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Cluster Randomized Stepped Wedge Blinded Controlled Trials (CRSWBCT) In Comparative Effectiveness Research (CER) – Part II: Implications for Temporomandibular Joint Disorders (TMD) Research

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Abstract

In the context of translational science and comparative effectiveness research (CER), we discuss here practical applications and implications of the Cluster Randomized Stepped Wedge Blinded Controlled Trials (CRSWBCT). CRSWBCT is a type of pragmatic trial that attempts to minimize inherent design flaws, including information bias, inferential bias, selection bias, and reporting quality of trials. Inherently and while complex in terms of analysis and power assessment, CRSWBCT can enhance statistical stringency by minimizing risk of bias, and preserve equipoise. In Part I, we outlined the design and inferential aspects of the CRSWBCT, and the need for a revision of the CONSORT10 checklist in pursuit of the best evidence base (BEB) accordingly. Here, we discuss practical aspects of the implications and applications of CRSWBCT specifically in the context of temporomandibular joint disorders (TMD) research.

Keywords: Comparative effectiveness research (CER); Best evidence base (BEB); Temporomandibular joint disorders (TMD); Consolidated Standards of Reporting Trials (CONSORT); Stepped wedge; Mindfulness meditation (MM); Dental anxiety (DA); Evidence-based decisions practice-based research network (EBD-PBRN); Cluster Randomized Stepped Wedge Blinded Controlled Trials (CRSWBCT)

Introduction

The Agency for Healthcare Quality and Research (AHRQ; ahrq.gov) houses the Effective Health Care Program, which is designed to improve healthcare decisions and choices. AHRQ defines comparative effectiveness research (CER) as the pursuit of the best evidence base (BEB) by the scientific process for the systematic pursuance of statistical and clinical consensus inference, directly pertinent to benefit/risk and cost effectiveness, from a cogently posed research hypothesis grounded on the PICOTS model (patient description, interventions under comparison, clinical outcome of interest, timeline, clinical setting). The primary evidence is generated from clinical research studies – primarily randomized blinded clinical trials, and secondarily from observational studies - that compare drugs, medical devices, tests, surgeries, or ways to deliver health care [1,2]. Research synthesis in CER consists of: (1) Identify new and emerging clinical situations that merit CER consideration, (2) Train, develop and standardize CER researchers, (3) Review and synthesize all available research (i.e., research synthesis on the bibliome), (4) Promote, generate, develop and validate (i.e., reliability, validity) new scientific evidence, and analytic tools for establishing the level and the quality of the evidence, (5) Extract data pertinent to the specific aim of the CER research synthesis, identify gaps in knowledge, particularly in terms of the needs of evidence-based clinical practice, and obtain the consensus of the best available evidence base, and (6) Translate and disseminate research findings to diverse stakeholders.

A novel type of pragmatic trial, that is a trial whose purpose is to inform decisions about practice, has been recently characterized, in which all the clusters begin the study in the placebo-control, and roll-out into the experimental treatment group in a systematic, sequential fashion that retains the stringency of random double-blind protocol. The Cluster Randomized Stepped Wedge Blinded Controlled Trial (CRSWBCT) minimizes biases inherent to pragmatic trials by means of a structure that incorporates a series of roll-outs/roll-ins from placebo to experimental arms, which removes the effects of placebo, and minimizes ethical issues of equipoise.

Methodological Rationale

As an example of the potential use of CRSWBCT in translational medicine and translational healthcare in general, let us take the hypothetical case of testing the effectiveness of mindful meditation in treating dental anxiety (DA) for patients with temporomandibular joint disorders (TMD).

TMD refers to several classes musculoskeletal, neuromuscular, or rheumatologic disorders of the temporomandibular joint. Clinically, TMD can be a functional pain syndrome, a psychogenic disorder, or a "central sensitivity syndrome". TMD might result from a centrally mediated sensitivity to pain, and can co-occur other pain syndromes (e.g., fibromyalgia, irritable bowel syndrome, interstitial cystitis, headache, chronic lower back pain and chronic neck pain). TMD is a cluster of related disorders that share common features, with trauma (posttraumatic TMD, pTMD), or idiopathic origins (iTMD). pTMD may lead to problems in the masticatory musculature (myogenous TMD), the jaw joint (arthogenous TMD), or both. Research Diagnostic Criteria consider TMD along 2 axes; Axis I - physical aspects, divided into 3 overlapping groups: Group I - muscle disorders, Group II - disc displacements, group III - joint disorders. Axis II - psychological status, divided into 2 groups: Group I mandibular function, Group II - TMD-related psychosocial disability. TMD can be distinguished for the length of duration of the symptoms: less than 3 months (acute), vs. protracted for more than 3 months (chronic). Certain factors predispose TMD (genetic, hormonal, anatomical), others precipitate TMD (trauma, occlusal changes), while still others prolong TMD (stress, anxiety) [3-

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10]. In part because of its complexity and varied manifestations, the prevalence of diagnostic failures of TMD is high. TMD-derived pain can be erroneously associated with third molar cracked tooth syndrome or pulpitis, retro-buccal ulcerations and abscesses, as well as issues of the masticatory or neck musculature, trigeminal neuralgia or fibromyalgia. Diagnostic failures and misuse of diagnostic testing carry a high-cost burden for health care organizations and patients alike, and therefore inform translational effectiveness in general and CER in particular [11].

Two principal views of TMD predominate, namely a psychosocial model and a theory of occlusal disharmony. Close to ten percent of the adult population suffers from dental phobia. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) describes dental phobia as a "*marked and persistent fear (of dental procedures and dentistry in general) that is excessive or unreasonable*". Dental phobia is more common in patients who suffer from other mental health problem (e.g., Generalized Anxiety Disorder, panic disorder/agoraphobia, depression, and about 20% of dental phobics have a concurrent mental health problem. Dental phobia is an extreme manifestation of dental fear, a lesser expression of which is DA. Exogenous DA (e.g., fear of painful dental procedures (75%), distrust of dental personnel; sights, sounds, and smells of a dental office (25%)) follows traumatic dental experiences. Endogenous DA emerges from other anxiety disorders. Women are twice as likely as men to report DA or dental phobia, although men are more likely either to avoid sharing their dental anxiety or to avoid a dental visit altogether. Oral health problems associated with anxiety disorders in general and DA in particular, include TMD [12]. The root causes of DA are complex.

In the proposed hypothetical study, placebo could involve controlled breathing/relaxation (i.e., controlled breathing: taking a big breath, holding it, and letting it out very slowly; combined with progressive muscle relaxation: tensing and relaxing different muscle groups in turn, such as jaw, neck, shoulders, and so on). This is a simple and effective means to control DA in most patients. It is beneficial psychologically because it empowers the patient with a perception of control over the breathing pattern and increases the patient's self-efficacy. Physiologically, this technique improves muscle oxygenation and overall metabolism, thus increasing a sense of well-being and peacefulness.

Mindfulness meditation (MM), the core of a new generation of psycho-biological intervention for stress and anxiety [13], could be the experimental arm. MM targets the patient's mental position on a given experience (e.g., breathing, heart rate) separate from the source of the anxiety in the moment-present. It elicits and facilitates a skillful – i.e., mindful – response to the situation, and often leads to a more effective and longer-lasting intervention than controlled breathing/relaxation. It can be taught and learned, trained and practiced, and most often becomes an effective long- term technique for preventing or controlling anxiety (e.g., effect size: 0.38, CI^{95} [0.12 - 0.64] 8 weeks, and effect size: 0.22 CI^{95} [0.02 - 0.43] 3-6 months) [14]. Typically, sessions are held weekly over the course of a 7-9 week period, with regular practice ensured by means of audio recordings and daily diary keeping. Outcomes are monitored weekly as improved scores on DA scales (e.g., Modified Dental Anxiety Scale, 6-item short Speilberger Trait Anxiety Inventory, Corah Dental Anxiety Scale).

Outcomes of anxiety in general and dental anxiety in particular can reflect significantly decreased neuro-psychological testing performance, with correlated significant alterations in the fMRI profile (Barkhordarian et al., in preparation). The Stroop test is not a tool to measure anxiety *per se*, but performance on the Stroop test, which quantifies the patients' difference in selective attention capacity and skills as well as their processing speed ability, is impacted by anxiety. Stroop measures can provide a useful neuro -psychological glimpse on the patients' psycho-cognitive executive processing function, which can aid in the diagnosis of certain neurological abnormalities [15].

Discussion

For testing the effectiveness of mindfulness meditation in patients with DA afflicted with TMD, a CRSWBCT could be designed that would involve sequential roll-out of the placebo controlled breathing/relaxation arm, and roll-in of the experimental MM intervention for randomized clusters on patients in a stepped wedge protocol over time. In the context of the EBD- PBRN to ensure both diversity of the subject population, and of the stakeholders [16] health care providers (i.e., dental, clinical psychology, counseling, medical ambulatory care) over time, the study will include several clusters of 3-4 dental practices (Figure 1), and up to 100 patients in each cluster, randomly selected among the population of high-medium vs. low baseline DA scores. At time zero, none of the clusters receives the experimental mindful meditation intervention. By the end of the study, all clusters have switched from placebo to the MM intevention arm. Since the order of roll-out/roll-in is random, the length of time of treatment with the experimental MM intervention will be random.

Complete data collection of DA (i.e., Modified Dental Anxiety Scale, 6- item short Speilberger Trait Anxiety Inventory, Corah Dental Anxiety Scale, Stroop), obtained at each roll-in time-point, will ensure repeated measure analysis (i.e., comparison of the data points in the placebo period vs. the intervention period for each patient within each practice of each cluster) to determine MM effectiveness.

Conclusion

In brief, CRSWBCT offers a number of opportunities for data analysis, particularly for modeling the effect of time on the effectiveness of the intervention, by incorporating data collection at each point where a new cluster rolls-out of placebo and rolls-in to receive the

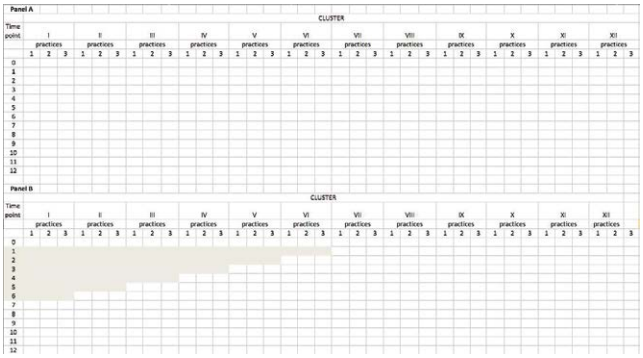

Figure 1: Figure 1 shows a typical CRSWBCT, such as could be the hypothetical design proposed here. It consists of 36 dental practices randomly obtained from a practice-based research network, such as could be the EBD-PBRN. Each dental practice is randomly assigned in one of twelve clusters (clusters I-XII). Panel A shows that at the onset of the study, time point 0, all the practices within all the clusters receive Placebo. At each monthly time point one cluster randomly rolls -out of placebo, and rolls-in the experimental intervention – in the hypothetical study proposed here, MM intervention for patients with DA). Panel B shows that at the mid-point of the study, on the sixth monthly time point, six clusters have rolled-out of Placebo into the intervention, and that of the six clusters in the intervention arm, the time in the intervention arm varies as per the roll-out/roll-in schedule, which is random, with a degree of freedom of n_c-1 (here n_c=12, df_c=11).

intervention. In the example proffered here, this design helps facilitate testing of overall efficacy and effectiveness of MM to favor the outcome of personalized dental care in TMD patients with DA.

This practical example also serves to demonstrates that, although CRSWBCT is a clinical trial with a complexity factor several orders of magnitude higher than the traditional parallel run- in or cross-sectional randomized blinded trials, it has enhanced statistical stringency because of the utilization of many patients in several practices within multiple clusters, randomization within clusters, and stepped wedge repeated measures, and permits individual patient data acquisition and analysis.

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