Chapter 1
Overview of the Single Subject Design

R.A. Fisher, though most often associated with multiple-subject designs, first introduced a single-subject (clinical trial of N-of-1) experimental paradigm in 1945 [1]. Since this introduction, the single subject design has been used most frequently within the social and educational sciences [2]. This design, however, has recently been applied for investigations in medicine that have involved a multitude of clinical and biomedical areas such as drug therapy [3], gastroenterology [4, 5], internal medicine [5], pediatrics [6], family medicine [7, 8], cardiology [9], and nutrition [10], among others [3, 6, 11–13, 14–31]. During the 1980s, McMaster University established a service to direct and collaborate with physicians in planning and conducting N-of-1 (N=1) trials [11]. It was reported [11] that of the 57 completed single-subject trials, 50 of those trials provided a definite clinical answer, while study results of 15 trials consequently led the physician to alter treatment of the patient. Based upon these results reported by the collaborative team at McMaster University [11], single subject trials afford important opportunities for application in biomedicine, including directly improving patient clinical care.

Several specific examples highlight the utility of single subject design research in improving patient care. A recent literature example by Langer, Wintrop, and Issenman [6] reported on a single subject randomized trial to assess the effect of cisapride on symptoms arising from gastroesophageal reflux in pediatric patients. The trial investigated a placebo phase (A phase) and cisapride phase (B phase), with three study periods (i.e., A-B-A-B-A-B). The outcome variables of interest, all clinical measurements, included the number of episodes per five days for vomiting, gagging, and stools. In addition, Guyatt et al. [13] reported on a single subject study of a randomized controlled investigation of theophylline. Two study periods consisting of drug and placebo phases were employed (A-B-A-B). Patient-reported outcomes were rated on a seven-point scale, which included symptoms of shortness of breath, the need for an inhaler, and sleep disturbance. Using relatively straightforward single subject design procedures, physicians and practitioners have been able to examine the impact of treatments on appropriate outcome variables.

In a more recent example, Avins, Bent, and Neuhaus [32] reported on the use of an embedded N-of-1 trial to improve adherence and increase information from a clinical study. The study included a randomized, double-blind, placebo-controlled

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clinical trial of a customary extract of saw palmetto berry for the treatment of benign prostatic hyperplasia (BPH) symptoms. Eligibility requirements for participation included males with moderated symptoms of BPH that were age 50 or older. The results, based on estimates derived from the systematic model, did not suggest a strong effect of the study medication on blood pressure. Patient withdrawal from clinical trials was often accounted for by adverse effects. Entrenched N-of-1 trials offer an innovative opportunity for helping improve participants′ adherence to clinical protocols. Thus, single subject trials can be nested within larger studies to improve patient care, increase treatment adherence, and address additional research questions.

Single Subject Design Methodology

A frequently used quasi-experimental research design involves longitudinal measurements on a single subject (N-of-1) that extend over time. This design has been titled a within-subject design, clinical trial of N=1, repeated-measures design, time-series design, N-of-1 study, A-B, A-B-A design, or a single subject design [33–41, 8]. This design is most often used to study a process over time, with or without interventions, and typically employed in medicine [3, 6–7, 11–13, 42], psychology [43–45], education [39], econometrics [37, 46], and other types of research [47–55, 14–31].

An Institute of Medicine report [56] has provided initial guidelines for the use of these small clinical trials. Specifically, warranted situations might include rare diseases, unique study populations, individually tailored therapies, isolated environments, emergency situations, and public health urgency [56]. In particular, practice-based research commonly encompasses individually tailored therapies (e.g., glycemic control), isolated environments (e.g., rural health), and unique study populations (e.g., an adolescent who is HIV-infected and pregnant) [8]. Furthermore, Janosky [8] has demonstrated the applicability of this design to practice-based research in general, and more specifically to primary care practice-based research.

Figure 1.1 presents an illustration of an implemented A-B single subject research design. An A-B single subject research design encompasses two investigated conditions, in which the first condition (A) is a baseline or control condition, and the second condition (B) is an intervention condition. Figure 1.1 and this design description can be found in Janosky [8]. In this single subject study, the research question of interest was whether a comprehensive intervention for diabetes management would be effective in lowering fasting blood glucose values. Patient selection for participation was a systematic process that included identifying patients considered as: (1) typical in terms of the practice demographics, (2) typical for the disease presentation and progression, (3) in need of lower fasting blood glucose values, (4) anticipated to be compliant for the treatment changes, and (5) anticipated to be compliant for the necessary consent. These screening procedures were used to ensure study completion and improve generalizability of the study results.

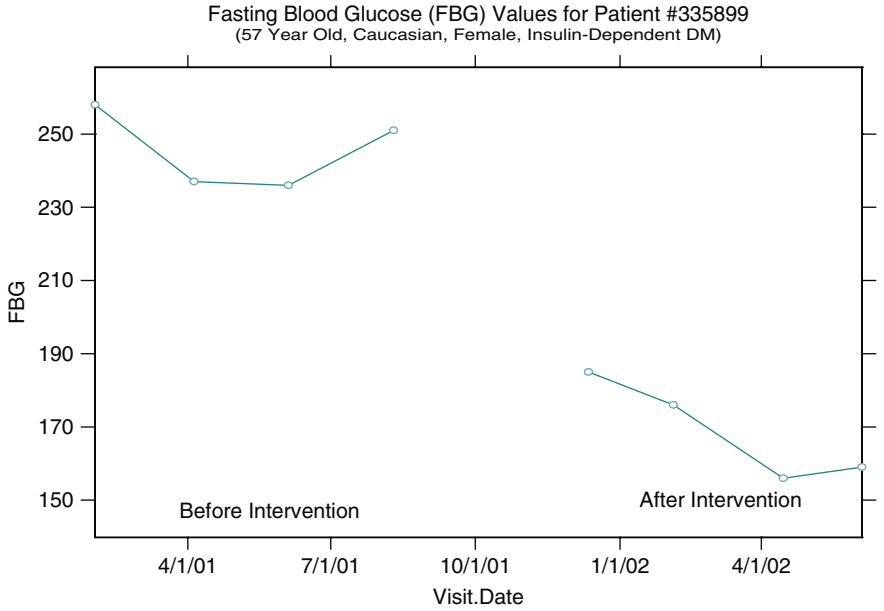

Fig. 1.1 An Example of data from a single-subject design

For this particular single subject design, there were two phases that included a baseline (A) and a treatment (B). The baseline and treatment were administered at distinct time periods. There were measurements across time, within both the baseline and treatment phases. Every two months the patient′s Fasting Blood Glucose levels were measured, as shown in Fig. 1.1. The patient was a 57-year-old, Caucasian female, with an onset of insulin-dependent diabetes in 1992. Presented are four measurements that were gathered every two months, which occurred before and after the intervention. A total of 8 observations are presented, and each observation was measured and reported (e.g., lab used, time of day, etc.) in the same manner. The goal of intervention was to improve diabetes management, which consisted of a prescribed exercise regimen, weight-management, and participation in a counseling session. Visual inspection of the figure reveals that the intervention was relatively effective in lowering the measured Fasting Blood Glucose in this subject.

As in all single subject designs, the research question of interest should guide the selection of the specific single subject design utilized in the study. When planning to implement a single subject design during the research design phase, the necessary specifications of conducting a multiple-subject randomized clinical trial must also be followed. The planning phase must incorporate forethought in the choice of outcome, variables, the subject(s), implementation of the treatment, number of phases, number of periods, and number of observations. Some guidelines have been prepared for these planning and implementation issues [3, 6, 11, 37, 42, 8].

Though much research has evaluated the methodology of these designs, additional research is needed to evaluate more thoroughly the data from these designs in order to determine their relative merits.

Arguably, clinical effectiveness of a single subject design intervention would ideally be assessed using inferential statistical techniques. Unfortunately, there is no uniformly accepted procedure for approaching these analyses. Many data analytic procedures have been proposed that include, but are not limited to, visual inspection, z-tests, t-tests, analysis of variance, time-series, the C-statistic, the split-middle technique, nonparametric smoothing, and curve fitting [36, 38, 45–46, 47–55, 57–67]. Visual inspection is primarily a descriptive technique, while all others involve varying degrees of hypothesis testing [62, 63, 68–71]. Research has not shown any inferential procedures to be uniformly valid for these types of designs. Janosky [36] discusses a portion of these methods in more detail. Though initially used primarily within social and educational research, the single subject design methodology is being increasingly incorporated into health sciences research and biomedicine. Recently, this design has been used as a means of investigation in medicine involving such areas as drug therapy [13], gastroenterology [4], internal medicine [5, 12], pediatrics [6], family medicine [8], cardiology [9], and nutrition [10]. The included annotated bibliography (See Chapter 7) identifies single subject design articles recently published in PsycInfo, MEDLINE, and PubMed.

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