

A Template for Clinical Trials in Evidence Based Behavioral Research

Overview

The evolution of clinical trials dates back to the 18th Century, when Lind evaluated 6 treatments for scurvy in 12 patients aboard the HMS Salisbury. The principles of random assignment, blindedness, followed in the early to mid 20th Century. Over the past 30 years, clinical trials have emerged as the preferred method of evaluating medical interventions.

A clinical trial is defined as a “prospective study comparing the effect and value of interventions against a control (or Standard of Care) in human subjects.” A clinical trial is considered the most definitive method of determining whether an intervention has the postulated effect. However, clinical trials methodology has primarily been employed in the study of pharmacological or surgical interventions; behavioral and social scientists have not had extensive exposure to this powerful epidemiological tool in either their training or clinical/research practice.

Participants in this Clinical Trials Workshop will have the opportunity to establish a template for a Clinical Trial, learn the key elements of Clinical Trials in behavioral research. Issues addressed in this workshop will include 1) recruitment and retention of representative samples from the target population; 2) quality assurance/quality control of assessment, intervention and data management strategies; 3) ethical issues pertinent to Institutional Review Board (IRB) and Data Safety and Monitoring Board (DSMB) concerns; and 4) special considerations relevant to Clinical Trials (e.g., “intent to treat” principle, “run-ins”). Pertinent examples will be drawn from trials currently being conducted by the presenters.

Generic Design Issues

Generic Design Issues will address five components: 1) choosing the appropriate population – cultural considerations (e.g., language and culture, access to care) and representativeness of sample, 2) selection of comparison conditions (e.g., standard of care), 3) “intent to treat” principle and 4) translation of the intervention to the community.

Introductory psychology college students have long been utilized as a population for behavioral research. Clinical Trials encourage study of populations based upon specific characteristics of relevance to the objectives of the study (e.g., culture, gender, health status). In addition, Trials must also consider special issues related to the selected populations (e.g., access to care, childcare resources). Participants will have the opportunity to discuss populations of interest for study and to consider appropriate comparison conditions, as well as learn from previous and ongoing study methods. Selection of comparison conditions is directly related to the state of science concerning the condition chosen for study. For example, in health care settings, placebo/control conditions have been replaced with the existing standard of care.

The “intent to treat” principle concerns the inclusion of all randomized participants, regardless of adherence to treatment (e.g., intervention attendance). The exclusion of study participants from the primary analysis on a systematic basis (for example, lack of compliance with assigned treatment) may introduce bias between treatment groups. Participants will have the opportunity to discuss issues surrounding “intent to treat” as well as its relationship to dose-response considerations.

The ultimate aim of the Clinical Trial is to improve the standard of care by influencing clinical or public health practices in the larger community. Participants will be provided with an overview of current translation strategies, and will be encouraged to brainstorm ideas on bridging the research/clinical practice gap.

Recruitment/Retention

Participants will learn a variety of strategies to increase recruitment and retention. Study participants are recruited from community health clinics, HIV counseling sites, health departments, HIV oriented community organizations, etc... Most recruitment efforts target case managers and health care providers, and maintaining a good working relationship with them is essential when working with special populations. Following initial contact, participants present for an orientation at the study site. The purpose of this is to make them aware of the location of future meetings and for them to become familiar with the study environment (i.e. staff, confidentiality, security). This greatly increases the chances of enrolling only those participants who are genuinely interested in the study. During orientation to the study, a demographic profile is obtained and issues such as confidentiality, risks and benefits are addressed. To assure a correct understanding of the informed consent the participant is asked to repeat their interpretation of the study protocol.

Run-in procedures are often used to maximize adherence in clinical trials. In one study, participants who miss more than two scheduled assessments prior to randomization, without giving prior notification, could be excluded. This “run-in” process assures a more reliable sample because only the participants committed to the study will be randomized. To maintain low attrition rates during long-term follow-up, an array of post-protocol retention strategies can be employed. These strategies must be tailored to the study population without compromising confidentiality. Helpful strategies for frequent and supportive contact include: pre-appointment reminder calls, birthday and missed appointment postcards, health care provider/case manager contact and free multi-vitamin refills. Ways of overcoming participation barriers include providing transportation vouchers, childcare, refreshments and home/clinic visits. Maintenance sessions can also maximize post-protocol attendance for follow-up visits. In the present study a protocol specific mixture of strategies have greatly improved our rate of retention.

QA/QC – Assessment/Intervention

The participants will be able to identify the importance of Quality Control in a multi-site Clinical Trial, specifically: fidelity of protocol, assessment, intervention and training. In the absence of stringent QC measures, findings may be unreliable and invalid due to within and across site variability in implementation of study protocol. QC should center upon the standardization of procedures within and across sites. Within sites, Project Directors, Assessment and Intervention coordinators will be responsible for ensuring adherence to the protocol and maintaining a current Manual of Operations, an integral part of the QC process.

Assessment - Within sites: In order to assure standardization of valid assessments, the Assessment Coordinator will train, certify, and supervise all assessors. All assessment sessions are audio-taped and periodically reviewed by Assessment Coordinator. **Across sites:** To ensure fidelity across sites, Assessment Coordinator will periodically observe assessments and/or QC audio-tapes from the various locations.

Intervention - The “gold standard” for delivery of the intervention is assured through the identification, training and maintenance of qualified therapists. Therapists should have the appropriate experience in the modality of the intervention. The goal of training therapists is to assure equal implementation of the therapy across sites. For example, in the SMART/EST Women’s Project, the therapist familiarizes him/herself with the Intervention Manual and views videotapes of the initial therapist training conducted by intervention coordinator. The intervention coordinator conducts individual training sessions with new therapists who will then co-lead a group with an experienced Therapist. The overall plan for supervision and monitoring of the intervention includes: a) a written checklist of clinician adherence to the protocol; b) monitoring of clinician performance by the Project Director at each site via monthly consultations and joint listening to audio-tapes; and c) across-site supervision of audio-tapes by the intervention coordinator.

Ethical Issues – Institutional Review Board Procedures, Informed Consent, Adverse Events.

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The presentation of ethical issues will enable the participant to 1) Develop an Ethics Checklist for use during protocol development and study implementation, 2) Navigate the Institutional Review Board application procedure, 3) Identify and address the ethical challenges of an Informed Consent: Provision of information, voluntary consent, coercion and appropriate language, 4) Obtain ethics information and training resources from a variety of sources and 5) Identify the components of an Adverse Event. Special attention will be given to ethical considerations for vulnerable populations.

Using a variety of previous and ongoing Clinical Trials, Ethical Issues will present an overview of four components of Human Subjects Research: 1) the role of the Office of Human Subjects Research (OHSR) and Title 45 CFR Part 46 – Protection Of Human Subjects; 2) Institutional Review Boards (IRB), creating different types of IRB protocols (e.g., expedited, exempt and full review), vulnerable populations, development of an Informed Consent and obtaining a Certificate of Confidentiality from the Department of Health and Human Services (DHHS); 3) Participant Consent Procedures, obtaining informed consent, assent and waived consent and assessing cognitive functioning for the provision of consent and 4) Ensuring Confidentiality, participant identifiers and participant record security.

Ethical Issues will also include the role of and requirement for a Data Safety Monitoring Board in the provision of planned interim analyses of 1) participant recruitment, 2) attendance by treatment sessions, 3) randomization balance by treatment, 4) discontinuance, 5) all-cause mortality and 6) early termination rules. Finally, the role of the Investigator in assessing, reporting and generating reports of Adverse Events, Serious Adverse Events and Mortality reports will be addressed.

Several issues concerning data management and analysis will be discussed during this portion of the workshop, based in part on our experience in the SMART/EST Women's Projects. Participants will learn principles of data management, including 1) establishing a database and developing a codebook, 2) data fidelity procedures and 3) data screening. Data analysis will include discussion of 1) random allocation, 2) intent to treat, 3) dose response analyses and 4) statistical power considerations.

Random allocation and the "intent to treat" principle are critical components of Clinical Trials. Patients randomized to one treatment group may not complete the treatment as assigned, or may withdraw prematurely, which may produce errors in the dichotomous classification of exposure to the treatment, tends to attenuate differences if they exist and biases the results of the trial toward the null hypothesis of no treatment effect.

Based on the "intent to treat" principle, all randomized study participants are included in the primary main effects analysis in their assigned treatment groups, regardless of compliance with the assigned treatment regimen. Other prognostic factors, such as compliance with the regimen, taken as a measure of exposure or dose, can be investigated using subgroup analyses.

Dose-response analyses look at the exposure to treatment as a covariate, and may provide the opportunity as a secondary analysis to examine psychological, biobehavioral, disease progression, and survival outcomes in relation to treatment exposures, regardless of initial random assignment to treatment. Clinical trials typically perform both types of analyses and compare the characteristics of the subgroups to those excluded from secondary analyses.

Finally, the provision of power of at least 80% for detecting medium multivariate effects will be discussed. Selection of effect sizes based on review of published studies and the use of over-recruitment to allow for loss to follow-up will be addressed.