Research and Scholarly Methods: Pragmatic Clinical Trials

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Pragmatic clinical trials (PCTs) have received increased attention within health services and pharmacy practice research due to their ability to test interventions in the real world, with emphasis on implementation and scalability in diverse practice environments. The purpose of this article is to introduce the PCT research design to health service and pharmacy practice researchers, followed by considerations and recommendations for conducting successful PCT research. It is organized into three parts, including a definition of PCTs, the process of selecting a PCT design, and general considerations and recommendations of PCTs. We conclude with the applications and trends in the use of PCTs in pharmacy research.

Part 1. Defining Pragmatic Trials

PCTs are conducted to answer the important question of how a treatment or intervention works in a normal, "real-world scenario" using a heterogeneous "real-world population" to test the effects (Gamerman et al. 2019). While no consistent definition exists in the literature, there are a number of study elements that are often used to define PCTs. First, study participant eligibility requires little selection outside the clinical indication of interest. PCTs have minimal subject inclusion and exclusion criteria since the design is meant to reflect the population for which the intervention or treatment is intended. Second, it is important that the study setting, including clinicians, clinical staff, patients, and other stakeholders involved in the intervention or treatment, are reflective of the naturally occurring environment and organizational structure. Finally, PCTs can be identified by the types of outcomes and endpoints of interest, focusing on the data that is readily available and collected within the context of routine care.

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Differences between Pragmatic and Explanatory Trials

Two statisticians, Daniel Schwartz and Joseph Lellouch, designated the two types of randomized clinical trials (RCTs) as 'explanatory' and 'pragmatic' (Schwartz & Lellouch 1967). In their 1967 paper, they described the explanatory approach to clinical trials as one which focuses on determining if a difference exists between two treatments, and the pragmatic approach as one focused on providing results that are more applicable to clinical practice and decision making (Schwartz & Lellouch 1967).

While an explanatory study is highly controlled in terms of the research environment as well as what groups of individuals are exposed to the treatment or intervention, a pragmatic trial depicts more normal or 'real life' conditions (McMahon 2002). General differences between traditional, explanatory RCTs and PCTs are presented in Table 1 (Weinfurt 2021). Explanatory studies focus results on outcomes or endpoints that are relatively unaffected by the context and health systems that patients may be exposed to. As a result, explanatory trials often lack generalizability to routine clinical practice (Sedgwick 2014), whereas pragmatic trials, which are undertaken in the typical conditions of the healthcare system in which stakeholders work (Zwarenstein 2017), are generalizable to clinical practice.

Contextualizing pragmatic trials within a broader spectrum of possible research designs

Research designs often used in pharmacy practice research include, but are not limited to, experimental, quasi-experimental, observational, qualitative, and mixed method designs (Awaisu et al. 2019). Experimental research designs are used to evaluate cause and effect relationships between a set of independent and dependent variables as shown in Figure 1 below (Portney 2020). PCTs largely fall within the category of experimental research designs, characterized by the random assignment of participants to at least two comparison groups (Portney 2020). Some may also fall within the category of exploratory trials, which are observational and seek to find relationships between variables (Portney 2020).

Differentiating Experimental Research Designs (Pragmatic Clinical Trials) from other Research Designs Used in Pharmacy Practice Research

Experimental research designs, including PCTs, differ from other research designs used in pharmacy practice. Quasi-experimental designs, for instance, are similar to experimental designs in structure, but do not involve randomization, making them useful when randomization is either impossible or unethical (Portney 2020). Observational designs, unlike experimental and quasi-experimental designs, do not involve any experimentation but may be used to find relationships among variables and develop hypotheses which can be tested using PCTs (National Institutes of Health 2016). Mixed method designs integrate both qualitative (descriptive) and quantitative elements, making them a good study design for conducting experiments quantitatively and describing populations qualitatively.

In pharmacy practice research, commonly used mixed method designs include the concurrent or convergent parallel design, exploratory sequential design, explanatory

sequential design, and the embedded design (Hadi et al. 2013, Pluye & Hong 2014). The choice of one type of mixed methods design over another depends on the research question being answered or the outcome that is desired. For instance, where a research question requires first collecting data using a quantitative method, followed by an explanation of that data using a qualitative method, an explanatory sequential design will be the design of choice (Creswell 2014).

Important standards to know when conducting pragmatic trials

The Pragmatic–Explanatory Continuum Indicator Summary tool (PRECIS-2)

Although clinical trials can be pragmatic or explanatory, most are a continuum and tend to have components of both elements in varying degrees (Williams et al. 2015). The nine-domain PRECIS tool (PRECIS-2 wheel) was developed to guide researchers into prospectively determining the extent to which their trials are pragmatic or explanatory in nature (Loudon et al. 2015).

According to the article by Loudon and others (Loudon et al. 2015), these domains include eligibility (the basis for trial participant selection), recruitment (manner of recruiting participants), setting (trial location), organization (expertise and resources required for intervention delivery), flexibility-delivery (manner of intervention delivery), flexibility-adherence (ways to ensure adherence to the intervention), follow-up (close monitoring), primary outcome (the extent of relevance), and primary analysis (the extent of data inclusion). In the PRECIS-2 wheel, each domain is scored on an explanatory-pragmatic scale from 1 (very explanatory) to 5 (very pragmatic).

The Consolidated Standards of Reporting Trials (CONSORT)

The CONSORT Group developed the CONSORT Statement to address challenges associated with the inadequate reporting of randomized controlled trials (RCTs). The focus of the statement is on reducing bias (internal validity), while improving a trial result's applicability, that is, generalizability or external validity (Zwarenstein et al. 2008).

According to the article by Schulz and others (Schulz et al. 2010), the statement consists of minimum recommendations for trial reporting in a complete and clear manner, facilitating thorough analysis and subsequent interpretation. The evidence-based CONSORT statement consists of a 25-item checklist and a flow diagram with information on the design, analysis, and interpretation of a trial (found in the checklist), as well as the progress of all participants through the trial (found in the flow diagram). Often, journals require authors to include the CONSORT diagram and checklist when submitting a manuscript for RCTs.

Part 2. Selecting A PCT Design

Clinical trial study designs include parallel group, cross-over, factorial, cluster randomized trial, equivalence trial, and adaptive trial designs (Greenberg 2015). In addition, the stepped wedge design has become increasingly used in pharmacy practice research. A brief but concise description of these designs, including their use, advantages, and disadvantages is illustrated in Table 2.

Important factors that guide the choice of a study design include the type of research question or research hypothesis, expertise of the investigator, availability of data, and funding opportunities (Awaisu et al. 2019). In pharmacy practice research clinical trials, factors to consider when selecting a study design include the number and characteristics of treatments to be compared, characteristics of the disease under study, study objectives, timeframe, treatment course and duration, carry over effects, duration of the study, cost and logistics, patient convenience, ethical considerations, statistical considerations, study subject availability, and inter and intra subject variability (Nair 2019).

Although many different study designs can be used to conduct PCTs as shown in Table 2, it is important that their characteristics help to answer the research question in the mind of a researcher determining which one to use. For instance, where two or more interventions can be given concurrently, the factorial or parallel arm design would be deemed appropriate (Nair 2019). On the other hand, when the time between inclusion of subjects into a study and assessment of the results is short compared with the time taken to recruit study subjects, the adaptive design would be considered suitable (Nair 2019).

Part 3: General Considerations and Recommendations of PCTs

When conducting PCTs in pharmacy practice research, recognizing certain considerations and recommendations from successful PCT researchers or studies can be invaluable. Gamerman and others (Gamerman et al. 2019), describe the 4 key design elements that should be considered minimum requirements of a PCT, including: 1) enrolling a real-world population; 2) conducting the trial in a real-world setting; 3) capturing relevant outcomes important to inform optimal healthcare treatment decisions; and 4) using an appropriate comparison arm (Gamerman et al. 2019).

1) Enrolling a real-world population

An ideal PCT is described as one which reflects the population for which the treatment is intended, is conducted at a high standard of quality, has a control group which receives an acceptable standard of care, and produces outcomes that are meaningful (Ford & Norrie 2016; Godwin et al. 2003).

2) Conducting the trial in a real-world setting

According to Margolis and others (Margolis et al. 2020), important design elements of a PCT include broad eligibility with few exclusions, an intention-to-treat analysis (which means that all participants are analyzed on the basis of the group to which they were randomized and not on the basis of their treatment adherence), and recruitment through usual clinic appointments.

Also, in their 2016 article (Ford and Norrie 2016), the authors draw attention to the challenges of enrolling trial participants, as many clinical trial subjects are comparatively healthier than the general population, making generalizing the results quite futile. To increase the number and representativeness of the sample, they suggest using financial incentives, minimizing inclusion and exclusion criteria, and reducing the number and complexity of study visits, procedures, and questionnaire burden.

3) Capturing relevant outcomes important to inform optimal healthcare treatment decisions

Outcomes of interest in clinical trials include morbidity, mortality, functional status, quality of life, and resource use and costs (Welsing et al. 2017). Consideration should be given to the appropriate selection of outcomes considered relevant for stakeholders (including administration, patients, and providers), and supportive of clinical decision-making.

4) Using an appropriate comparison arm

In PCTs, arms refer to groups of participants that either receive or do not receive an intervention. Experimental arms, which receive the intervention, are compared to control arms which might be active (receiving an active therapy) or placebo (receiving an inactive therapy). Selecting an appropriate comparison arm is important because it provides information that allows relevant treatment decisions to be made for patients seen subsequently (Gamerman et al. 2019). To ensure comparability in treatment arms, and maximize external validity (generalizability), while not compromising internal validity, randomization is often used (Godwin et al. 2003).

Statistical Considerations—In addition to the general considerations discussed above, there are also statistical considerations that researchers in pharmacy practice research should recognize when conducting PCTs. These include the determination of an end point, the establishment of an effect size, and the determination of power, error rates, and sample size (Zabor et al. 2020). These are briefly discussed below.

End point: In selecting an end point, it is important to consider outcomes that can be measured objectively to enable comparison between control and experimental groups (Zabor et al. 2020). The end point can be routinely obtained from usual practice such as Electronic Health Records (Gamerman et al. 2019). Examples of end points include morbidity and survival.

Effect Size: Effect sizes represent the difference between the present result and the desired outcome. They can also be used to estimate the sample size and hypothesis required for the study. Although the hypothesis can either be one or two-sided, a two-sided hypothesis (which identifies the difference from a hypothesized value in either direction), gives a good measure of the effect of the intervention, but may require a larger sample size, unlike the one-sided hypothesis (which identifies the difference from a hypothesized value in one direction only) for which a smaller sample size may be sufficient (Zabor et al. 2020).

Power and Error rates: Statistical Power is defined as the probability of detecting a treatment effect or the ability of a study to detect a true difference between groups when the treatment really works (Waning & Montagne 2000). It is given by 1-Beta (β) where Beta is a type II error (when a study does not find a difference between treatment groups, although a difference actually exists).

Power calculation can be done prospectively or retrospectively, and is determined by certain factors, including the statistical test in use, the effect size, sample attributes, and the level of

power considered acceptable (Houser 2007). The conventional standard for power in clinical trials is 80 percent (0.8), with Beta at 20 percent (Prajapati et al. 2010).

Sample size: An adequate sample size is important in pragmatic trials for the results to be generalizable and for long-term follow-up to account for patients who drop out of the study (MacPherson 2004). According to Kirby and others (Kirby et al. 2002), the factors influencing sample size calculation in a clinical study include i) power (usually set at 80% but could be set at 90% for large trials), ii) significance level (the 1% or 5% chance of reporting a significant effect in error), iii) the rate of event occurrence in the population (this can be estimated from previous studies), and iv) the treatment effect size (the difference in the event rate with and without the intervention). The sample size increases at smaller significance levels and higher power, and is inversely proportional to the square of the intervention-induced difference (Kirby et al. 2002).

Applications and trends in the use of PCTs in Pharmacy

PCTs have been used in different types of pharmacy studies as shown in Table 3. One particular study design, the stepped-wedge cluster randomized trial, has been used in pharmacy practice research in areas such as medication safety and adherence, as well as in evaluation, comparative, and intervention studies (Hemming et al. 2015). Although still a relatively new design, it is becoming quite popular as it has several advantages over the parallel cluster randomized trial design, including its usefulness where there are political, ethical, and logistical concerns (Hemming et al. 2015).

The following examples (medication adherence, comparative, and intervention) show studies in pharmacy practice research that have utilized a pragmatic approach. In a medication adherence study by Gong and others (Gong et al. 2016), telephone-based enhanced pharmacy care was compared to usual care for smoking cessation. The study design involved randomizing qualified participants - patients recently prescribed smoking cessation medication) into two groups - enhanced pharmacy care (EPC) and usual care (UC) and utilizing pharmacists to provide telephone counseling sessions to only the EPC group. The study results indicated that a pharmacist-enhanced program may benefit smokers by increasing adherence to prescription medications for smoking cessation.

In a comparative PCT study by Radley and others, (Radley et al. 2020), the clinical effectiveness of a pharmacist-led antiviral treatment for hepatitis C virus was tested against conventionally delivered treatment in patients receiving opioid substitution therapy. This study used a cluster-randomized trial design in which pharmacies were randomized into the two groups (with patients receiving either a pharmacist-led intervention or conventionally delivered treatment). The study results found more accessible testing and high treatment success rates were obtained when pharmacists were used.

An intervention PCT study by Evans and others (Evans et al. 2010) evaluated the impact of a community pharmacy intervention on statin adherence, through the integration of a cluster randomization and an outcome evaluation design. The study combined the rigor of a randomized trial with the pragmatism of collecting results in community pharmacy settings,

a novel idea which could set a precedent for future research study designs in the area of medication adherence, and possibly other areas of pharmacy practice research.

Conclusion

PCTs are useful in health services and pharmacy practice research because of their real-world applicability. In our paper, we have presented an overview of the utility of PCTs in pharmacy practice research. Our recommendations and considerations for PCT designs are not exhaustive, however, and are meant to introduce these concepts to the health services and pharmacy practice research audience while providing additional resources to further guide PCT research.

Acknowledgements

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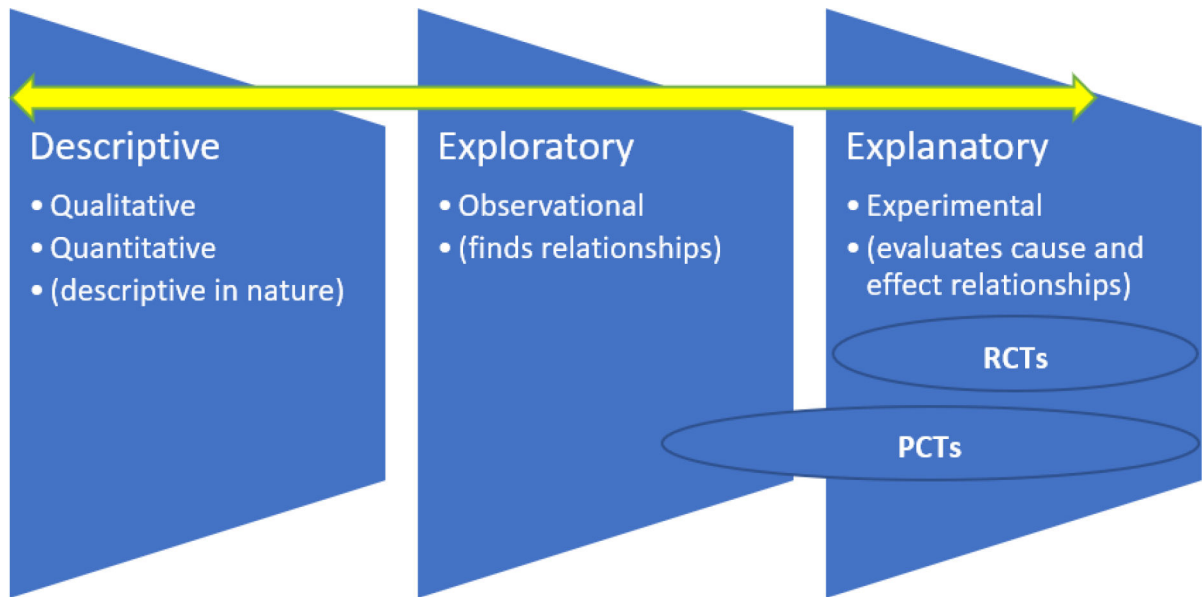
Figure 1:

Contextualizing PCTs and RCTs in the descriptive – explanatory continuum. Adapted from Portney 2020.

Table 1.

General Differences between Randomized Controlled Trials (RCT) and Pragmatic Clinical Trials (PCT)

Study Design Attribute	PCT	RCT
Who develops the study questions?	Collaborative process between researchers/clinicians	Researchers
What is the purpose?	To improve intervention processes and inform clinical and policy decisions	To determine treatment causes and effects
What question does it answer?	Does the intervention work under usual conditions?	Does the intervention work under ideal conditions?
Who is enrolled?	Heterogeneous groups to accommodate real-world populations	Groups that meet explicit inclusion and exclusion criteria
What is studied?	The effect of an intervention or treatment within and across a variety of institutional settings and heterogeneous populations	Effect of intervention or treatment on biological or biomarker outcomes in a more rigorously controlled environment
Adherence to Intervention	Flexible, reflective of real-world practice	Strictly enforced for continued study participation
Outcomes	Directly relevant to the patients, providers, and other stakeholders involved in the study, collected within routine care processes	May be surrogates or other outcomes deliberately collected for the purpose of the study

Table adapted from the Weinfurt article (Weinfurt 2021)

Table 2:

Description, use, advantages, and disadvantages of different types of study design used in PCTs

Design Type	Description	Use	Advantages	Disadvantages
Parallel group	Randomization of participants to one or more study arms, with each study arm allocated a different intervention (Nair 2019)	Situations where experiments can be run simultaneously in a number of groups (Nair 2019)	Can be used to study many diseases (Nair 2019)	Contamination may occur if unplanned co-interventions or cross-overs occur (Nair 2019)
Cross-over	Participants serve as their own control, but are randomized to sequences of treatments (Greenberg 2015)	Where performance of control and intervention activities is required.	Since each subject is its own control, a smaller sample size can be studied (Greenberg 2015)	Result validity may be affected if subjects drop-out before the second treatment period (Greenberg 2015)
Factorial (2 × 2)	Evaluation of two interventions compared with a control within a single trial (Greenberg 2015)	Appropriate for: Studying two or more interventions in various combinations in one study setting. Studying the interactive effects resulting from combination of interventions (Nair 2019)	Can answer many research questions with a single trial and delivers more value when sample size is small (Nair 2019)	Trial complexity, including statistical analytical complexities, inability to combine two incompatible interventions, and complex protocols (Nair 2019)
Cluster randomized	Randomization of groups of subjects into treatment and control groups, as opposed to individual subjects (Zabor et al 2020)	When practical issues make individual randomization difficult (Cook et al 2016)	Avoidance of contamination which occurs when aspects of an intervention are adopted by participants of the study who were randomized to *not* receive that intervention (Minneci & Deans 2020)	Contamination may occur (Cook et al 2016)
Equivalence (non-inferiority trials)	Assessment of the equivalence of a new intervention to one that is already established (Greenberg 2015)	Useful where there are ethical issues associated with assigning patients to a placebo (Hahn 2012)	Non-inferiority can be established with a much smaller sample than that required for superiority trials (Hahn 2012)	Not useful where the control or standard therapy lacks established efficacy (Greenberg 2015)
Adaptive	Predefined design adaptations are made to trial procedures of ongoing clinical trials (Greenberg 2015)	To adjust different adaptations during the course of the trial as evidence accumulates (Greenberg 2015)	Has the potential to accelerate therapeutic development (Greenberg 2015)	Can lead to unequal group sizes, which could affect statistical power negatively (Greenberg 2015)
Stepped wedge	Cross over (switching of treatments) of one or several clusters at different time points (called periods) and in a randomized manner, from the control treatment to the intervention treatment (Ford & Norrie 2016)	Where there are ethical concerns about withholding a treatment from some of the participants (Brown & Lilford 2006)	When the treatment cannot be started concurrently in all participants (Nair 2019)	Carry-over effects i.e., when the effects of the first treatment are not allowed to completely clear away before treatment is received for the next or second period (Copas et al 2015)

Table 3:

Studies showing the latest trends in the use of PCTs in Pharmacy

Studies	Where conducted	Purpose	Outcomes
Medication Adherence (Choudhry et al 2018)	Multispecialty group practice	To enhance medication adherence for patients suffering from chronic conditions	Increase in adherence Significant increase in patients achieving disease control Non-significantly improved disease control for all eligible conditions
Evaluation study (Carter et al 2018)	Private Family Medicine offices	To evaluate a centralized clinical pharmacy service	Statistically significant improvement in the intervention group from 63.3% at baseline to 67.8% at 12 months (p = 0.02) with an estimated benefit of the intervention of 5.0% ± 2.4% (95% CI = −0.5 to 10.4%, p=0.07)
Intervention study (Margolis et al 2013)	Primary Care clinics	a) To determine whether an intervention combining home blood pressure (BP) telemonitoring with pharmacist case management improves control compared with usual care b) To determine whether BP control is maintained after the intervention stops	After 6 months: BP was controlled in 71.8 % (95% CI, 65.6% – 77.3%) of Telemonitoring Intervention patients and 45.2% (95% CI, 39.2% – 51.3%) of Usual Care patients, P < 0.0001 At 12 months BP was controlled in 71.2% (95% CI, 62.0% – 78.9%) of Telemonitoring Intervention patients and 52.8% (95% CI, 45.4% – 60.2%) of Usual Care patients, P=0.005
Comparative study (Margolis et al 2020)	Primary care clinics	To inform health systems about the benefits, strengths, and limitations of implementing home BP telemonitoring with pharmacist management	Control of systolic BP to less than 140 mm Hg and diastolic BP to less than 90 mm Hg (<130/80 mm Hg in patients with diabetes or chronic kidney disease) at 6 and 12 months. Secondary outcomes were change in BP, patient satisfaction, and BP control at 18 months
Medication safety (Kane-Gill et al 2020)	Nursing homes (NHs)	a) To transform the medication regimen review process using telemedicine to prevent adverse drug events (ADEs) b) To assess the impact of pharmacist-led and patient-centered telemedicine services in high-risk medication management	The number of ADEs for NH 1 declined while that of NH 2 and NH 3 did not. In NH 1, the decline was attributed to an increase in the willingness by physicians to heed pharmacists' recommendations. Also, when compared to usual care, there was a lower incidence of ADEs in the intervention group.
Implementation (Kennelty et al 2021)	Primary care clinics	Examine implementation of sustainment of a remote, centralized cardiovascular risk service in organizational and culturally diverse medical centers	Barriers to intervention implementation Real-world effectiveness of blood pressure and diabetes control between patients in the usual care vs intervention group Sustainment and adaptation of the intervention in primary care clinics