health system. ASHAs and other CHWs have great potential to contribute to community-based health programs in LMIC and their involvement in such programs has been expanding recently in many countries such as Ethiopia, Bangladesh, and India (28). Patient screening, lifestyle education, support for self- management and assistance to navigate the health care system are tasks which can and have been successfully undertaken by CHWs for those with non-communicable diseases (9, 29).

There have been many reports of the use of CHWs in delivering reproductive, maternal, and child health services (30) and cardiovascular risk factor management programs (31–33). These studies identify the importance of structured training, an emphasis on participant education and lifestyle change, cultural adaptation, and resources to support the program (34). In line with this evidence base, the CHIRI study included a 5-day training program, which emphasized enhancing knowledge, culturally appropriate and practical self-management skills, frequent weight, and BP monitoring with automatic BP machines, and a training manual and program resources to support implementation of the program. The program also included ongoing mentoring and support of ASHAs by the research team.

ASHAs identified that the training they had received increased their skills and standing in their communities and within the health workforce. Ongoing supervision and support by the RO during the meetings were also identified as helpful during the program delivery. During the evaluation of the ASHA training program ASHA reported historical issues with timely remuneration and lack of supportive supervision (19). Motivating ASHAs by training them effectively, providing salaries on time and maintaining quality through monitoring and supportive supervision are essential steps in task-sharing (31). Supportive supervision and positive feedback can enable and strengthen the collaboration between the health system, CHWs and their communities. It can also facilitate appropriate data collection to allow for ongoing monitoring and evaluation of a program (35).

When assessing scalability, we know that diagnosis and treatment of hypertension in India is a significant problem (36). Many of the major components of the CHIRI program are transferable for the prevention and self-management of other chronic diseases such as diabetes, cardiovascular disease, stroke, and promotion of good mental health.

The fidelity of and the extent to which the CHIRI intervention was implemented in the three different study sites supports the wider implementation of this approach. The group-based approach of the program is also less resource intensive than an individually delivered approach. The effectiveness of group-based programs for the self-management and prevention of chronic diseases is also supported by several earlier studies (37, 38). Therefore, our approach is very appropriate for a resource-constrained setting.

Interviews with ASHAs in the CHIRI program (19) and other studies (39, 40) identify that current remuneration for ASHAs is insufficient and should be revised in the context of their expanding role in the health system (12, 41). The current position of ASHAs in the wider health workforce in India is an important consideration for future program scalability (42).

Strengths and Limitations

A major strength of this process evaluation was the inclusion of multiple sources of information collected at several time points in each of the study sites. The inclusion of process measures from the start of the intervention allowed measurement of implementation and process measures over the duration of the study. The presence of the RO at each meeting provided an independent assessment of the implementation process. Some of the measures are based on self-perception and evaluation which may have changed over time between the end of the intervention and the time of evaluation, potentially resulting in recall bias.

Staffing and conducting the community-based group meetings within the context of the existing health workforce in rural India was also a significant strength of the model. All project materials were piloted and refined incorporating local input which enhanced local acceptability and cultural suitability of the program.

Generalizability of this program with respect to urban and other settings in India is a limitation of this study. The sample size of the intervention study was small and restricted to five rural clusters in southern India. Furthermore, attendance at every community meeting by a supervisor or ASHA supporter (like the RO as part of the study team in this study) may not be practical in a real-world setting and other options to provide supportive supervision may need to be explored. Upscaling of this program will require further testing in other states of India which have more diversity in culture and educational attainment.

CONCLUSION

The CHIRI program is a good "fit" with the existing health care system of India to address the increasing burden of hypertension as well as other chronic conditions. The program was delivered by ASHAs who have been identified as being very important contributors to the future delivery of such programs in rural India, in particular. The intervention was co-designed with end users, including health care professionals and policymakers. Tools to measure evaluation of the implementation included meeting reports from ASHAs, RO reports that summarized activities occurring in each session, IDIs with health workers, FGDs with participants and IDIs with non-participants, to understand why the project was working or facing difficulties. This process evaluation suggests that the CHIRI intervention and program delivery model is a successful, scalable model based on the outcomes and effectiveness of the program. The capacity of ASHAs to deliver the intervention suggests the future sustainability and scalability of CHIRI delivery as they are already part of the existing rural health services.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

ETHICS STATEMENT

Ethics approval was obtained from Sree Chitra Tirunal Institute for Medical Sciences and Technology (Trivandrum, India; SCT/IEC-484/July-2013), the Centre for Chronic Disease Control (CCDC-IEC-09-2012), Christian Medical College (Vellore, India), the Health Ministry Screening Committee of the Government of India (58/4/1F/CHR/2013/NCD II), and Monash University (CF13/2516–2013001327). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants for being included in the study. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MR, RJ, KT, CC, BO, RE, AM, KKal, KKar, NT, PM, VS, SA, RV, and AT: conceptualization. MR and GM: formal analysis. MR, GM, and KC: writing—original draft. MR, RJ, KT, CC, BO, RE, AM, KKal, KKar, OS, NT, GM, PM, VS, SA, KC, RV, RG, FD'E, and AT: writing—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.771822/full#supplementary-material

REFERENCES

1. Murray CJL, Aravkin AY, Zheng P, Abbafati C, Abbas KM, Abbasi-Kangevari M, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* (2020) 396:1223–49. doi: 10.1016/S0140-6736(20)30752-2
2. Anchala R, Kannuri NK, Pant H, Khan H, Franco OH, Di Angelantonio E, et al. Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension. *J Hypertens.* (2014) 32:1170–7. doi: 10.1097/HJH.0000000000000146
3. Busingye D, Arabshahi S, Evans RG, Riddell MA, Srikanth VK, Kartik K, et al. Knowledge of risk factors for hypertension in a rural Indian population. *Heart Asia.* (2019) 11:e011136. doi: 10.1136/heartasia-2018-011136
4. Attaei MW, Khatib R, McKee M, Lear S, Dagenais G, Igumbor EU, et al. Availability and affordability of blood pressure-lowering medicines and the effect on blood pressure control in high-income, middle-income, and low-income countries: an analysis of the PURE study data. *Lancet Pub Hlth.* (2017) 2:e411–9. doi: 10.1016/S2468-2667(17)30141-X
5. Milman T, Joundi RA, Alotaibi NM, Saposnik G. Clinical inertia in the pharmacological management of hypertension: a systematic review and meta-analysis. *Medicine.* (2018) 97:e11121. doi: 10.1097/MD.0000000000011121
6. Anand TN, Joseph LM, Geetha AV, Prabhakaran D, Jeemon P. Task sharing with non-physician health-care workers for management of blood pressure in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Global Health.* (2019) 7:e761–71. doi: 10.1016/S2214-109X(19)30077-4
7. Fisher EB, Boothroyd RI, Elstad EA, Hays L, Henes A, Maslow GR, et al. Peer support of complex health behaviors in prevention and disease management with special reference to diabetes: systematic reviews. *Clin Diab Endocrinol.* (2017) 3:4. doi: 10.1186/s40842-017-0042-3
8. Joshi R, Alim M, Kengne AP, Jan S, Maulik PK, Peiris D, et al. Task shifting for non-communicable disease management in low and middle income countries – a systematic review. *PLoS ONE.* (2014) 9:e103754. doi: 10.1371/journal.pone.0103754
9. Joshi R, Thrift AG, Smith C, Praveen D, Vedanthan R, Gyamfi J, et al. Task-shifting for cardiovascular risk factor management: lessons from the Global Alliance for Chronic Diseases. *BMJ Global Health.* (2018) 3(Suppl. 3):e001092. doi: 10.1136/bmjgh-2018-001092
10. National Rural Health Mission. National Rural Health Mission (2005-2012)–Mission document. *Indian J Public Health.* (2005) 49:175–83.
11. Saprii L, Richards E, Kokho P, Theobald S. Community health workers in rural India: analysing the opportunities and challenges Accredited Social Health Activists (ASHAs) face in realising their multiple roles. *Hum Resour Health.* (2015) 13:95. doi: 10.1186/s12960-015-0094-3
12. Ved R, Gupta G, Samatha M. *ASHA, Which Way Forward? Evaluation of ASHA Programme*. (2011). Available online at: https://nhm.gov.in/images/pdf/communitisation/asha/Studies/Evaluation_of_ASHA_Program_2010-11_Report.pdf
13. Gamage DG, Riddell MA, Joshi R, Thankappan KR, Chow CK, Oldenburg B, et al. Effectiveness of a scalable group-based education and monitoring program, delivered by health workers, to improve control of hypertension in rural India: a cluster randomised controlled trial. *PLoS Med.* (2020) 17:e1002997. doi: 10.1371/journal.pmed.1002997
14. Riddell MA, Joshi R, Oldenburg B, Chow C, Thankappan KR, Mahal A, et al. Cluster randomised feasibility trial to improve the Control of Hypertension In Rural India (CHIRI): a study protocol. *BMJ Open.* (2016) 6:e012404. doi: 10.1136/bmjopen-2016-012404
15. Heisler M. *Building Peer Support Programs to Manage Chronic Disease: Seven Models for Success*. Oakland, CA: California Healthcare Foundation (2006).
16. Lorig KR, Sobel DS, Stewart AL, Brown BW Jr, Bandura A, Ritter P, et al. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: a randomized trial. *Med Care.* (1999) 37:5–14. doi: 10.1097/00005650-199901000-00003
17. Franek J. Self-management support interventions for persons with chronic disease: an evidence-based analysis. *Ont Health Technol Assess Ser.* (2013) 13:1–60.
18. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ.* (2015) 350:h1258. doi: 10.1136/bmj.h1258
19. Abdel-All M, Thrift AG, Riddell M, Thankappan KRT, Mini GK, Chow CK, et al. Evaluation of a training program of hypertension for accredited social health activists (ASHA) in rural India. *BMC Health Serv Res.* (2018) 18:320. doi: 10.1186/s12913-018-3140-8
20. National Rural Health Mission. *Guidelines for Community Processes - 2013*. New Delhi (2013). Available online at: https://www.nhm.gov.in/images/pdf/communitisation/vhsnc/order-guidelines/Guidelines_for_Community_Processes_2014%20English.pdf
21. National Rural Health Mission. *Guidelines for Village Health Sanitation Nutrition Committee Part B*. New Delhi: Ministry of Health and Family Welfare (2013). Available online at: https://www.nhm.gov.in/images/pdf/communitisation/vhsnc/order-guidelines/Guidelines_for_Community_Processes_2014%20English.pdf (accessed August 12, 2021).
22. Daivadanam M, Ingram M, Sidney Annerstedt K, Parker G, Bobrow K, Dolovich L, et al. The role of context in implementation research for non-communicable diseases: answering the 'how-to' dilemma. *PLoS ONE.* (2019) 14:e0214454. doi: 10.1371/journal.pone.0214454
23. Census Organization of India. *Population Census, 2011*. (2011). Available online at: https://www.census2011.co.in/district.php (accessed October 17, 2021).
24. Limbani F, Goudge J, Joshi R, Maar MA, Miranda JJ, Oldenburg B, et al. Process evaluation in the field: global learnings from seven implementation research hypertension projects in low-and middle-income countries. *BMC Public Health.* (2019) 19:953. doi: 10.1186/s12889-019-7261-8
25. Boulware LE, Ephraim PL, Hill-Briggs F, Roter DL, Bone LR, Wolff JL, et al. Hypertension self-management in socially disadvantaged African Americans: the Achieving Blood Pressure Control Together (ACT) randomized comparative effectiveness Trial. *J Gen Intern Med.* (2020) 35:142–52. doi: 10.1007/s11606-019-05396-7
26. He FJ, Tan M, Ma Y, MacGregor GA. Salt reduction to prevent hypertension and cardiovascular disease: JACC State-of-the-art review. *J Am Coll Cardiol.* (2020) 75:632–47. doi: 10.1016/j.jacc.2019.11.055
27. Whitehead L, Jacob E, Towell A, Abu-Qamar M, Cole-Heath A. The role of the family in supporting the self-management of chronic conditions: a qualitative systematic review. *J Clin Nurs.* (2018) 27:22–30. doi: 10.1111/jocn.13775
28. Perry H, Crigler L, Lewin S, Glenton C, LeBan K, Hodgins S. A new resource for developing and strengthening large-scale community health worker programs. *Hum Resour Health.* (2017) 15:13. doi: 10.1186/s12960-016-0178-8
29. Nebhinani M, Saini S. Leveraging role of non-physician health workers in prevention and control of non-communicable diseases in India:

enablers and challenges. *J Family Med Primary Care.* (2021) 10:595–600. doi: 10.4103/jfmpc.jfmpc_1516_20
30. Shelley KD, Belete YW, Phiri SC, Musonda M, Kawesha EC, Muleya EM, et al. Implementation of the Community Health Assistant (CHA) cadre in Zambia: a process evaluation to guide future scale-up decisions. *J Community Health.* (2016) 41:398–408. doi: 10.1007/s10900-015-0110-5
31. Heller DJ, Kumar A, Kishore SP, Horowitz CR, Joshi R, Vedanthan R. Assessment of barriers and facilitators to the delivery of care for noncommunicable diseases by nonphysician health workers in low- and middle-income countries: a systematic review and qualitative analysis. *JAMA Netw Open.* (2019) 2:e1916545–e. doi: 10.1001/jamanetworkopen.2019.16545
32. Jafar TH, Hatcher J, Poulter N, Islam M, Hashmi S, Qadri Z, et al. Community-based interventions to promote blood pressure control in a developing country. *Ann Intern Med.* (2009) 151:593–601. doi: 10.7326/0003-4819-151-9-200911030-00004
33. Joshi R, Chow CK, Raju PK, Raju KR, Gottumukkala AK, Reddy KS, et al. The rural Andhra Pradesh cardiovascular prevention study (RAPCAPS): a cluster randomized trial. *J Am Coll Cardiol.* (2012) 59:1188–96. doi: 10.1016/j.jacc.2011.10.901
34. Khetan AK, Purushothaman R, Chami T, Hejjaji V, Madan Mohan SK, Josephson RA, et al. The effectiveness of community health workers for CVD prevention in LMIC. *Glob Heart.* (2017) 12:233–43 e6. doi: 10.1016/j.gheart.2016.07.001
35. Crigler L, Gergen J, Perry H. Supervision of community health workers. In: Perry H, Crigler L, editors. *Developing and Strengthening Community Health Worker Programs at Scale: A Reference Guide and Case Studies for Program Managers and Policymakers*. Maternal and Child Health Integrated Program (MCHIP). (2014). p. 205–32. Available online at: https://pdf.usaid.gov/pdf_docs/pa00jxwd.pdf (accessed August 1, 2021).
36. Joshi SR, Parikh RM. India–diabetes capital of the world: now heading towards hypertension. *J Assoc Phys India.* (2007) 55:323–4.
37. Deakin T, McShane CE, Cade JE, Williams RD. Group based training for self-management strategies in people with type 2 diabetes mellitus. *Cochrane Database Syst Rev.* (2005) CD003417. doi: 10.1002/14651858.CD003417.pub2
38. Thankappan KR, Sathish T, Tapp RJ, Shaw JE, Lotfaliany M, Wolfe R, et al. A peer-support lifestyle intervention for preventing type 2 diabetes in India: a cluster-randomized controlled trial of the Kerala Diabetes Prevention Program. *PLoS Med.* (2018) 15:e1002575. doi: 10.1371/journal.pmed.1002575
39. Agarwal S, Curtis SL, Angeles G, Speizer IS, Singh K, Thomas JC. The impact of India's accredited social health activist (ASHA) program on the utilization of maternity services: a nationally representative longitudinal modelling study. *Hum Resour Health.* (2019) 17:68. doi: 10.1186/s12960-019-0402-4
40. Bhatia K. Community health worker programs in India: a rights-based review. *Perspect Public Health.* (2014) 134:276–82. doi: 10.1177/1757913914543446
41. Ministry of Health and Family Welfare. *National Multisectoral Action Plan (NMAP) for Prevention and Control of Common NCDs (2017-22)*. New Delhi: Ministry of health and Family Welfare (2017).
42. Milat A, Lee K, Conte K, Grunseit A, Wolfenden L, van Nassau F, et al. Intervention Scalability Assessment Tool: a decision support tool for health policy makers and implementers. *Health Res Policy and Syst.* (2020) 18:1. doi: 10.1186/s12961-019-0494-2
43. Scott K, Glandon D, Adhikari B, Ummer O, Javadi D, Gergen J. *India's Auxiliary Nurse-Midwife, Anganwadi Worker, and Accredited Social Health Activist Programs*. (2014). Available online at: https://chwcentral.org/indias-auxiliary-nurse-midwife-anganwadi-worker-and-accredited-social-health-activist-programs/

Conflict of Interest: RG is a shareholder in several global medical and bio-pharmaceutical companies as part of his investment portfolio.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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GLOSSARY

104 Mobile Clinic-Mobile medical vans that provide primary health care services on fixed days of a week in villages of India.
ASHA-Accredited Social Health Activist receive 4–5 weeks training, promote reproductive, maternal, neonatal and child health, encouraging immunization, institutional-based deliveries, and family planning and providing home-based newborn care and some medicines, such as oral contraceptives. They also receive incentives for malaria case identification, TB treatment support and conducting village health committee meetings (43).
ANM-Auxiliary Nurse Midwife, receive 2 years training and provide immunization, health education, antenatal care and conduct deliveries (43).

AWW-Angawadi worker, receive 3–4 weeks training, run preschool programs, provide supplementary food to young children, adolescent girls, and lactating women, and provide health and nutrition education to pregnant women, mothers, and adolescent girls (43).
BP-Blood Pressure.
CHW-Community Health Worker.
CHIRI-Controlling Hypertension in Rural India.
FGD-Focus Group Discussion.
HCP- Health Care Provider.
IDI-In-depth Interview.
LMIC-Low-and Middle-Income Country.
NCD-Non-Communicable Disease.
NPHW-Non-Physician Health Worker.
RO-Research Officer.

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Process Evaluation of a Randomised Controlled Trial for TeleClinical Care, a Smartphone-App Based Model of Care

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Background: A novel smartphone app-based model of care (TeleClinical Care – TCC) for patients with acute coronary syndrome (ACS) and heart failure (HF) was evaluated in a two-site, pilot randomised control trial of 164 participants in Sydney, Australia. The program included a telemonitoring system whereby abnormal blood pressure, weight and heart rate readings were monitored by a central clinical team, who subsequently referred clinically significant alerts to the patients' usual general practitioner (GP, also known as primary care physician in the United States), HF nurse or cardiologist. While the primary endpoint, 30-day readmissions, was neutral, intervention arm participants demonstrated improvements in readmission rates over 6 months, cardiac rehabilitation (CR) completion and medication compliance. A process evaluation was designed to identify contextual factors and mechanisms that influenced the results, as well as strategies of improving site and participant recruitment and the delivery of the intervention, for a planned larger effectiveness trial of over 1,000 patients across the state of New South Wales, Australia (TCC-Cardiac).

Methods: Multiple data sources were used in this mixed-methods process evaluation, including interviews with four TCC team members, three GPs and three cardiologists. CR completion rates, HF outreach service (HFOS) referrals and cardiologist follow-up appointments were audited. A patient questionnaire was also analysed for evidence of improved self-care as a hypothesised mechanism of the TCC app. An implementation research logic model was used to synthesise our findings.

Results: Rates of HFOS referral (83 vs. 72%) and cardiologist follow-up (96 vs. 93%) were similarly high in the intervention and control arms, respectively. Team members were largely positive towards their orientation and training, but highlighted several implementation strategies that could be optimised for TCC-Cardiac: streamlining of the enrolment process, improving the reach of the trial by screening patients in non-cardiac wards, and ensuring team members had adequate time to recruit (>15 h per week). GPs and cardiologists viewed the intervention acceptably regarding potential benefit

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of closely monitoring, and responding to abnormalities for their patients, though there were concerns of the potential additional workload generated by alerts that did not merit clinical intervention. Clear delineation of which clinician (GP or cardiologist) was primarily responsible for alert management was also recommended, as well as a preference to receive regular summary data. Several patients commented on the mechanisms of improved self-management because of TCC, which could have led to the outcome of improved medication compliance.

Discussion: Use of TCC was associated with several benefits, including higher patient engagement and completion rates with CR. The conduct and delivery of TCC-Cardiac will be improved by the findings of this process evaluation to optimise recruitment, and establishing the roles of GPs and cardiologists as part of the model.

Keywords: process evaluation, digital health, mHealth, acute coronary syndrome, heart failure, smartphone

INTRODUCTION

Globally, patients with heart failure (HF) and acute coronary syndromes (ACS) are often readmitted into hospital within 30 days (1, 2). Often, this is due to a lack of engagement with outpatient services, which may stem from inadequate coordination, communication or access (3). Readmission rates among Australian patients approach 20% in the first month after discharge for both HF (4) and myocardial infarction (5), although many are preventable (6). For HF alone, readmissions are estimated to carry an annual cost of over $600 million (7). Apart from the natural progression of the disease, contributing factors to readmissions include inadequate treatment of risk factors, such as hypertension, and non-adherence with medications and lifestyle advice. Mobile phone based (mHealth) interventions, which encompasses both short message service (SMS) based, and telemonitoring interventions, have been trialled for patients diagnosed with either ACS or HF, albeit with mixed results. A recent meta-analysis demonstrated that overall, the use of mHealth interventions was associated with an overall reduction in HF hospitalisations (8), but only one study of five showed a statistically significant reduction (9). In ACS patients, the focus of mHealth studies has been medication adherence, with no randomised trials reporting the endpoint of hospitalisation.

A collaboration between the cardiology department at Prince of Wales Hospital (POWH) and the Graduate School of Biomedical Engineering at UNSW Sydney, Australia, resulted in the design of a mobile application (app) named TeleClinical Care (TCC) that aimed to improve patients' self-management, and to provide clinicians with daily home-based readings blood pressure (BP), heart rate (HR) and weight. The data were measured using three Bluetooth-enabled digital devices: a sphygmomanometer, weighing scale and fitness wristband. The data were automatically transmitted to the app and to a web-based server (KIOLA), where a pair of clinicians (a cardiologist and a cardiology nurse practitioner) alternated the role of monitoring readings during business hours. A randomised control pilot trial of TCC was undertaken to compare TCC plus standard care, vs. standard care alone in patients being discharged after a hospitalisation due to either acute coronary syndrome (ACS) or heart failure (HF), and the results are briefly summarised here ($n = 164$, intervention arm $n = 83$, control arm $n = 81$). The average age was 61.5 years in both groups. 78% had a primary diagnosis of ACS, the remainder (22%) having a primary diagnosis of HF. There was no significant difference in the primary outcome (11 readmissions in both groups at 30 days, $P = 0.97$). However, at 6 months, there was a statistically significant difference in total readmissions (41 in the control arm, and 21 in the intervention arm, hazard ratio 0.51, 95% CI 0.31–0.88, $P = 0.015$), as well as readmissions due to cardiac causes (25 vs. 11, $P = 0.025$). There was an improvement in medication compliance as measured by self-reported questionnaire (Morisky-Green-Levine [MGL] score). The proportion of patients who reported good adherence (MGL score 4/4) increased significantly in the intervention arm (48% to 75%, $P < 0.001$). In contrast, this proportion did not significantly change in the control arm (61% to 50%, $P = 0.19$). The overall interaction favoured the intervention arm ($P_{interaction n =} 0.002$). ACS patients in the intervention arm were more likely to complete CR (20/51, 39 vs. 9/49, 18%; OR 2.9; 95% CI 1.15–7.17; $P = 0.02$). There was no significant difference in other secondary endpoints, including BP, weight, quality of life, patient activation (a measure of patient engagement in healthcare), waist circumference and six-minute walk distance (6MWD), although the loss of data due to cancellation of in-person follow-up appointments during the COVID-19 pandemic reduced the statistical power to detect any differences.

The purpose of providing physiological data to the monitoring team was to identify early deterioration in the patient's condition to manage them safely in the community, thus preventing hospitalisation.

The app also allowed the patient, general practitioner (GP, also known as primary care physician in the United States) or cardiologist to review the readings and also provided educational push notifications for patients. GPs and cardiologists were invited to use the KIOLA server to review their patients. Patients underwent study follow-up at 6 months. The primary endpoint was the incidence of all-cause readmissions at 30 days. Key

secondary endpoints included all-cause and cardiac readmissions at 6 months, CR completion and medication adherence.

The typical patient journey involved all patients being encouraged to see their GP within a week of discharge, and their cardiologist within ∼30 days. ACS patients would be invited to attend CR, usually commencing 2 weeks after discharge. This program typically involved 12 twice-weekly sessions, although uptake has traditionally been low (10). HF patients are usually referred to the HF outreach service (HFOS). The nurse practitioner or nurse would contact and educate the patient, and perform home visitation if necessary.

Hundred and sixty four patients were recruited during business hours from two metropolitan hospitals in Sydney, Australia, during the pilot study of TCC (81 intervention arm, 83 control arm). Recruitment commenced at POWH in February 2019, and at The Sutherland Hospital (TSH) in August 2019. Recruitment was terminated on March 20, 2020 due to the COVID-19 pandemic, as patients with cardiovascular disease were highly vulnerable to the effects of infection (11), and exposure to research staff was considered an unacceptable risk. TCC was the first cardiac digital health intervention (DHI) trialled at either hospital. Two doctors and two nurses were trained in patient recruitment by observing the recruitment process and reviewing an orientation manual.

In summary, the TCC pilot trial is a complex DHI with a model of care that we hypothesised would improve patient self-management and result in early detection and management of any deterioration for patients with ACS and HF who had been discharged from hospital, thereby, reducing preventable readmissions into hospital at 30 days and beyond. While we found no difference between groups at 30 days, there was a statistical reduction of hospital presentations at 6 months, and improved medication adherence. A mixed-methods process evaluation alongside this pilot randomised trial was conducted with the aim to identify for who, how and why this model of care had an impact on, and in doing so, to identify reasons and mechanisms underlying the variation of outcomes. Additionally, the success of this pilot study has resulted in the planning of a large, fully-powered multicentre RCT, with a planned enrolment of over 1,000 patients (TCC-Cardiac). The process evaluation in this paper aims to identify factors that will optimise the implementation of this larger trial.

MATERIALS AND METHODS

The process evaluation was designed in line with guidance published by the Medical Research Council (MRC) for process evaluations (12). Three individuals worked on its development, including two who were involved with the design of the original trial (SO & PI) and one who was not (HL).

Specifically, the aims of the process evaluation were:

1. To identify strategies to maximize patient, team member and site participation in preparation for the large, multi-centre TCC-Cardiac trial.
2. To identify the contextual determinants that influenced the success of the TCC program, specifically
   a) Rates of CR and HFOS referral
   b) Follow-up with cardiologists after discharge
3. To evaluate and explore the engagement of GPs and cardiologists with the TCC model of care and KIOLA server and,
4. To identify the impact of TCC participation on patient self-management.

The inclusion criteria for the RCT included English-speaking patients over the age of 18 who were admitted with ACS or HF and owned a compatible smartphone. Patients from outside Sydney, those who were travelling overseas after discharge, those being discharged to another hospital or an aged care facility and those who could not operate the app or provide informed consent due to language barrier or physical or cognitive limitations were excluded.

Table 1 summarises the data sources and methods used to obtain data for each component of the process evaluation.

Interviews

Semi-structured interviews were conducted by HL and PI between June and October 2020. We have reported this according to the Consolidated Criteria for reporting of qualitative research (see completed checklist, **Appendices A, B**) (14). The interview guide (see **Appendix C**) was designed by consensus discussion between HL and PI. PI closely understood the TCC project, while HL is experienced in qualitative research. All four TCC team members, three GPs and three cardiologists (selected by purposive sampling) were invited by email and interviewed by telephone with verbal consent for audio recording. Face-to-face contact was discouraged due to the COVID-19 pandemic. None of the GPs or cardiologists were involved in the design or day-to-day management of the study.

Domains of inquiry for TCC team members included:

1. The quality of their orientation to TCC.
2. The 'learning curve' involved in the recruitment process.

Domains of inquiry for GPs and cardiologists included:

1. Whether or not they would use the KIOLA server to access patient data and why/why not?
2. Current and future integration of TCC with their clinical care.

While a series of pre-defined questions was asked, new questions were added to facilitate further discussion of points raised by the interviewee (see **Appendix C**). There were no refusals to participate. All subjects were assured that their identity would remain confidential. The interviews were transcribed verbatim by PI, and the data were analysed according to the Framework Method for the analysis of qualitative data (15). Specifically, the transcribed text was coded by PI under eight prespecified categories (see **Appendix D**). Each category was then systematically reviewed. No repeat interviews or transcript clarification were required.

Analysis

The results of the process evaluation are intended to inform the refined implementation research logic model (16) (IRLM)

TABLE 1 | Methods utilised in this process evaluation.

Aim	Sub-aim	Method of data collection
1. To identify methods to maximise patient, team member and site participation in preparation for the large, multi-centre TCC-Cardiac trial	Analysis of screening and recruitment (reach)	A database of patients screened for enrolment was compared against a list of patients and their coded diagnoses provided by the data management team at the respective hospitals, according to the Australian Coding Standards (13).
	An analysis of the training and overall experience of team members	Semi-structured interviews with four team members
	Creation of a checklist to assess any new trial site prior to involvement in TCC-Cardiac	- Lead investigator's own experience - Semi-structured interviews with four team members
2. To identify the contextual factors that influenced the success of the TCC program	CR for ACS patients	CR attendance and completion rates were calculated for each site, for patients enrolled in the trial two months before the cessation of cardiac rehab due to COVID-19 (March 2020).
	HFOS	At recruitment, TCC team members documented if the patient was known to, or referred to, the local HFOS.
	Post-discharge cardiologist consultation	An audit of 20 discharge summaries from each site was conducted to identify the timing of post-discharge cardiologist appointment. The cardiologist offices were contacted to confirm if follow up occurred. If a follow-up range was given, then the longest duration within the range was defined as the prescribed follow-up interval (e.g., "4–6 weeks" would translate as 42 days).
3. To evaluate and explore the engagement of GPs and cardiologists with the TCC model of care and KIOLA server	Identifying attitudes of GPs and cardiologists	- Timestamps from KIOLA records to confirm the number of GPs who accessed the platform. - Semi –structured interviews with three GPs and three cardiologists.
4. To identify the impact of TCC participation of patient self-management and their overall rating of the app	Analysis of quotes from patients regarding a possible improvement of self-care due to TCC	All patients in the intervention arm were asked to complete a questionnaire regarding their experience. Within the questionnaire were the questions "what did you like the most about the TCC app" and "in what ways do you feel like the TCC app benefited you" and responses were reviewed for self-care references. The average overall patient rating out of 5 was calculated.

ACS, acute coronary syndrome; CR, cardiac rehabilitation; GP, general practitioner; HFOS, heart failure outreach service; TCC, TeleClinical Care.

used to synthesise our findings for the planned TCC-Cardiac trial (**Figure 1**). The IRLM allows for analysis of a multifocal, complex intervention. It includes the contextual determinants, implementation and mechanisms, and outcomes as per the UK MRC process evaluation guidance, and also embeds the traditional logic model (12, 16). There are four conceptual and theoretical themes contained within the IRLM which relate to the actors involved (patients, TCC recruitment team, TCC monitoring team and health care providers). Each is colour coded, and is linked to the four aims of the process evaluation. Each theme has unique implementation strategies, mechanisms and outcomes. For example, the aim of maximising participation (aim 1) is examined by focusing on the TCC team members responsible for recruitment, represented by blue text in the IRLM.

Aims 2 and 3 focus on GPs and cardiologists (green) and aim 4 focuses on patients (brown).

For statistical analysis, categorical variables were expressed as percentages. Odds ratios were calculated using the Pearson Chi-Square test. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp). All analyses applied the intention-to-treat principle.

RESULTS

Aim 1: Strategies to Maximise Patient, Team Member and Site Participation in Preparation for the Large, Multi-Centre TCC-Cardiac Trial

Reach and Recruitment

Reach is defined as the extent to which the target audience encounters the intervention, in this case, the TCC RCT (17). It is an important concept to identify the transferability of the trial and understanding of the trial outcomes. It addresses the question of "*Did we recruit the types of patients that we intended TCC for*?"

A total of 565 patients were screened for eligibility, and 164 (29%) were included in the trial. While this result may appear limited, the major barrier to enrolment was smartphone ownership. Of the 401 screened patients who were not included, mobile phone ownership data was available for 359 (89.5%). Of these, 206 (57%) did not have a smartphone, and 34 (9%) owned an incompatible smartphone. A detailed evaluation of smartphone ownership patterns is beyond the scope of this process evaluation but will occur in a separate analysis. A comparison of exclusion criteria met at each site is presented in **Figure 2**.

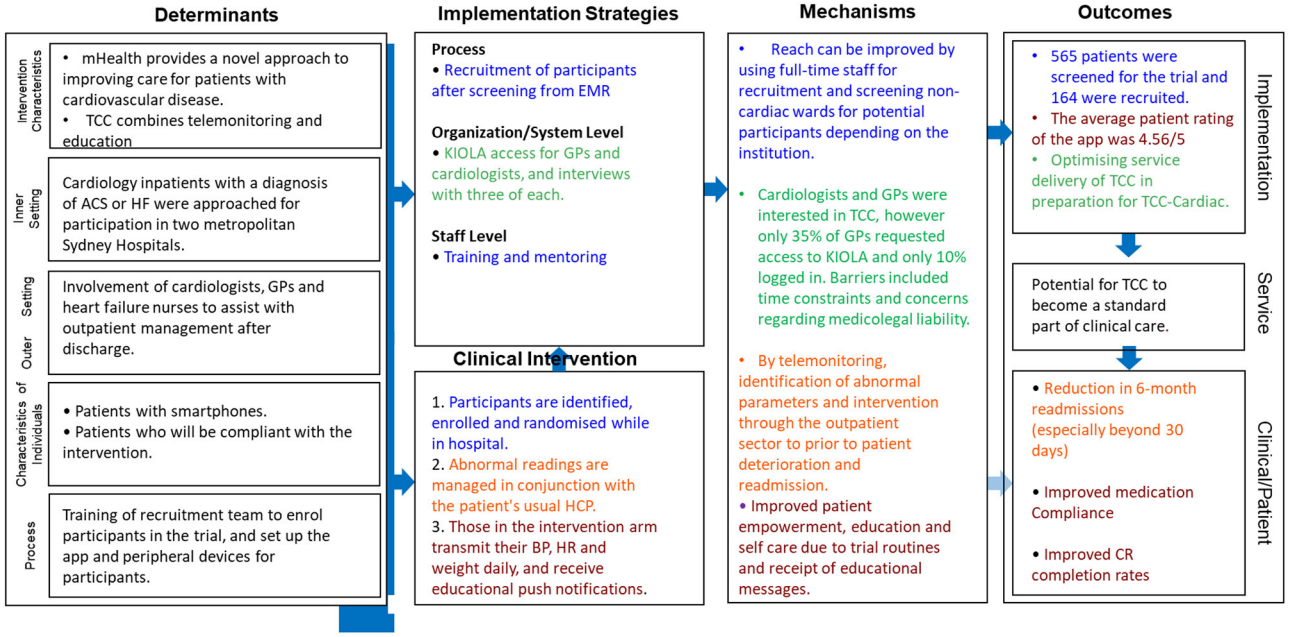

FIGURE 1 | Implementation research logic model (IRLM) for the TCC process evaluation, which describes the contextual determinants, implementation and mechanisms, and outcomes as per the standard process evaluation procedure. The four themes as identified within the refined IRLM relate to the actors involved: the hospital staff providing and delivering the intervention (blue colour within IRLM), the staff monitoring and responding to the patient recordings, healthcare practitioners who care for patients after discharge (GPs, cardiologists and HFOS) and patients participating in the TCC program (brown)". ACS, acute coronary syndrome; BP, blood pressure; EMR, electronic medical record; GP, general practitioner; HCP, healthcare provider; HF, heart failure; HFOS, heart failure outreach service; HR, heart rate; TCC, TeleClinical Care.

Challenges in the Screening and Recruitment Process Affecting the Reach of the Study

During the study period, a search of patients using International Classification of Diseases (ICD) codes revealed 795 patients were admitted to POWH with either an ACS or HF during the study period. Of these, only 394 (49.6%) were screened for eligibility. This was due to discrepancies between the ICD codes and the research team diagnosis. Furthermore, 115 patients were screened for eligibility who were not identified by the hospital dataset, suggesting these patients were also miscoded.

At TSH, 244 patients were admitted with a diagnosis of either ACS or HF according to the hospital dataset during the study period. Twenty five (10%) were screened for eligibility. An additional 29 patients were identified as having an admission diagnosis of ACS or HF, despite not being identified by ICD codes. A total of 54 patients were screened at TSH over seven months. Of these, 28 were recruited, giving an enrolment rate of 52%. The lower proportion of patients screened at TSH was attributable to several factors including:

- The lack of a dedicated full-time TCC staff member at the site, which was particularly challenging when the department was short-staffed.
- Institutional policies that resulted in many patients with cardiac conditions being admitted under alternate specialties such as respiratory medicine and aged care, and thus who were not identified during the screening process (121 of 244 patients, 49.6%).

Training and Overall Experience of Team Members

Orientation to TCC

All four team members praised their orientation. All benefited from the 1-on-1 approach to observing and then undertaking supervised patient enrolment. The orientation manual was used by 3 of the 4 team members, but only one used it frequently. The others preferred to contact the lead investigator directly for assistance and troubleshooting. Two team members commented that their primary use of the manual was for scoring questionnaire results. One team member commented on the importance of hearing a formal presentation about TCC, as well as being able to use the peripheral devices themselves, to understand the complete picture.

> *"The first introduction was when [the principal investigator] gave an orientation talk, which was valuable to understand the greater vision behind TCC and communicated the key messages of the project. Secondly, I was [allowed to use] the actual equipment which was valuable. It was a certainly a sound introduction to the project." – Team Member (TM) 4*
>
> *"It's a very useful, user friendly manual. I must say I didn't always use it when I could have." – TM3*
>
> *"To be honest I rarely used [the manual], because it's easier to ask for help!" – TM1*

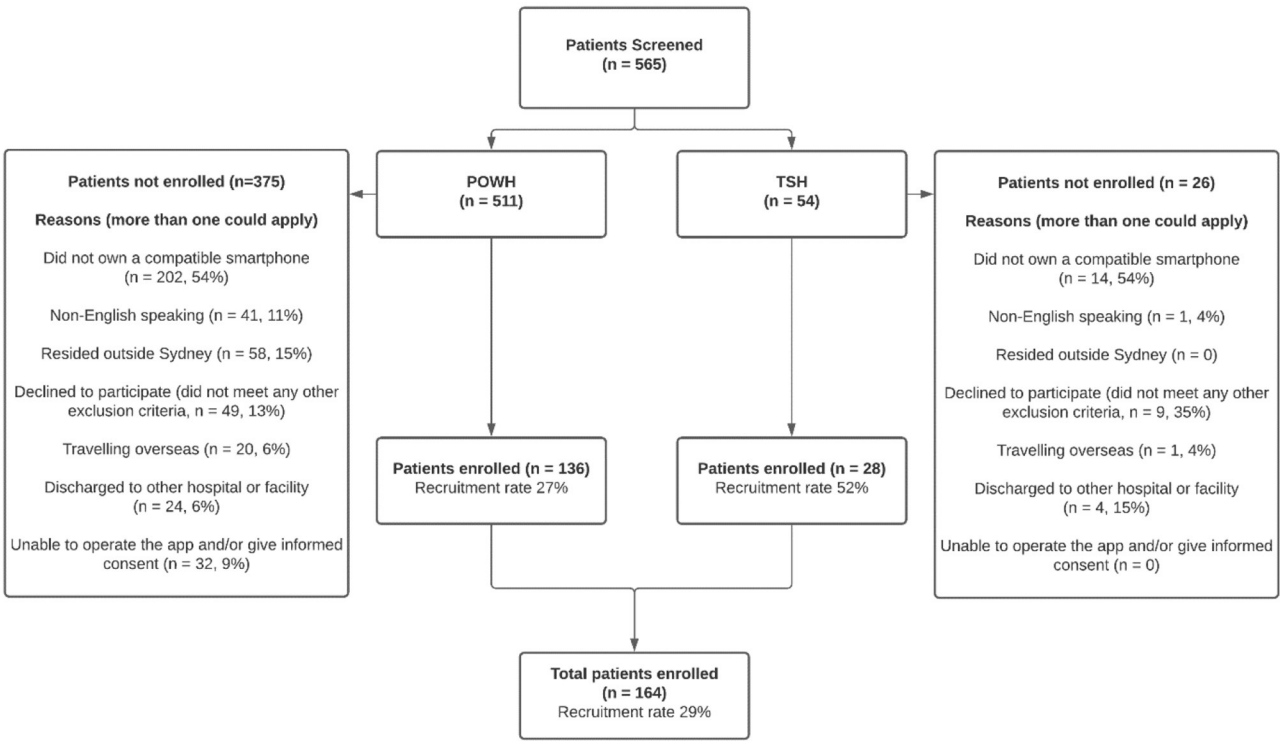

FIGURE 2 | Recruitment patterns between sites. POWH, Prince of Wales Hospital; TSH, The Sutherland Hospital.

The Learning Curve and Challenges of Patient Enrolment

All team members felt confident in being independently able to enrol a patient after 2–4 attempts. When asked to estimate the time taken to enrol a patient, responses varied (10 min, 30 min, 60–90 min, 120–180 min). Delays in the enrolment process can be divided into trial-related and intervention-related. The major trial-related delay was coordination of the 6MWD test. Intervention related delays included: patients and team-members being unfamiliar with the patient's smartphone, and questions from family members of the patients. App installation and device pairing was considered the most time-consuming part of the enrolment process.

> *"[Recruitment] could take a good 2-3 h. I met the patient briefly, explained the study and gave them the information sheet to read. Then I would return, and we would go through the sheet together. During enrolment I had to fill in various parameters, it was not always possible to do all of it at once, especially the 6 min walk test. Sometimes you had to go back and request blood tests that hadn't been done. The enrolment could be done over a number of days. It wasn't really that simple–it could be quite time consuming." – TM3*

Challenges of completing the enrolment were generally related to time constraints in the busy hospital setting, as patients were often unavailable due to procedures, or were keen to be discharged as soon as possible. Many patients had short inpatient stays.

> *"You do have this narrow window between discharge and the patient leaving the hospital. If you're having a busy day, it's hard. I started planning more in advance and trying to predict discharges. I would block out time and discussed it with the patient beforehand to avoid holding up their discharge. With a little trial and error, I managed to smooth it out." – TM2*
>
> *"Sometimes it was a bit difficult getting all of the data that was needed. We had to wait for procedures and tests to be done, and then had to catch [the patient] before discharge." – TM1*

Three team members commented on the difficulty in identifying the operating system (OS) of a patient's smartphone, particularly when it was a different OS to their own personal phone.

> *"Mostly this was a problem with the Android machines. It was difficult to work out [which] OS it was running and also how to download the app from the Play Store. I just wasn't used to that process" – TM3*

Technical Support

While not part of enrolment, the provision of technical support after the patient had commenced the trial was considered challenging by three of the four team members.

> *"Troubleshooting technology things over the phone to an elderly person was quite challenging at times- trying to explain step-by-step the things that they needed to do. At times you couldn't get the message across properly and we would do a home visit." – TM1*

TABLE 2 | Cardiac rehabilitation attendance rate and completion rate.

Parameter	Intervention ($n = 51$)	Control ($n = 49$)	Statistical analysis
Attendance rate	28/51 (55%)	21/49 (43%)	NS
Completion rate (attendees only)	20/28 (71%)	9/21 (43%)	OR 3.3 (95% CI 1.01–11) $P = 0.04$
Completion rate	20/51 (39%)	9/49 (18%)	OR 2.9, (95% CI 1.15–7.17) $P = 0.02$

NS, not significant; OR, odds ratio.

Time Commitments

Questions regarding time commitments were targeted at the two team members from TSH who worked on TCC in addition to their full-time clinical duties. They stated the time commitment required was approximately 10–15 h per week, which was challenging. The addition of a second staff member should be considered in this scenario.

> *"When you are busy, you cannot enrol the patient in one [session]. You have to repeatedly visit the patient throughout the course of their admission. It is better to do things in cross-section. It would probably take 10–15 h per week to do a proper job of it." – TM4*
> *"There are things that need to be done by a medical professional, and others that can be done by an adjunct staff member. Educating the patient on using the devices and taking the blood pressure correctly all takes a fair bit of time. I do think enrolment needs to be done by a clinical person but spending the time to instal the app and equipment does not." – TM4*

Creation of a Checklist to Assess Any New Trial Site Prior to Involvement in TCC-Cardiac

Prior to recruiting a site for TCC-Cardiac, several key factors must be met (see **Appendix D**). Broadly, necessary components of the hospital included an inpatient cardiology service with CR and a HFOS. Access to all diagnostic results is necessary, as is sufficient storage and office space. An orientation manual and opportunities to observe the recruitment process and perform it under supervision are considered essential.

Aim 2: Assessing the Contextual Determinants That Influenced the Success of the TCC Program

CR

TCC was designed to work in concert with CR, by reinforcing the educational messages and lifestyle modifications that are recommended by the CR program. Due to the COVID-19 pandemic, however, a full course of CR could only be offered to 100 of the 128 (78%) ACS patients in the trial. Patients in the intervention arm were more likely to complete CR (**Table 2**).

HFOS

The POWH HFOS is managed by a nurse practitioner and a clinical nurse specialist. They conduct home visits and phone calls for over 200 patients. The HFOS at TSH is staffed by more junior nursing staff. They work closely with GPs to instigate management changes. Referral rates are provided in **Table 3**. There was a high rate of HFOS referral in both trial arms, and no significant difference was found.

TABLE 3 | Heart failure outreach service referral rates among patients recruited to TeleClinical Care.

	HF (all patients)	Intervention	Control
Prince of Wales	25/32 (78%)	13/16 (81%)	12/16 (78%)
Sutherland	3/4 (75%)	2 /2 (100%)	1 / 2 (50%)
Both sites	**28/36 (78%)**	**15/18 (83%)**	**13/18 (72%)**

Two patients were referred to other regional services as their residences were out of area. HF, Heart failure.

TABLE 4 | Patterns of cardiologist follow-up recommendations at the time of discharge and attendance.

	Intervention arm	Control arm	Total
n	23	14	37
Mean follow up suggestion	42 days	34 days	39 days
Mean actual follow up	40 days	36 days	38 days
Patients who attended follow-up with a cardiologist	22 (96%)	13 (93%)	35 (95%)
Patients who attended follow up 1 week or more after recommended time	7 (30%)	3 (23%)	10 (27%)

Post-discharge Consultation With Cardiologists

Forty patients were randomly selected for analysis of follow-up attendance (20 from each site). At the scheduled time of follow-up, one patient was deceased, and two others were hospitalised, leaving 37 patients for analysis. Over 90% of the sampled patients had follow-up with a cardiologist during their time in the trial, with the majority doing so in a timely fashion (**Table 4**).

Aim 3: Engagement of GPs and Cardiologists With the TCC Model of Care and KIOLA Server

GPs and Access to KIOLA

3/81 intervention arm patients did not nominate a GP. For the other 78 patients, there was a total of 73 GPs, five of whom were uncontactable. Of the 68 contacted GPs, only 24 (35%) requested access to KIOLA, 7 of whom (29%) accessed the server.

GP and Cardiologist Perspectives

The Low Uptake of KIOLA Among GPs

It was proposed by GP2 that time constraints were the major reason behind the low uptake. Other concerns included issues of medico-legal liability. It was also suggested by GP3 that certain GPs may not be comfortable with new technology.

> *"When there are only 15-min slots, it can be quite pressured...the GP would have far less time and be less inclined to look at additional information." - GP2*

The Usefulness of TCC in Clinical Practise

All three cardiologists and two of three GPs felt TCC was likely to be a useful addition to their clinical practise. The main advantage described was having an accurate long-term BP record. GP1 felt that automatic sphygmomanometers were unreliable, and she relied on in-office manual readings. One cardiologist praised the ability to detect asymptomatic atrial fibrillation, which resulted in a significant change in treatment for his patient.

> *"It's challenging as the GP to figure out what the patient's blood pressure actually is, based on a single reading" - GP3*
> *"Blood pressure is one of the hardest things to get right. A single reading in the office can be meaningless." - Cardiologist 2 (C2)*

Receiving Alerts

Two out of the three cardiologists expressed concerns about the volume of alerts that they would potentially receive, but both were still in favour of receiving them.

> *"Do I want to be called about every minor abnormality? I think the answer is no. If there is a significant change, and I feel I can have an impact on their therapy, then yes." – C1*

Viewing Patient Data

All three cardiologists and two of three GPs stated they would be interested in viewing a patient's data. Three options were provided to do so – (1) KIOLA access via office desktop computer, (2) viewing the data on the patient's smartphone and (3) receiving a patient summary from the TCC team. The clinicians were asked to select their preferred option.

GP1 was not asked this question based on her previous answers. GP2 stated he would be happy with any option, and GP3 preferred option 1. All three cardiologists preferred a report-based option, generated monthly, in either an electronic or paper form to be stored in the patient's file. This option is to be considered for TCC-Cardiac.

A common theme was the ability to recall which patients were involved in the trial, as patients may not volunteer this during their visit, and thus the data would not be viewed. GP2 stated it should be the patient's responsibility to remind the clinician. C2 suggested that the TCC team contact the cardiologist's rooms so that it is flagged in the patient's file, and C3 suggested a mobile-phone-based reminder of which patients were involved.

Which Clinician Should Primarily Manage Alerts?

GP1 was happy that either clinician managing the alerts, with the requirement of correspondence provided to the other. GP2 preferred the cardiologist be responsible, and GP3 felt the GP should be responsible, but would manage the alerts with some guidance from the cardiologist.

Of the three cardiologists, the responses also varied. C1 stated that the GP should be the first point-of-contact, but the cardiologist should be involved if the GP is uncertain how to proceed. C2 felt GPs should ideally be responsible but doubted whether that was practicable. C3 felt it would be situation-dependent.

> *"[The responsibility] should go to the cardiologist in heart failure. In ACS, it needs to be a time-based thing. First three months—cardiologist. After that—GP. Early on, [the patient] may not have even seen the GP! They may not be seeing their cardiologist for 9 months." – C3*
> *I think it should go to the GP. Prevention is our job. It would be best if instructions were given by the cardiologist to me, so that I could just follow the plan." – GP3*

Medicolegal Liability

Two of the three GPs were concerned about medicolegal liability. None of the three cardiologists felt this to be a major concern in widespread adoption of TCC.

The Impact of TCC Participation on Patients

The app was positively received by patients, with an average rating of 4.56 out of 5. While not directly targeted in the questionnaire, several participants volunteered that TCC impacted their self-care and motivation. A sample of representative answers are provided below:

> *"[TCC] was giving me incentive to stay on top of my condition" (male patient, age 61)*
> *"It creates a focus on maintaining a healthy lifestyle" (male patient, age 67)*
> *"It is something that encouraged me to have a little bit of discipline" (male patient, age 76)*
> *"It helped me to feel like I was in control, and was a reminder to look after myself" (female patient, age 57)*
> *"It made me accountable for my own readings and checking the progression of my own health" (male patient, age 53)."*

DISCUSSION

The TCC pilot study demonstrated several significant benefits to participants. There was a statistically significant reduction in total readmissions, driven by a reduction in cardiac readmissions. This finding is of great importance, as although meta-analysis has shown that mHealth interventions are associated with a reduction in HF hospitalisations (8), this is only the second individual RCT to show an impact on hospitalisation. The first was a text messaging intervention implemented in China (9). Other telemonitoring studies in HF have failed to show a benefit in hospitalisation rates (18–20), although one Belgian study demonstrated a mortality benefit (21). In patients with ischemic heart disease or ACS, the impact of telemonitoring on hospitalisation rates has not been examined previously in any mHealth RCT.

This process evaluation aimed to identify the factors required to establish a digital health trial in two metropolitan hospitals that previously had no experience in the field, as well as identifying underlying contextual factors that may have contributed to the results of the trial, and evaluating potential strategies to optimise implementation of the TCC model of care to multiple sites in the planned TCC-Cardiac RCT. The reach of the trial is difficult to quantify due to the lack of a clear denominator in terms of patients admitted with ACS or HF. This is attributed to over-diagnosis, under-diagnosis or miscoding of patients. Patients may

TABLE 5 | Features of the training process for TCC team members.

Description in the TCC trial	Method of optimisation for TCC-cardiac study
• An orientation manual was used by 3 of 4 team members. It was positively described but not used frequently, except to score questionnaire results and identify smartphone compatibility. • The lead investigator was easily contactable for assistance with recruitment.	• Provide all team members with the orientation manual. • Provide email and phone number of lead investigator so problems can be rectified at short notice. • All team members to receive an orientation lecture, and the TCC app and equipment for self-testing. • Team members to observe two recruitments, and perform two more under supervision.

have been diagnosed as having an ACS despite not meeting established standard definitions for this diagnosis, and vice versa. This is likely to be a problem in the TCC-Cardiac trial also, and without auditing each patient individually, the true reach of the project cannot be known. When considering screening and recruitment rates at new sites, an understanding of the workforce and institutional admission patterns is required. For example, the tendency of patients with HF to be admitted under specialties other than cardiology at TSH reduced the reach. In order to maximise patient participation, it is recommended that for TCC-Cardiac, that non-cardiac wards are screened for potential enrolments, and that staff can commit 15 h per week for enrolment duties.

Interviews with TCC team members revealed details of the training process, the learning curve, and the challenges of the enrolment process. The answers provided by the team members have been used in the creation of the site setup form. Proposed methods to optimise the orientation experience are summarised in **Table 5**. Looking ahead to TCC-Cardiac, participating sites must meet several pre-requisites prior to commencement of enrolment. "Usual care" should be standardised. Thus, sites are required to have an inpatient cardiology service, as well as outpatient options for CR, HFOS and cardiologist follow-up. Recruitment for the trial is clearly optimal when there is full-time coverage, as evidenced by the lower recruitment rate at TSH. Clinicians performing recruitment as an addition to other clinical duties may struggle to screen and recruit potential participants, particularly when their other roles are busier than expected, or when they must cover for a colleague on leave. Ideally, 10–15 h per week to recruit participants should be "protected". Given how patients are often unavailable or inappropriate to approach for recruitment due to their clinical condition, investigations, procedures and discharge planning, this time commitment may be sporadic, rather than continuous, and new team members should be warned of these challenges. It should be noted that one of the major delays during enrolment was the 6-min walk test, which will not be required outside the clinical trial setting.

TCC is designed to support, rather than replace, the benefits of GP care, cardiologist care, CR and HFOS. CR, which comprises education and exercise, is considered a cornerstone of post-infarction care and is recommended for all patients who are admitted with an ACS (22, 23). The CR completion rate prior to COVID-19 at POWH was similar to the previously quoted worldwide average of 20–30% (24). Due to the pandemic, 22% of enrolled ACS patients were denied a full course of CR. Due to randomisation, this is assumed to have affected both groups equally.

Referrals to HFOS were relatively high in both arms (83% intervention vs. 72% control). This was crucial to the success of the trial, as the HFOS was often required to respond to abnormal clinical parameters. TCC is designed to improve the workflow of the HFOS by two specific mechanisms: (i) it allows rapid vital sign assessment of a large population of patients rather than requiring manual phone calls or home visits to gather this data and (ii) identification of stable and unstable patients, which allows for optimal allocation of time and resources to the patients at highest risk for hospitalisation. The combination of these two factors will thus potentially allow an increase in the capacity of the number of patients that can be cared for under the HFOS. Since HFOSs have been shown to improve readmission rates and mortality (25), institutions should be aiming for 100% referral rates, and TCC-Cardiac may potentially provide an incentive to do so. In settings where HFOS referral rates are low, the magnitude of readmission reduction due to TCC will likely diminish.

Follow-up rates with cardiologists were high in a random sample of 37 patients. The typical suggested follow-up time was approximately 6 weeks, consistent with published recommendations (26). Previous work has found that follow-up within 7 days lowers the rates of readmission within 30 days (27), however this is not routine practise in either site, and would have been an important confounder for the primary endpoint of 30 day all-cause readmission.

Given the high rates of HFOS referral and cardiologist follow-up in both groups, it can be concluded that variations in usual care were not responsible for the positive findings in the TCC trial. The mechanism of TCC in improving readmission rates, CR and medication adherence is likely a combination of telemonitoring and improved patient self-care. Several participants expressed that their involvement in the trial created a focus on their condition, lifestyle, and health choices. Several previous mHealth studies have demonstrated an improvement in medication adherence (28–31), typically by motivating patients. Improved adherence is likely a key factor in improving outcomes potentially in many chronic diseases. Improved self-care, medication adherence and CR completion may only develop after several months, which may explain why a reduction in readmissions was seen at 6 months and not at 30 days. Therefore, the primary endpoint of the TCC-Cardiac trial will be all-cause readmissions at 6 months. Whether these benefits persist beyond 6 months remains unknown and requires further study.

The Role of GPs and Cardiologists

For the TCC-Cardiac trial, it is proposed that the cardiologist be the primary point of contact for the research team in

responding to alerts, and that this should be clearly established for each patient. Most GPs who were offered access to KIOLA did not access it. Reasons identified in the series of interviews included time constraints, resistance to change, and concerns over medicolegal liability. Each GP cared for only 1–2 patients in the trial, whereas cardiologists had several more, and over time may become more familiar with the TCC model. A specialist may be less available for urgent and semi-urgent consultations than a GP, however, thus a reasonable alternative would be for the cardiologist to recommend a GP visit if they were unable to see the patient themselves and provide some guidance to the GP in managing the clinical issue. The research team could facilitate this discussion. The best approach, also to be considered for TCC-Cardiac may be to individualise a customizable action plan on a case-by-case basis. This plan could be established by speaking to the patient, the GP and the cardiologist at the point of enrolment. Regardless of which clinician is the primary point-of-contact, correspondence should be provided to the other regarding investigations or treatment changes.

Other considerations for TCC-Cardiac included a robust method of identifying patients who were involved. Ideas proposed included informing the practise secretary to identify the patient prior to consultation, and the provision of a report containing trends in the parameters (weight, HR and BP), delivered every 1–3 months by electronic means. Both are simple modifications, which are to be considered for TCC-Cardiac. Ultimately, since TCC requires the input of the GP and/or cardiologist, it may serve to strengthen the doctor-patient relationship by providing a means of closer monitoring. This, in turn, could lessen the risk of future readmissions. The use of TCC may also improve links between practitioners, if one or both are taking an active role in the management of alerts generated by the program.

Broader Applications of This Process Evaluation

The COVID-19 pandemic has led to an increase in DHIs, and it is presumed that this will continue after the pandemic's eventual resolution. There is great heterogeneity among DHIs—ranging from simple text messaging programs to more complex telemonitoring solutions such as TCC. Also, the target patient cohort can vary widely, as DHIs can be applied to a large variety of medical conditions, and are inherently scalable to large populations. Therefore, in the digital health sphere, process evaluations are of critical importance and we urge all triallists to consider undertaking them. Several findings of this process evaluation are applicable to the broader digital health context. For example, when assessing the potential reach of mHealth interventions, smartphone ownership may be a rate-limiting factor, and this must be considered. Patients lacking smartphones are at risk of being excluded from beneficial models of care, and strategies are required to address this gap. This may include loaning or rental of smartphones or tablets, with education and instruction in their operation. An understanding of the challenges and time commitments for team-members is also necessary, as for many, this may be their first experience with a DHI.

Further, complex DHIs such as TCC exist within the healthcare ecosystem and involve multiple healthcare practitioners, as well as the patient. In this case, TCC required the input of GPs, cardiologists and HFOS staff. Depending on the nature of the intervention, other medical specialists or allied health staff will be required to interact with patients. Consideration of how the intervention will involve, and be received by, practitioners outside the immediate investigating team is necessary to maximise the benefit to the patient. Investigators should consider whether the intervention will lead to an increased or streamlined workload for these practitioners, and whether care coordination will be improved or complicated, and whether any challenges such as medicolegal liability may be perceived.

DHIs, of any nature, will have an impact on the patient. Potential positive effects include improved medication adherence and self-care, and methods of evaluating these should be considered for all digital health trials. Additionally, when considering the endpoints for digital health trials, these factors should be considered. For example, as medication adherence and self-care improvement take time to develop, clinical outcomes may only prove to be different after several months of using the intervention, rather than immediate. Therefore, endpoints such as 30-day readmissions may not be influenced by certain DHIs, but the trial should not be considered negative if this is the case. Rather, long-term endpoints should be used to adjudicate the efficacy of these interventions, such as 6-month or 1-year readmission rates.

Limitations

The COVID-19 pandemic resulted in removal of CR from standard care, and resulted in premature termination of enrolment. Thus, the sample size at TSH was smaller than anticipated. Analysis of timing of follow-up was limited to a representative sample of participants rather than all participants. Interviewing a greater number of GPs and cardiologists may have resulted in gathering of further data. Specific questioning of patients regarding mechanisms of benefit such as improved self-care should be considered in the TCC-Cardiac trial. Miscoding of patient diagnoses was also identified which precluded accurate calculation of the reach of the trial.

CONCLUSION

The TCC model of care has significant potential for reducing the strain on healthcare systems, as well as empowering patients to achieve better outcomes for secondary prevention of ACS or decompensated HF.

This mixed-methods process evaluation identified differences in the enrolment process and service delivery at both sites involved in the original TCC trial. Thus, it provided a template and pathway for the initiation of new sites into a larger multicentre trial (TCC-Cardiac). This trial is expected to be a pivotal trial into encouraging widespread implementation of this model of care to cardiac patients across the state of New South

Wales, provided that clinical benefits are replicated, and that cost-effectiveness is acceptable. Mechanisms of change, such as exploring benefits relating to improved self-care among patients, should be further characterised. This process evaluation also identified options that would streamline the transition of the system from a research project to mainstream clinical practise, and highlights concepts applicable to DHIs outside cardiology.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by South Eastern Sydney Local Health District Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PI: conduct of most aspects of data collection and analysis and primary author of the manuscript. UB: data analysis of the patient questionnaire data. HL: interviewed all team members and provided extensive guidance into the concept and design of the process evaluation. SR: supervision of the project from a technical/engineering perspective. JY: assistance with data analysis and supervision of the project from a medical perspective. NL and S-YO: co-supervisor of the overall project. All authors contributed to the conception, design, and performance of the work and have reviewed the manuscript and accept accountability for it.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.780882/full#supplementary-material

REFERENCES

1. Oliveira L, Costa I, Silva DGD, Silva J, Barreto-Filho JAS, Almeida-Santos MA, et al. Readmission of patients with acute coronary syndrome and determinants. *Arq Bras Cardiol.* (2019) 113:42–9. doi: 10.5935/abc.20190104
2. Reddy YNV, Borlaug BA. Readmissions in heart failure: it's more than just the medicine. *Mayo Clin Proc.* (2019) 94:1919–21. doi: 10.1016/j.mayocp.2019.08.015
3. Desai AS, Stevenson LW. Rehospitalization for heart failure: predict or prevent? *Circulation.* (2012) 126:501–6. doi: 10.1161/CIRCULATIONAHA.112.125435
4. Al-Omary MS, Davies AJ, Evans TJ, Bastian B, Fletcher PJ, Attia J, et al. Mortality and readmission following hospitalisation for heart failure in australia: a systematic review and meta-analysis. *Heart Lung Circ.* (2018) 27:917–27. doi: 10.1016/j.hlc.2018.01.009
5. Rana S, Tran T, Luo W, Phung D, Kennedy RL, Venkatesh S. Predicting unplanned readmission after myocardial infarction from routinely collected administrative hospital data. *Aust Health Rev.* (2014) 38:377–82. doi: 10.1071/AH14059
6. Johnston J, Longman J, Ewald D, King J, Das S, Passey M. Study of potentially preventable hospitalisations (PPH) for chronic conditions: what proportion are preventable and what factors are associated with preventable PPH? *BMJ Open.* (2020) 10:e038415. doi: 10.1136/bmjopen-2020-038415
7. Chan YK, Tuttle C, Ball J, Teng TK, Ahamed Y, Carrington MJ, et al. Current and projected burden of heart failure in the Australian adult population: a substantive but still ill-defined major health issue. *BMC Health Serv Res.* (2016) 16:501. doi: 10.1186/s12913-016-1748-0
8. Indraratna P, Tardo D, Yu J, Delbaere K, Brodie M, Lovell N, et al. Mobile Phone Technologies in the Management of Ischemic Heart Disease, Heart Failure, and Hypertension: Systematic Review and Meta-Analysis. *JMIR Mhealth Uhealth.* (2020) 8:e16695. doi: 10.2196/16695
9. Chen C, Li X, Sun L, Cao S, Kang Y, Hong L, et al. Post-discharge short message service improves short-term clinical outcome and self-care behaviour in chronic heart failure. *ESC Heart Fail.* (2019) 6:164–73. doi: 10.1002/ehf2.12380
10. Ritchey MD, Maresh S, McNeely J, Shaffer T, Jackson SL, Keteyian SJ, et al. Tracking Cardiac Rehabilitation Participation and Completion Among Medicare Beneficiaries to Inform the Efforts of a National Initiative. *Circ Cardiovasc Qual Outcomes.* (2020) 13:e005902. doi: 10.1161/CIRCOUTCOMES.119.005902
11. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. *JAMA Cardiol.* (2020) 751–3. doi: 10.1001/jamacardio.2020.1105
12. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ: British Medical Journal.* (2015) 350:h1258. doi: 10.1136/bmj.h1258
13. Australian Consortium for Classification Development. *ICD-10-AM. 11 Edn.* Sydney, NSW: Independent Hospital Pricing Authority (IHPA) (2019).
14. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care.* (2007) 19:349–57. doi: 10.1093/intqhc/mzm042
15. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol.* (2013) 13:117. doi: 10.1186/1471-2288-13-117
16. Smith JD, Li DH, Rafferty MR. The Implementation Research Logic Model: a method for planning, executing, reporting, and synthesizing implementation projects. *Implementation Sci.* (2020) 15:84. doi: 10.1186/s13012-020-01041-8
17. Seguin M, Dodds C, Mugweni E, McDaid L, Flowers P, Wayal S, et al. Self-sampling kits to increase HIV testing among black Africans in the UK: the HAUS mixed-methods study. *Health Technol Assess.* (2018) 22:1–158. doi: 10.3310/hta22220
18. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Böhm M, et al. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. *Circulation.* (2011) 123:1873–80. doi: 10.1161/CIRCULATIONAHA.111.018473
19. Scherr D, Kastner P, Kollmann A, Hallas A, Auer J, Krappinger H, et al. Effect of home-based telemonitoring using mobile phone technology on the outcome of heart failure patients after an episode of acute

decompensation: randomized controlled trial. *J Med Internet Res.* (2009) 11:e34. doi: 10.2196/jmir.1252
20. Vuorinen AL, Leppanen J, Kaijanranta H, Kulju M, Helio T, van Gils M, et al. Use of home telemonitoring to support multidisciplinary care of heart failure patients in Finland: randomized controlled trial. *J Med Internet Res.* (2014) 16:e282. doi: 10.2196/jmir.3651
21. Dendale P, De Keulenaer G, Troisfontaines P, Weytjens C, Mullens W, Elegeert I, et al. Effect of a telemonitoring-facilitated collaboration between general practitioner and heart failure clinic on mortality and rehospitalization rates in severe heart failure: the TEMA-HF 1 (TElemonitoring in the MAnagement of Heart Failure) study. *Eur J Heart Fail.* (2012) 14:333–40. doi: 10.1093/eurjhf/hfr144
22. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* (2012) 33:2569–619. doi: 10.1093/eurheartj/ehs215
23. McMahon SR, Ades PA, Thompson PD. The role of cardiac rehabilitation in patients with heart disease. *Trends Cardiovasc Med.* (2017) 27:420–5. doi: 10.1016/j.tcm.2017.02.005
24. Ades PA, Keteyian SJ, Wright JS, Hamm LF, Lui K, Newlin K, et al. Increasing cardiac rehabilitation participation from 20% to 70%: a road map from the million hearts cardiac rehabilitation collaborative. *Mayo Clin Proc.* (2017) 92:234–42. doi: 10.1016/j.mayocp.2016.10.014
25. Feltner C, Jones CD, Cené CW, Zheng ZJ, Sueta CA, Coker-Schwimmer EJ, et al. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. *Ann Intern Med.* (2014) 160:774–84. doi: 10.7326/M14-0083
26. Faridi KF, Peterson ED, McCoy LA, Thomas L, Enriquez J, Wang TY. Timing of first postdischarge follow-up and medication adherence after acute myocardial infarction. *JAMA Cardiology.* (2016) 1:147–55. doi: 10.1001/jamacardio.2016.0001
27. Tung YC, Chang GM, Chang HY, Yu TH. Relationship between early physician follow-up and 30-day readmission after acute myocardial infarction and heart failure. *PLoS ONE.* (2017) 12:e0170061. doi: 10.1371/journal.pone.0170061
28. Fang R, Li X. Electronic messaging support service programs improve adherence to lipid-lowering therapy among outpatients with coronary artery disease: an exploratory randomised control study. *J Clin Nurs.* (2016) 25:664–71. doi: 10.1111/jocn.12988
29. Khonsari S, Subramanian P, Chinna K, Latif LA, Ling LW, Gholami O. Effect of a reminder system using an automated short message service on medication adherence following acute coronary syndrome. *Eur J Cardiovasc Nurs.* (2015) 14:170–9. doi: 10.1177/1474515114521910
30. Park LG, Howie-Esquivel J, Whooley MA, Dracup K. Psychosocial factors and medication adherence among patients with coronary heart disease: A text messaging intervention. *Eur J Cardiovasc Nurs.* (2015) 14:264–73. doi: 10.1177/1474515114537024
31. Quilici J, Fugon L, Beguin S, Morange PE, Bonnet JL, Alessi MC, et al. Effect of motivational mobile phone short message service on aspirin adherence after coronary stenting for acute coronary syndrome. *Int J Cardiol.* (2013) 168:568–9. doi: 10.1016/j.ijcard.2013.01.252

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METHODS
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Process Evaluation of an Implementation Trial: Design, Rationale, and Early Lessons Learnt From an International Cluster Clinical Trial in Intracerebral Hemorrhage

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Background: The third INTEnsive care bundle with blood pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT3) is an ongoing, international, multicenter, stepped-wedge cluster, prospective, randomized, open, blinded endpoint assessed trial evaluating the effectiveness of a quality improvement "care bundle" for the management of patients with acute spontaneous intracerebral hemorrhage (ICH) in low- and middle-income countries (LMICs). An embedded process evaluation aims to explore the uptake and implementation of the intervention, and understand the context and stakeholder perspectives, for interpreting the trial outcomes.

Methodology: The design was informed by Normalization Process Theory and the UK Medical Research Council process evaluation guidance. Mixed methods are used to evaluate the implementation outcomes of fidelity, reach, dose, acceptability, appropriateness, adoption, sustainability, and relevant contextual factors and mechanisms affecting delivery of the care bundle. Semi-structured interviews and non-participant observations are conducted with the primary implementers (physicians and nurses) and patients/carers to explore how the care bundle was integrated into routine care. Focus group discussions are conducted with investigators and project operational staff to understand challenges and possible solutions in the organization of the trial. Data from observational records, surveys, routine monitoring data, field notes and case report forms, inform contextual factors, and adoption of the intervention. Purposive sampling of sites according to pre-specified criteria is used to achieve sample representativeness.

Discussion: Implementation outcomes, and relevant barriers and facilitators to integrating the care bundle into routine practice, will be reported after completion of the process evaluation. The embedded process evaluation will aid understanding of the

causal mechanisms between care bundle elements and clinical outcomes within complex health systems across diverse LMIC settings.

Trial Registration: The INTERACT3 study is registered at ClinicalTrials.gov (NCT03209258).

Keywords: process evaluation, stroke, intracerebral hemorrhage, clinical trial, implementation science

INTRODUCTION

Intracerebral hemorrhage (ICH) is the most severe and least treatable type of stroke, contributing to the significant global burden of disease (1) particularly in low- and middle-income countries (LMICs) (2, 3). Protocols to systematically monitor and control key physiological parameters such as blood pressure (BP) and blood glucose level, may improve the outcome in patients with acute ICH (4). The third INTEnsive care bundle with blood pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT3) is an international, multicenter, stepped-wedge cluster, prospective, randomized, open, and blinded endpoint assessed trial which aims to determine the effectiveness of a quality improvement "care bundle" in patients with acute ICH in LMICs. This care bundle comprises early intensive BP lowering (achieving systolic BP $<$ 140 mmHg), glycemic control (achieving 6.1–7.8 mmol/L and 7.8–10.0 mmol/L without and with diabetes mellitus), treatment of pyrexia (achieving temperature level $<$ 37.5°C), and reversal of anticoagulation [achieving international normalized ratio (INR) $<$ 1.5], within 1 h of initiation of treatment and maintained for 7 days. The stepped-wedge study design requires a smaller sample size compared to a parallel-arm design but creates potential problems for retention due to time lags between recruitment and when the intervention starts, as well as potential confounding caused by variation in time. Therefore, it is important to ensure that the delivery of the care bundle is consistent across sites as planned (5). As a complex intervention with multiple components and involving organizational change, there is a need to provide details of how the care bundle is delivered and what local contextual factors impact outcomes (6, 7). Insufficient details of how the complex intervention, such as the care bundle in INTERACT3, and its components were implemented may limit the transferability of the evidence to other contexts, which is a recognized barrier to providing optimal care and treatment (8, 9). Moreover, consideration of how implementation can address knowledge gaps in real world settings can better inform potential sustainability and scale-up (10). The process evaluation of the INTERACT3 trial allows an examination of the complexities of implementation strategies, provides explanations for discrepancies between expected and observed outcomes, offers insights into how context influences outcomes, and aids in considering the potential for wider implementation (11–13).

A process evaluation (PE) was embedded into INTERACT3 with three principle aims: (i) determine implementation outcomes of the care bundle through fidelity (whether the care bundle was delivered as intended), dose (what quantity and quality was delivered), reach (whether all eligible ICH patients received all components), acceptability (whether the care bundle was agreeable and acceptable to participants), appropriateness (participant views on the perceived fit or relevance of the care bundle in their practice settings), and adoption and sustainability (whether the care bundle was integrated and incorporated within routine practice and local policies); (ii) provide information to explain the trial results regarding possible barriers and facilitators related to the implementation on each component of the care bundle, their integration into routine practice, and possible context factors; and (iii) determine transferability and sustainability of the care bundle in LMICs through provision of participant perspectives on how and why the care bundle can (or cannot) be implemented at a national level.

METHODS

Study Design

INTERACT3 is a cluster stepped-wedge design that aims to evaluate the effectiveness of a care bundle in 8,360 patients at 110 hospitals in 10 LMICs [Brazil, Chile (identified as a high-income country in 2021), China, India, Mexico, Nigeria, Pakistan, Peru, Sri Lanka, and Vietnam] from December 2017 to October 2022. The unit of randomization is the hospital sites, randomly assigned by a blinded statistician into three groups which undergo four phases (**Figure 1**). All sites start in a control "usual care" phase before being randomly allocated to transfer to the intervention phase where the care bundle protocol is to be implemented as part of the routine standard of care. The procedures of the trial intervention implementation are described in greater detail in **Supplementary Appendix 1**. The stepped-wedge cluster design allows implementation of the care bundle through a one direction cluster switch (from control to treatment) at different time points, reduces contamination between control and intervention patients, and allows evaluation of implementing multi-faceted system-wide changes (14). Details of the study design are described elsewhere (15).

Theoretical Approach

The PE for INTERACT3 is informed by the UK Medical Research Council (MRC) (10) process evaluation guidance and Normalization Process Theory (NPT). The MRC guidance framework includes three main components of inquiry: implementation of the intervention, mechanisms of impact, and context to result in the trial outcomes. NPT is used to understand adoption and integration of the care bundle into routine medical care practice (16). It is an implementation science theory that provides a deeper understanding of embedding integration and sustainability of a new model of care or guidelines, and

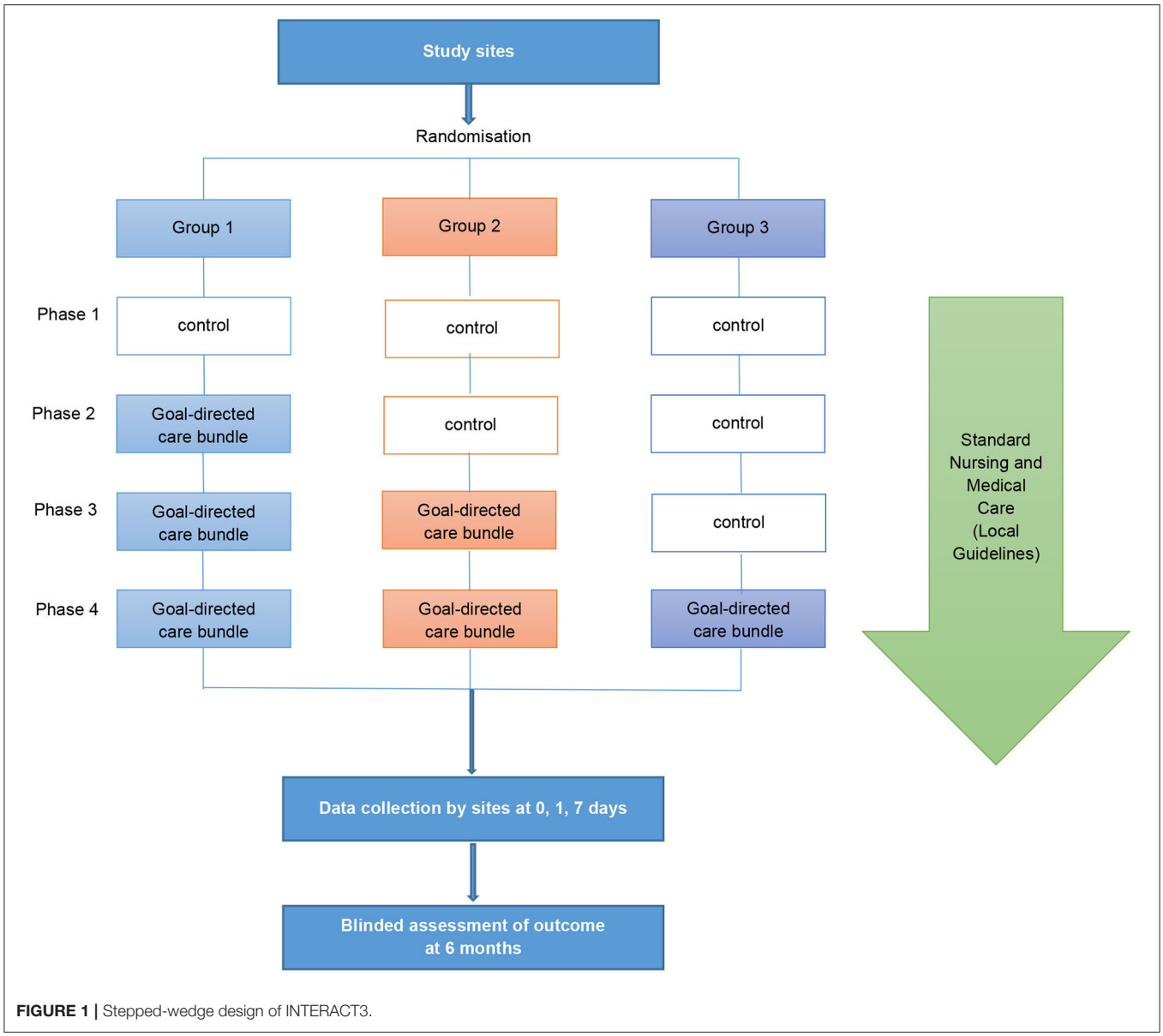

FIGURE 1 | Stepped-wedge design of INTERACT3.

to enhance understanding of the outcome data (17). The core components of NPT include coherence, cognitive participation, collective action, and reflexive monitoring (18). A logic model of contextual determinants and intervention components was developed to describe how the care bundle and research activities result in short- and long-term outcomes, and to inform data collection of relevant process indicators (**Figure 2**). Considering the different contexts of each country, a separate implementation research logic model for each country is being generated to guide the PE (19).

Setting

The study is being undertaken across different areas of hospitals, including emergency, acute stroke unit, intensive care unit, and neurology and neurosurgery areas/wards, where representative health professionals are being recruited through purposive sampling for a semi-structured interview, (20) stratified by country. With at least two sites being sampled for interviews in each participating country, it is estimated that 28–32 sites will be included covering geographical location (across regions), level of hospital (tertiary vs. secondary), department (neurosurgical vs. neurology or emergency), and performance (e.g., recruitment speed, and cooperation), although the final number will be determined by saturation of themes and available resources.

Participants

Participants for the PE include key stakeholders involved in implementing the INTERACT3 intervention, such as study investigators, ward clinicians and nurses, patients (or carers) who have received the care bundle, and clinical research

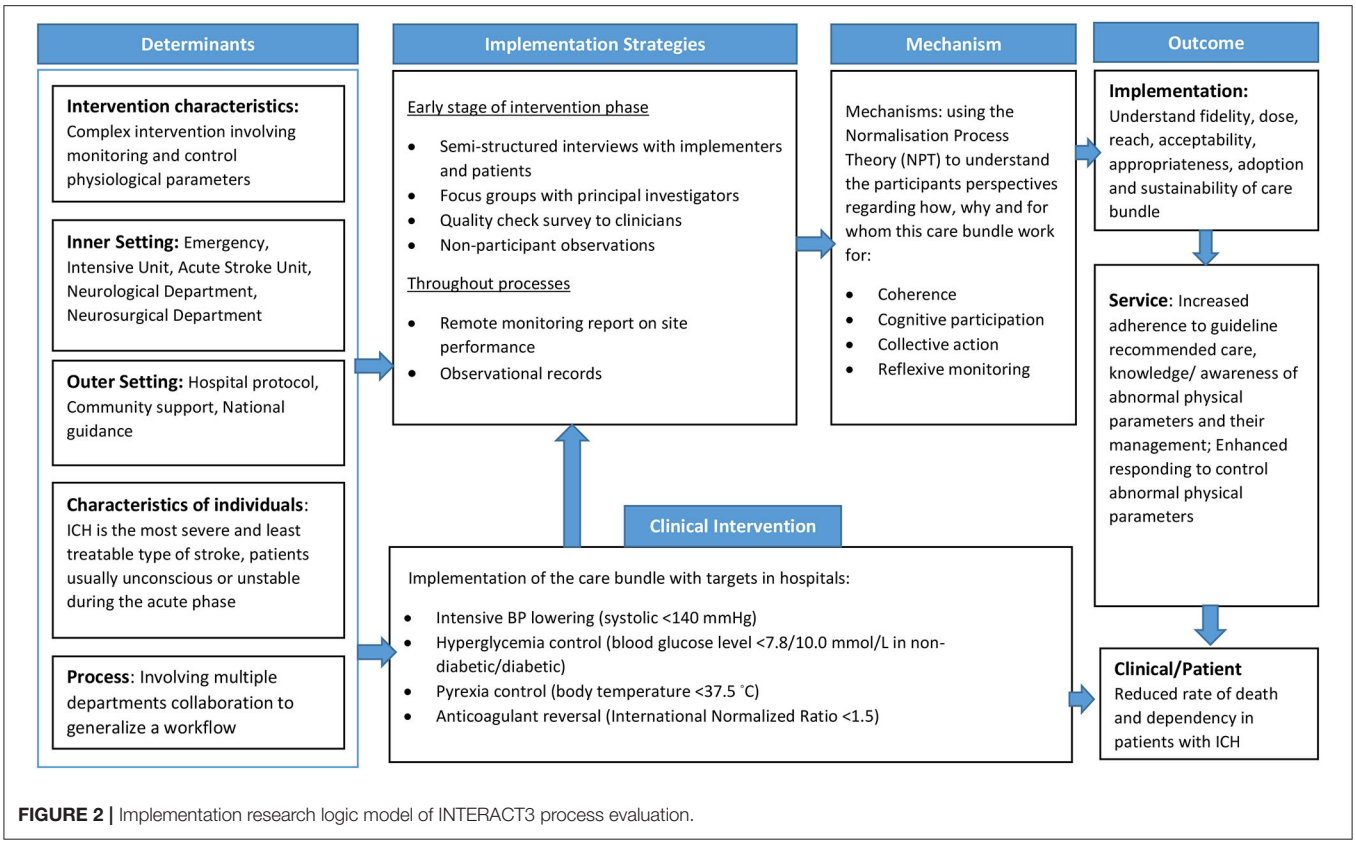

FIGURE 2 | Implementation research logic model of INTERACT3 process evaluation.

associates (CRAs) involved in training site staff in delivering the intervention. An information sheet and consent form will be sent to potential participants about the PE and inviting them to an interview and/or focus group discussion with a member of the PE team.

Data Collection

A parallel mixed-method approach is designed for data collection, (21) to provide different perspectives, validation, and triangulation from multiple sources (11). **Tables 1**, **2** outline the approach for both qualitative (semi-structured interviews, focused groups discussion, non-participant observation) and quantitative (surveys) methods to explore implementation outcomes. Other data sources include observational records and a hospital organization questionnaire to provide additional context for the participating sites and inform the sampling frame. The time point for data collection will be at an early phase of intervention, ideally after 2–5 patients have been enrolled, in order to obtain feedback from site staff about implementation challenges and allow the operations team to better support sites to optimize implementation of the care bundle.

Semi-structured Interviews

Semi-structured interviews will be conducted with implementers (physicians and nurses) and patients/carers from purposively sampled sites at an early phase of the intervention. At each sampled site, 3–4 implementers and 1–2 patients/carers are invited to interview. For the implementers, the evaluation will explore options on challenges to implement the intervention, facilitating factors, context, progress on implementation, and perspectives of the intervention. For patients/carers, the interview will focus on their perspectives of receiving the goal-directed care bundle, and their thoughts and concerns about participating in the study. Only patients who are medically stable will be invited to participate in an interview. The timing of the patient interview will be at hospital discharge (face to face) or during their follow up (*via* telephone) according to the patient's conditions and request. A semi-structured interview guide (see Appendix 2 in **Supplementary Material**) has been developed, based on the objectives of the PE and after pilot testing. Early findings from interviews are discussed with the project operation team to allow any modifications to procedures. Trained interviewers collect the qualitative data under the supervision of an experienced qualitative researcher by a face-to-face or teleconference interview.

Focus Group Discussion

Focus group discussions (see Appendix 3 in **Supplementary Material**) are conducted to explore contextual factors and implementation barriers of the care bundle as part of an international collaboration. Two sets of focus group discussions are conducted, involving the clinical trial coordinating team and principal investigators (PIs) or sub-principal investigators (Sub-Is) from selected sites. For the former, the group discussion will mainly involve CRAs to

TABLE 1 | Summary of data collection methods.

Item	Data collection method	Participants	Participant number	Time point of data collection
1	Semi-structured interviews	Clinicians and nurses from selected sites	3–4 sampled sites	At early stage of intervention phase (e.g., 5–10 enrolled intervention patients)
2	Semi-structured interviews	Patients/carers from selected sites	2–3 sampled sites	Patients with a stable condition (before discharge) in the intervention group
3	Non-participant observations	Selected sites	Purposive sampling sites (assume 16–20)	Onsite monitoring visit
4	Focus group discussions	PI invited	Purposive sampling sites (assume 16–20)	Investigator meetings and quality control meetings
5	Focus group discussions	All CRAs	Purposive sampling sites (assume 16–20)	At the early phase of the intervention phase
6	Questionnaires	Clinicians		
7	Survey	Clinicians and nurses	All sites	Quality control meetings and at the time of study close out
8	Monitoring records, including routine monitoring data, field notes, recruitment logs, and case report forms	N/A	All sites	Throughout the study

TABLE 2 | Implementation outcomes summary.

Implementation outcomes	Aims	Data sources
Fidelity	Whether the care bundle under investigation in INTERACT3 was delivered as intended	Semi-structured interviews Non-participant observations Surveys Routine monitoring data, field notes, and case report forms
Dose	What the quantity and quality of the care bundle and each component delivered were	Semi-structured interviews Surveys Routine monitoring data, field notes, and case report forms
Reach	Whether all eligible patients received all components of the care bundle	Semi-structured interviews Non-participant observations Recruitment logs
Acceptability	Whether the care bundle was agreeable and acceptable to participants	Semi-structured interviews Focus group discussions Survey
Appropriateness	Participant views on the perceived fit or relevance of the care bundle in their practice settings	Semi-structured interviews Focus group discussions
Adoption and sustainability	Whether the care bundle was integrated and incorporated into routine practice and local policies	Semi-structured interviews Non-participant observations Focus group discussions Routine monitoring data, field notes, and case report forms

evaluate how well the training sessions were delivered to site implementers and received and how well they find and assist in overcoming the barriers in covering presentations, on-site monitoring visits, and communications and interactions with implementers. The focus group discussions involving national PIs and Sub-Is from participating sites aim to identify barriers at coordinating the site, including roles and responsibilities, leadership, staff training, and in providing daily support. These discussions are facilitated by the PE team from the International Coordinating Center *via* teleconference.

Non-participant Observation

The non-participant observation (see Appendix 4 in **Supplementary Material**) aims to understand contextual factors, recruitment processes, and delivery of the care bundle. An observation template was adapted from a PE for another stroke trial (22) to allow collection of information on implementer behavior of operational staff alongside an on-site monitoring visit. Trained observers from the Regional Coordinating Center conduct the observation at the purposively sampled site.

Survey

A quality check survey informed by NPT is used to collect perceptions of the intervention and other relevant information from clinicians (see Appendix 4 in **Supplementary Material**) during the intervention phase. The quality check survey has been piloted at meetings with investigators from 20 sites who had

completed the initial vanguard phase in China. All sites outside of China are invited to complete the survey at an early phase of intervention as a part of the PE.

Contextual information of health services are collected through a Hospital Organization Questionnaire (HOQ) sent to all sites prior to patient recruitment (see Appendix 6 in **Supplementary Material**). Monitoring records, field notes, and case report forms are obtained to allow an evaluation of whether the intervention has been delivered as intended. These quantitative data are reviewed monthly as part of routine monitoring of patient recruitment, data quality, and adherence to the protocol. Monthly performance reports, highlighting recruitment targets and details of protocol adherence and intervention implementation, will also be retrieved to assist sampling of the participating sites.

Data Management

Data will be stored electronically in a secure password-protected system only accessible to specified members of the research team. Interview transcripts will be uploaded into the software program NVivo V.9 for data analysis.

Analysis and Report

Qualitative data from focus groups, semi-structure interviews, non-participant observations, and free text answers to sections of the survey will be thematically analyzed (23, 24). Inductive findings of the interviews involving the first three sites will be discussed by the PE team to explore emerging themes to guide subsequent interviews. Interim analysis will be performed after 5–10 interviews to further adapt the interview format and to generate themes for subsequent interviews. The data will be independently coded by two trained researchers using a coding framework developed through iterative input from investigators to reveal consistency in patterns of data. Descriptive statistics will be undertaken on the survey data, with frequencies and percentages used to summarize categorical variables, and for means or median reported for continuous variables. Analysis will be initially stratified by the country to understand local context, and to co-design implementation strategies for that context. The integration of quantitative and qualitative data will be done through merging and comparison across the numerical and textual data, addressing similar research questions (25). Reporting of the integrated data will be done through a mixed methods joint display (26) that synthesizes data with a visual display and summarizes the meta-inference of the findings.

The qualitative findings will be reported in accordance with the consolidated criteria for reporting qualitative research (COREQ), (27) with the implementation outcomes used to monitor and document fidelity to the project plan.

DISCUSSION

LMICs face different barriers in implementing interventions in comparison to high-income countries (HICs), such as limited human resources, limited access to health care, and limited skills of healthcare providers (28). The emerging issues of acute care for stroke in LMICs are often relate to the limited health systems. For example, compared to HICs, stroke care units are less common in LMICs and relevant acute care treatment such as intensive blood pressure reduction are seldom offered (29). In addition, in other LMIC settings, such as in Africa, stroke patients are cared for by non-specialized health providers without the support of a multidisciplinary team due to a lack of allied health professionals such as physiotherapists and speech therapists (30). PE is crucial to understanding contextual factors that may impact intervention implementation, especially as to whether the intervention can be adapted and implemented effectively across other contexts in LMICs (13). Contextual factors (COVID-19 impact, current policies, and settings resources, etc.) that could influence delivery of the intervention can be identified through interviews, focus group discussions, observations, and survey to enable a better understanding of the results, and the opportunity for future scale-up of the intervention to other LMICs. The INTERACT3 PE aims to inform a broader implementation plan that can be tailored to local contextual factors to improve the quality of care for patients with ICH, the most severe type of stroke. Relevant data pertaining to local stroke protocols and care pathways will provide a useful assessment of health systems for planning further studies that incorporate PE to strengthen the implementation and assessment of complex health service interventions in multicenter clinical trials that include participation from LMICs.

A systematic review of the use of PE in translational research indicates that most evaluations involve data collection at the post-intervention phase, but which has limited value in optimizing implementation of the trial in complex health systems (31). In INTERACT3, we have taken the opportunity to conduct a PE at the early phase of the intervention to assist in the timely identification of barriers and facilitators, to allow the coordinating team to address any issues that arise, and to foster clinician confidence through support and training (17). For example, in some earlier interviews, we found a shortage of suitable antihypertensives, which then had to be budgeted for and advocated for by the project operation team. Moreover, implementation outcomes will also be useful in explaining what was actually done in real world settings and allow a better unpacking of any potential variation in the proposed treatment effect under investigation in the trial. The causal relationship between the intervention and trial outcome in real-life implementation might be affected by adaptability/unpredictable actors and by a wide range of influencing elements at geographical and organizational levels (e.g., the impact of the COVID-19 pandemic on workforce capacity, and patient engagement with health services).

Strength and Weakness of Our Process Evaluation Design

Key strengths of this study include the use of multiple methods and diverse sources of data to obtain a comprehensive picture of the implementation of a goal-directed care bundle. Mixed methods evaluations draw upon strengths of both qualitative and quantitative approaches to provide a more holistic understanding of multi-level processes and the nature of an individual's experience (25). The PE has been conducted across different

health care systems in multiple countries to document variable care pathways and health system factors (e.g., workforce, medication availability), and to assist in understanding the value of implementation research and its generalizability. However, there are limitations such as selection and information bias due to voluntary participation in interviews, which is further influenced by the COVID-19 pandemic in restricting on-site visits for patient interviews and observations, and the need to conduct many interviews by teleconference/video conference. Data provided through remote monitoring and regional coordinating data can go some way in mitigating these issues. In addition, the survey focuses on barriers in embedding the care bundle into routine care that can result in biased answers, without the opportunity for positive feedback, which we aim to amend in future trials. Even flexible time points were offered for patient interviews, this may have introduced recall bias in relation to patient-reported experiences of the care bundle.

Timeline of the PE

The PE is being undertaken in stages and will be completed within 6 months of sites being activated in participating countries. However, due to the emergence of the COVID-19 pandemic in early 2020, timelines were extended in China since patient recruitment, transfer to intervention phase, and project staffing resources were all affected. The PE in other countries commenced in 2021, but again progress depends on the degree of the ongoing COVID-19 impact in each country.

Trial and PE Status

In October 2021, there were 5,986 patients recruited into INTERACT3, including 261 enrolled outside of China. In China, focus group discussions involved 14 investigators from 9 sites, and 24 interviews with doctors/nurses at 9 sites, during January to December 2020. Preliminary findings of the PE in China have been reported to the project team to enhance daily operation and monitoring. In other participating countries, semi-structured interviews and focus group discussions have been completed in Chile and Peru. Due to the ongoing nationwide strike of health workers in Nigeria from August 2021, recruitment and PE have paused until the situation changes.

Reflections

The PE in our large multicenter international clinical stroke trial has improved capacity building at regional coordinating centers in their qualitative research skills for conducting interviews and observations. However, the involvement of multiple countries requires significant ongoing efforts to address local language and cultural barriers. Although this has been time and resource intensive as a crucial component of the PE, it has strengthened international collaborations through sharing experiences. For example, contextual determinants such as medication supply shortage in rural centers in China and the delay in the ED to obtain a timely scan in Nigeria were discussed with the project operation teams in order to improve the implementation. However, in hindsight, some of these barriers could have been identified previously. Therefore, we recommend the collection of preliminary data prior to intervention delivery across countries to better understand local health systems and inform focus group discussions. This could be facilitated by co-developing an implementation logic model and implementation strategies to overcome anticipated local barriers with the local PIs and the trial coordinating team.

ETHICS AND DISSEMINATION

Ethical approval for this study has been obtained from central and site-specific ethic committees in each country. The information sheet will be provided to the participants prior to individual interviews and focus group discussions. Written consent will be obtained prior to interviews and verbal consent will also be taken prior to any participation in a focus group discussion.

CONCLUSIONS

The PE of the INTERACT3 study will not only provide insights necessary to optimize implementation of the care bundle intervention across diverse settings in LMICs, but it will also lead to better understanding of the relationship between elements of the care bundle and outcomes. Our embedded PE will advance the future conduct of international pragmatic stroke clinical trials to optimize intervention implementation within complex health system contexts.

DATA AVAILABILITY STATEMENT

Datasets generated and/or analyzed for INTERACT3 will be available to all study investigators, and investigators from other institutions around the world, according to a strict data sharing agreement. Data sharing will be available from 12 months after publication of the main results. Investigators are to make a formal request for data sharing through the Research Office of The George Institute. Access will be controlled by the Principal Investigators, with the approval of the Trial Steering Committee.

ETHICS STATEMENT

All written informed consent to participate in the study were obtained. The Biomedical Ethics Committee of West China Hospital approved the INTERACT3 study before the commencement of any patient recruitment (Ethics Reference No. 22017 Review [217]). According to funding request from Medical Research Council, additional approval (Ethic Reference: 26596-tgr2r-ls: cardiovascular sciences, deptof) had been obtained from Research Ethics Committee of the University of Leicester, United Kingdom. Ethics approval was obtained in each site before site activation. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HL, SJ, LS, and MO contributed to the concept and rationale for the study. MO wrote the first draft of manuscript with input from HL and CA. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.813749/full#supplementary-material

REFERENCES

1. van Asch C, Luitse M, Rinkel G, van Der Tweel I, Algra A, Klijn C. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol*. (2010) 9:167–76. doi: 10.1016/S1474-4422(09)70340-0
2. Feigin V, Lawes C, Bennett D, Barker-Collo S, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol*. (2009) 8:355–69. doi: 10.1016/S1474-4422(09)70025-0
3. Krishnamurthi RV, Ikeda T, Feigin VL. Global, regional and country-specific burden of ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage: a systematic analysis of the global burden of disease study 2017. *Neuroepidemiology*. (2020) 54:171–9. doi: 10.1159/000506396
4. Parry-Jones AR, Sammut-Powell C, Paroutoglou K, Birleson E, Rowland J, Lee S, et al. An intracerebral hemorrhage care bundle is associated with lower case fatality. *Ann Neurol*. (2019) 86:495–503. doi: 10.1002/ana.25546
5. Dreischulte T, Grant A, Donnan P, Guthrie B. Pro's and con's of the stepped wedge design in cluster randomised trials of quality improvement interventions: two current examples. *Trials*. (2013) 14: O87. doi: 10.1186/1745-6215-14-S1-O87
6. Campbell M, Katikireddi SV, Hoffmann T, Armstrong R, Waters E, Craig P. Tidier-php: a reporting guideline for population health and policy interventions. *BMJ*. (2018) 361:k1079. doi: 10.1136/bmj.k1079
7. Hoffmann TC, Walker MF. 'Tidier-ing up' the reporting of interventions in stroke research: the importance of knowing what is in the 'black box'. *Int J Stroke*. (2015) 10:657–8. doi: 10.1111/ijs.12524
8. Scott SD, Rotter T, Hartling L, Chambers T, Bannar-Martin KH. A protocol for a systematic review of the use of process evaluations in knowledge translation research. *Syst Rev*. (2014) 3:149. doi: 10.1186/2046-4053-3-149
9. Wallin L. Knowledge translation and implementation research in nursing. *Int J Nurs Stud*. (2009) 46:576–87. doi: 10.1016/j.ijnurstu.2008.05.006
10. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: what it is and how to do it. *BMJ*. (2013) 347:f6753. doi: 10.1136/bmj.f6753
11. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: medical research council guidance. *BMJ*. (2015) 350:h1258. doi: 10.1136/bmj.h1258
12. Grant A, Treweek S, Dreischulte T, Foy R, Guthrie B. Process evaluations for cluster-randomised trials of complex interventions: a proposed framework for design and reporting. *Trials*. (2013) 14:15. doi: 10.1186/1745-6215-14-15
13. Limbani F, Goudge J, Joshi R, Maar MA, Miranda JJ, Oldenburg B, et al. Process evaluation in the field: global learnings from seven implementation research hypertension projects in low-and middle-income countries. *BMC Public Health*. (2019) 19:953. doi: 10.1186/s12889-019-7261-8
14. Fayers PM, Jordhoy MS, Kaasa S. Cluster-randomized trials. *Palliat Med*. (2002) 16:69–70. doi: 10.1191/0269216302pm503xx
15. Song L, Hu X, Ma L, Chen X, Ouyang M, Billot L, et al. Intensive care bundle with blood pressure reduction in acute cerebral hemorrhage trial (interact3): study protocol for a pragmatic stepped-wedge cluster-randomized controlled trial. *Trials*. (2021) 22:943. doi: 10.1186/s13063-021-05881-7
16. May C, Finch T. Implementing, embedding, and integrating practices: an outline of normalization process theory. *Sociology*. (2009) 43:535–54. doi: 10.1177/0038038509103208
17. May C, Cummings A, Girling M, Bracher M, Mair F, May C, et al. Using normalization process theory in feasibility studies and process evaluations of complex healthcare interventions: a systematic review. *Implement Sci*. (2018) 13:80. doi: 10.1186/s13012-018-0758-1
18. Murray E, Treweek S, Pope C, Macfarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. *BMC Med*. (2010) 8:63. doi: 10.1186/1741-7015-8-63
19. Smith JD, Li DH, Rafferty MR. The implementation research logic model: a method for planning, executing, reporting, and synthesizing implementation projects. *Implement Sci*. (2020) 15:84. doi: 10.1186/s13012-020-1041-8
20. Suri H. Purposeful sampling in qualitative research synthesis. *Qual Res J*. (2011) 11:63–75. doi: 10.3316/QRJ1102063
21. Shorten A, Smith J. Mixed methods research: expanding the evidence base. *Evid Based Nurs*. (2017) 20:74–5. doi: 10.1136/eb-2017-102699
22. Liu H, Lindley R, Alim M, Felix C, Gandhi DBC, Verma SJ, et al. Protocol for process evaluation of a randomised controlled trial of family-led rehabilitation post stroke (ATTEND) in india. *BMJ Open*. (2016) 6:e012027. doi: 10.1136/bmjopen-20166-012027
23. Nowell LS, Norris JM, White DE, Moules NJ. Thematic analysis: striving to meet the trustworthiness criteria. *Int J Qual Methods*. (2017) 16:1–13. doi: 10.1177/1609406917733847
24. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol*. (2006) 3:77–101. doi: 10.1191/1478088706q66qp0p63o33oa
25. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs-principles and practices. *Health Serv Res*. (2013) 48:2134–56. doi: 10.1111/1475-6773.12117
26. Johnson RE, Grove AL, Clarke A. Pillar integration process: a joint display technique to integrate data in mixed methods research. *J Mix Methods Res*. (2019) 13:301–20. doi: 10.1177/1558689817743108
27. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (coreq): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. (2007) 19:349–57. doi: 10.1093/intqhc/mzm042
28. Lazo-Porras M, Liu H, Miranda JJ, Moore G, Burri M, Chappuis F, et al. Process evaluation of complex interventions in chronic and neglected tropical diseases in low- and middle-income countries—a scoping review protocol. *Syst Rev*. (2021) 10:244. doi: 10.1186/s13643-021-01801-7
29. Thrift AG, Pandian J, Abd-Allah F, Yaria J, Phan HT, Roth G, et al. The state of stroke services across the globe: report of world stroke organization–world health organization surveys. *Int J Stroke*. (2021) 16:889–901. doi: 10.1177/17474930211019568
30. Baatiema L, Aikins A, Sav A, Mnatzaganian G, Chan CK, Somerset S. Barriers to evidence-based acute stroke care in

Ghana: a qualitative study on the perspectives of stroke care professionals. *BMJ Open*. (2017) 7:e015385. doi: 10.1136/bmjopen-2016-015385

31. Scott SD, Rotter T, Flynn R, Brooks HM, Plesuk T, Bannar-Martin KH, et al. Systematic review of the use of process evaluations in knowledge translation research. *Syst Rev*. (2019) 8:266. doi: 10.1186/s13643-019-1161-y

Conflict of Interest: CA and LS declare that they received speaker fees and travel reimbursement from Takeda.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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