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Lessons learned in the conduct of a global, large simple trial of treatments indicated for schizophrenia

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ABSTRACT

Large, "practical" or streamlined trials (LSTs) are used to study the effectiveness and/or safety of medicines in real world settings with minimal study imposed interventions. While LSTs have benefits over traditional randomized clinical trials and observational studies, there are inherent challenges to their conduct. Enrollment and follow-up of a large study sample of patients with mental illness pose a particular difficulty. To assist in overcoming operational barriers in future LSTs in psychiatry, this paper describes the recruitment and observational follow-up strategies used for the ZODIAC study, an international, open-label LST, which followed 18,239 persons randomly assigned to one of two treatments indicated for schizophrenia for 1 year. ZODIAC enrolled patients in 18 countries in North America, South America, Europe, and Asia using broad study entry criteria and required minimal clinical care intervention. Recruitment of adequate numbers and continued engagement of both study centers and subjects were significant challenges. Strategies implemented to mitigate these in ZODIAC include global study expansion, study branding, field coordinator and site relations programs, monthly site newsletters, collection of alternate contact information, conduct of national death index (NDI) searches, and frequent sponsor, contract research organization (CRO) and site interaction to share best practices and address recruitment challenges quickly. We conclude that conduct of large LSTs in psychiatric patient populations is feasible, but importantly, realistic site recruitment goals and maintaining site engagement are key factors that need to be considered in early study planning and conduct.

1. Introduction

Large, simple or streamlined trials (LSTs) are used to study the effectiveness and/or safety of medicines in real world settings with minimal clinical care interventions in an effort to maximize clinical utility for researchers/practicing clinicians [1–7]. Because LSTs combine both randomization and follow-up with minimal intervention, several researchers proposed the LST as an ideal design for studying drug effectiveness and post-approval safety, especially when the necessary scientific and operational conditions for its use are met [5]. While LSTs have benefits over traditional randomized clinical trials (RCTs) and observational studies, there are inherent challenges to LSTs [4,6–8]. Recruitment and follow-up can be more difficult when studying approved drugs, which can be assessed by other means (i.e., cohort studies using electronic medical records or claims databases). As a result, their use to assess post-approval safety is limited [5]. March et al. [9] and others [8,10] have advocated practical clinical trials in psychiatry and have outlined key

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features and challenges of their use to evaluate effectiveness and safety of psychiatric medications. Some challenges associated with LSTs can be amplified in studies of mental illness (e.g., complexities in obtaining outcomes in patients with Alzheimer's disease and psychoses [11]). Recurrence of intermittent episodic psychiatric disorders can result in premature patient drop out [12–15] and complicate the maintenance of diagnostic follow-up long-term [14,15]).

Despite these challenges, several LSTs or LST-like studies were conducted to study psychiatric drug effects including: the Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation Study (BALANCE) [12]; the International Clozaril/Leponex Suicide Prevention Trial (InterSePT) [16,17]; the National Institute of Mental Health (NIMH) funded trials in patients with schizophrenia (CATIE), bipolar disorder, Alzheimer disease (CATIE-AD) [14,15,18], and the Child and Adolescent Psychiatry Trials Network (CAPTN) [3]; and the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) [19–21]. In addition to similarities in LST design elements, e.g., large sample size, minimal physician/patient burden, and naturalistic follow-up, these studies shared similar challenges in recruitment and retention of psychiatric patients.

The largest and most recently completed of these LSTs, ZODIAC, was an international, open-label LST, which followed more than 18,000 persons treated for schizophrenia for 1 year. ZODIAC faced significant challenges in recruiting, then following thousands of subjects with schizophrenia, but overcame these challenges using robust national and regional strategies. To minimize challenges to future LSTs in similar populations, closer examination of these strategies, and why they were successful, is warranted.

The aim of this paper is to describe the recruitment and observational follow up strategies used for ZODIAC and draw lessons learned from our experience implementing them. Our goal is to highlight useful operational tactics to mitigate slow enrollment for the successful conduct of future LSTs.

2. Methods

2.1. Study design

Detailed information on ZODIAC's design, study outcomes, endpoint adjudication, and study results was described elsewhere [19–21] and is summarized in Table 1. Patients were enrolled from February 2004 to February 2006. The primary study endpoint was non-suicidal death, and study endpoints were screened, coded, and adjudicated by an independent study Endpoint Committee (EC) using pre-specified endpoint algorithms.

Table 1
Design characteristics of ZODIAC, a large simple trial (LST).

Design characteristic	ZODIAC
Randomization schedule	1:1
Treatment	Ziprasidone vs. olanzapine
Sample size	Large; 18,000 subjects
Inclusion criteria	Intentionally broad (per locally approved label)
Primary outcome	Nonsuicide mortality
Secondary outcome	All-cause mortality, cardiovascular mortality, suicide, etc.
Required patient visits/ procedures	Baseline; 12 month disposition
Study monitoring	Minimal; at increments of 50 subjects enrolled
Primary analytic method	Intent to treat

Consistent with observational studies, and in particular LSTs, study inclusion criteria were intentionally broad to simulate routine clinical practice and allow recruitment of a representative study sample. ZODIAC enrolled patients with schizophrenia from various clinical settings in 18 countries in North America, South America, Europe, and Asia. In keeping with the observational "real world" nature of this study, investigators were local product labels but broad inclusion/exclusion criteria were used. Thus, the investigator enrolled a subject if he/she believed olanzapine or ziprasidone was a suitable treatment based on his/her medical judgment. We did not specify diagnostic criteria; rather physicians were asked to confirm that the patient was diagnosed with schizophrenia. Therefore it is possible that some patients with schizophrenia spectrum disorders were included if investigators considered the patient eligible. After the physician determined the subject was eligible, randomized assignment to olanzapine or ziprasidone was done, followed by unblinded follow-up per routine clinical care.

2.2. Special design features

Several elements of LSTs were employed to minimize interference in normal medical care as described herein.

2.2.1. Drug dispensing

We utilized naturalistic drug dispensing practices meaning, where possible, dispensing via usual channels (e.g., prescription filled at U.S. and Swedish pharmacies). In other countries where this approach was not possible, study medication was reimbursed by the sponsor, obtained locally in commercial supply centers, and dispensing/tracking was overseen by local country monitors.

2.2.2. Subject follow-up

To minimize physician burden, data collection instruments were brief and collected only basic information at baseline and at routine follow-up visits [20]. With the exception of the baseline and 1-year final visits, there were no required study visits. Alternative contact information (e.g., next of kin name, address, and telephone number) was obtained during the informed consent process, and used if the patient was unable to be contacted. If repeated attempts at contact were unsuccessful, patients were deemed lost to follow-up (LTFU) at the 1 year final visit.

2.2.3. Study monitoring

Because the study aimed to minimize investigator burden, it followed hard endpoints, and was not a traditional RCT, the study's Scientific Steering Committee (SSC) and the Data Safety Monitoring Board (DSMB) endorsed a streamlined monitoring plan for all centers participating in the study, whereby sites would be monitored i) as their enrollment reached 50 subjects and at increments of 50 thereafter, and ii) at random for a sample of sites with less than 50 subjects, with more frequent site monitoring to reinforce protocol adherence as needed. Most centers outside the United States (US) were routinely monitored (e.g., quarterly) to comply with international research