Clinical trials: Bridging the gap between efficacy and effectiveness

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Abstract
The need for clinical psychiatry research to provide practical information to clinicians, families, and consumers has led to the development of new approaches to clinical trials. Efficacy trials, the historical backbone of clinical research, have many shortcomings in delivering practical information to stakeholders. The ‘effectiveness’ or ‘public-health’ model of intervention research targets a diverse group of patients across multiple settings that are outside of academic medical centres, with study design and outcomes that are selected on the basis of their potential to produce clinically meaningful information. The National Institute of Mental Health has funded three such clinical trials in recent years, respectively targeting schizophrenia and Alzheimer’s disease, depression, and bipolar disorder. Each of these studies has made a major impact, and provided new insights into the challenges of public health orientated trials in psychiatry. In this review, we describe the underlying principles and practical considerations in efficacy and effectiveness-orientated trials.

Introduction
In psychiatry, and in medicine in general, a major concern of clinicians is that research does not provide them with the kind of information they need to improve their practice. Researchers, on the other hand, have observed that the uptake of empirically-based interventions in ‘real world’ community settings is minimal. Even when a novel treatment appears to be efficacious upon completion of a clinical trial and the treatment is adopted into routine care, it will rarely work in the same way as it did in the research study. This ‘chasm’ between research and clinical practice has been described in position statements issued by the Institute of Medicine (Berwick, 2002), the National Advisory Mental Health Council and the National Institute of Mental Health (Lebowitz, 1997).

There are many social and fiscal factors at play in translating, or failing to translate, research into practice. In recent years, a variety of authors have observed that the most familiar form of the clinical trial, the efficacy study, needs to be fundamentally rethought to tell us about what we really want to know in clinical encounters: What treatments work for which patients under what conditions? Efficacy studies, rather than being seen as the completion of the process, are better viewed as an intermediate step in treatment development. In 2006, the Director of the National Institutes of Health described an ideal future of medicine in terms of four ‘Ps’: Predictive, pre-emptive, personalized, and participatory (Zerhouni, 2006). In this optimized system, a clinician would know which treatment to select, based on the patient’s characteristics and preferences, and would do so in a manner that would prevent future occurrences and ramifications of their illness.

In short, efficacy trials as traditionally conceived cannot, and will not, deliver this ideal to the public. Moreover, the sequential progression of a new treatment from Phase III trial (demonstration of efficacy in a controlled setting) to Phase IV trial (demonstration of effectiveness in the real world) is appealing from a logical standpoint but rarely occurs in reality. This is because (1) efficacy and effectiveness research represent very different values and a single treatment can rarely satisfy both value systems (Glasgow, Davidson, Dobkin, Ockene, & Spring, 2006), and (2) most research protocols end at Phase III.

However, there is emerging hope that a middle ground between efficacy and effectiveness paradigms can be attained. In this review, we discuss the efficacy...
and effectiveness in clinical trials in psychiatry, drawing from experiences of three noteworthy public-health orientated studies that were funded by the National Institute of Mental Health (NIMH): Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) for schizophrenia and Alzheimer disease, Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), and Sequenced Treatment Alternatives to Relieve Depression (STAR*D). Although our focus will be on the NIMH-funded trials, there have been a number of large European naturalistic and effectiveness trials in schizophrenia, including the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) (Jones et al., 2006), the European Schizophrenia Cohort (EuroSC) (Bebington et al., 2005), and the Schizophrenia Outpatient Health Outcomes (SOHO) (Haro & Salvador-Carulla, 2006) studies. Together, these investigations represent massive commitments on the part of researchers, clinicians, patients, and funders, and they are just beginning to yield new insights into enhancing mental health care as it is practised in clinical settings.

**Efficacy trials**

Since the United Kingdom Medical Research Council evaluated streptomycin in 1948, the randomized placebo-controlled clinical trial (RPCCT) has been the gold standard in biomedical intervention research. To establish a claim that a treatment is safe and effective, governmental agencies such as the US Food and Drug Administration (FDA) require that drugs and medical devices undergo rigorous testing in human subjects. In psychotherapy research, there has been a parallel movement to identify (and potentially require in the case of third-party payers) ‘empirically based treatments’ that have undergone randomized controlled trials in the same way that a new drug would. The hoped-for outcome in such a study is that efficacy is established, and that side effects are minimal (Norquist, Lebowitz, & Hyman 1999) referred to such efficacy-based clinical trials as falling under the ‘regulatory’ model of research; that is, efficacy trials are a necessary first step in discovering whether a novel treatment may be beneficial and safe enough for distribution to the public.

The goal of the efficacy study is thus to determine what works under ideal conditions, maximizing the probability of success of the experimental intervention. The approach to designing an efficacy trial is to maximize internal validity, wherein researchers strive to control all extrinsic factors that can contribute variability to treatment effects. Factors that contribute to variability in clinical trials are many, including whom the treatment is provided to, how and by whom it is delivered, and what ‘yardstick’ will be used to determine efficacy.

Essential to efficacy trials is the high degree to which participant selection is narrow and homogenizing. Participants are selected on the basis of a particular disease categorization (e.g. depression). In psychiatry, this often means excluding potential participants who have co-occurring psychiatric disorders, as well as participants with medical comorbidities, cognitive impairment, or substance use disorders. It may also mean categorically excluding groups of patients, such as persons who are older than age 65 or pregnant women who have high risk of discontinuation and/or barriers to tolerability. Moreover, participants may also be excluded who had previous exposure to the experimental intervention. It also generally has to be assumed that participants do not have a preference for any one experimental treatment over another. The cumulative effect of these exclusions is that as many as 80–90% of patients are determined to be ineligible for the trial (Lebowitz, 2004; Schneider et al., 1997; Zimmerman, Mattia, & Posternak, 2002).

In addition to participant selection, efficacy trials also decrease the ‘noise’ in the delivery of the intervention. Efficacy trials are typically carried out in academic research settings, with interventions provided by highly trained clinicians who follow a formalized protocol. In psychopharmacology trials, dosing is generally rigid and ascribed a priori. Furthermore, participants may have weekly contact with a project coordinator to gather assessments on symptoms and side effects. In psychotherapy trials interventions are delivered by clinicians who have mastered the psychotherapeutic approach (often even developed it), in accordance with a manual routinizing each session. Adherence to the study regimen by the participant and the treating clinician is assumed, monitored, and/or actively encouraged by study personnel. Importantly, interventions are mostly provided to participants free of charge, thus eliminating the potential biases of participant fiscal constraints or third-party payers. With a few exceptions, efficacy trials evaluate a single intervention, rather than the utility of augmentation or combination strategies.

The effect of the intervention is measured in terms of an outcome that corresponds to disease symptoms. In depression treatment research, a 50% reduction in the Hamilton Depression Rating Scale (Hamilton, 1967) is the prototypical outcome. Time until depressive or manic relapse may be an outcome, but generally the interest is in reducing acute psychopathology over the short-term (e.g. three months). The duration of the trial is fixed,
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generally the minimum length of time required to demonstrate the effect in question.

Efficacy is a question of central tendency, with mean scores in the sample of the primary interest. Beginning with the null hypothesis that experimental treatment and placebo are equal, if, on average, participants have fewer symptoms of disease ‘X’ after the study period (with less than a 5% probability that this finding could arise by chance), then one has fulfilled the efficacy test. The number of subjects necessary to conduct an efficacy trial is determined by statistical power analysis performed to determine the minimum required to reject the null hypothesis. Discontinuation prior to study conclusion is often ‘rolled in’ to the final ascertainment sample, with the final available value carried forward in an intent-to-treat analysis.

Efficacy trials can tell us a great deal. In addition to whether the treatment worked under these tightly controlled conditions, we can surmise, in the relatively complication-free participant, whether treatments produce side effects that are not observed in the placebo condition or whether participants are satisfied with that treatment at a particular dose. Efficacy trials may be seen as ‘proof of concept’, with sufficient information to gauge whether a treatment should be made available.

Even a cursory observation of routine clinical practice will indicate what is not addressed by efficacy trials. First, the characteristics of real-world participants are not reflected. In psychiatry, the rate of comorbidity is substantial – for instance some 60% of people with bipolar disorder also have a co-occurring substance use disorder (Cassidy et al., 2001). Most people who suffer from major depression also meet criteria for an anxiety disorder (Kaufman & Charney, 2000). In elderly people, nearly 80% have a chronic medical illness (Administration on Aging, 2006). Second, outcome measures may accurately reflect symptoms, but may not be functionally significant. A 50% reduction in depressive symptoms, while an important outcome, does not address the kinds of concerns that patients seek treatment for in the first place – returning to work, improving relationships, and feeling well. More than most diseases, psychiatric disorders have a multidimensional impact on the patient’s mental and physical state, their capacity to participate in social roles, and their need for a variety of services. Third, clinicians and administrators must select treatments based on their assumed cost-effectiveness, not solely their efficacy. Whereas a new 24-week manualized psychotherapy may show dramatic gains in research study participants, a community mental health clinic may not have sufficient resources to provide intensive psychosocial or psychotherapeutic services. Fourth, adherence to treatment and preferences, of both patient and clinician, cannot be assumed. In a registry of persons taking lithium for bipolar disorder, the mean duration of usage is about 76 days (Johnson & McFarland, 1996). If real-world patients will not take a particular medication or complete a course of psychotherapy, demonstration of its efficacy is necessary but far from sufficient to enhance clinical outcomes. Fifth, treatment for mental disorders, for most individuals, is not provided in a research-driven specialty setting by highly trained clinicians. Notably, the most common setting for initiation of anti-depressants is in primary care. In sum, the efficacy trial cannot offer the kind of information desired by the administrators, clinicians, or patients.

Effectiveness trials

Much has been written about practical clinical trials in medicine (Tunis, Stryer, & Clancy 2003), practical behavioural trials in psychiatry (Glasgow et al., 2006; Wells, Miranda, Bruce, Alegria, & Wallerstein, 2004), large simple trials (Yusuf et al., 1984), and the ‘public health model’ of clinical research (Norquist et al., 1999). There are some distinctions between each of these models, but the common goal is to produce findings that have greater leverage in translating research to clinical practice.

It should be noted that efficacy and effectiveness-type trials are not wholly discrete categories – there is a continuum that emphasizes internal validity on one end (efficacy) and external validity on the other (effectiveness). Wells et al. have noted that hybrid designs are possible (Wells, 1999), and in many ways CATIE, STEP-BD, STAR*D, and European studies combine elements of efficacy (e.g. blinding, randomization) and effectiveness (e.g. employing minimal exclusion criteria) orientations.

The goals of trials at the effectiveness/public health model end of the spectrum are to maximize generalizability and to ‘address practical questions about the risks, benefits, and costs of an intervention as they would occur in routine clinical practice’ (Tunis et al., 2003). The selection of participants is deliberately broad – there are few exclusion criteria with respect to psychiatric and medical comorbidities, age, gender, and previous exposure to treatment. The exclusion criteria that do exist are generally based on safety, rather than the effort to restrict the sample to a homogeneous group.

In terms of outcomes, (Tunis et al., 2003) described the goal of measuring intervention effects on a broad array of outcomes that extend beyond change in disease symptoms. These outcomes include quality of life and performance in
social roles, such as work and relationships, as well as the cost-effectiveness of the intervention in that setting. Moreover, experimental interventions are designed to be implemented as closely to what might be offered in an actual clinical setting, with experimental treatments delivered by clinicians with limited training and oversight. The intervention in practical clinical trials typically compares ‘clinically meaningful alternatives’, aiming to address questions that are important to every-day clinical decision making – e.g. if anti-depressant treatment is not working, should another medication or psychotherapy be added, and which one?

Once important clinical questions are identified, a major task in developing practical clinical trials is to emphasize generalizability by enrolling a large and diverse subject pool in an array of clinical settings. Public health model trials are typically run in multiple sites, extending beyond academic settings into mental health clinics, primary care, or other community-based sites. Generalizability is also enhanced by implementing the intervention in a non-rigid fashion, mimicking the variability of what might occur in a clinical setting. Adherence to the intervention, rather than a variable to control, becomes an outcome in and of itself. Participants and clinicians, rather than being completely blind to which treatments are being evaluated, may have input about which treatments they would prefer to (or are unwilling to) initiate. Dosing is typically more flexible and designs may incorporate flexibility in terms of adding another treatment, combining multiple treatment approaches, or switching to a new intervention.

Therefore, the effectiveness research paradigm treats many of the factors that are so deliberately controlled in efficacy trials as moderators and mediators. Researchers can capitalize on the variability by patient or setting characteristics in, for example, treatment response, to address some of the decisions that clinicians routinely need to make. However, the challenges in conducting public health model trials are numerous. Effectiveness trials, while not necessarily costing more per participant, require a great deal more development time, coordination and planning than is typical in an efficacy trial. In a way, developing an effectiveness trial entails creating a miniature health care system, requiring tools for data tracking, safety, communication and reporting, and quality assurance. These become topics that can be addressed scientifically through the publication of papers describing the study design and other technical aspects of the overall trial (Nierenberg et al., 2004; Sachs et al., 2003; Schneider et al., 2001; Warden et al., 2005).

**Sample size and characteristics**

To begin to address what treatment works for which patients, sample sizes must be much larger to enable analyses of moderation (as opposed to central tendency). Whereas typical randomized clinical trials in psychiatry are 50 to 100 participants per group, public health orientated trials typically sample thousands of participants. With the emphasis on generalizability, the sample must document how representative it is of the population in question. These trials introduce new moderators, including differing settings, levels of exposure to the treatment, and patient comorbidities, and the planned sample sizes based on power analysis must take these blocking factors into account.

**Non-academic settings**

Conducting research in clinical sites that may not have experience with clinical trials raises an interesting set of obstacles. Mental health agencies generally operate on tight budgets, and their primary motivation is to provide services, not to advance science. Clinical settings may perceive that they do not benefit from contributing to a research study, and they may be sceptical about research – citing the same kinds of concerns as they do when they read research reports – i.e. that research has not traditionally helped them in their practice. There is little slack time for clinicians to fill out rating scales.

An essential part of effectiveness trials is therefore ‘buy-in’ from community sites, attained by putting in place expectations that participating in research will improve practise, not just in the future, but at the time of the study. This ‘buy in’ must extend from administrators, to managers, to front-line mental health workers, to consumers. Research must then address concerns that are relevant to the entire system – by comparing clinically meaningful alternatives and assisting front-line clinicians with patient management and decisions that need to be made on a daily basis. Whereas efficacy trials demand a great deal from study clinicians (e.g. rating scales, measures of adherence, weekly two-hour psychotherapy sessions), the burden of research on community clinicians and participants must be substantially reduced. Moreover, successful collaborations between an academic research setting and a clinical organization involve a partnership that is mutually beneficial, egalitarian, and jointly coordinated (see Minkler, Blackwell, Thompson, & Tamir 2003 for a review of community-based participatory research). Involving key stakeholders in the design of the study is a way of partnership and a lesson from any introductory social psychology textbook – humans are more likely to follow through
with a plan if they believe that they had a hand in developing it.

**Research design and statistical analysis**

There are many design differences between efficacy studies and practical trials. In an attempt to mirror routine clinical practice, such typical requirements as masking of treatment, placebo controls, and independent raters may need to be modified. Treatment as usual becomes a more typical comparator and a range of treatment alternatives may be offered. Randomization that does not consider patient or clinician preferences does not reflect actual practices. Retaining masked raters and clinicians may not be feasible or desirable, or may be perceived of as too much of a burden by participating sites. Furthermore, if the questions are to determine the effectiveness of a combination strategy, or a sequence of treatments (if the initial intervention did not work), the research design will become complex.

When fully randomized controlled trials cannot feasibly be employed, alternate approaches can be used. These may include quasi-experimental, quality improvement, or multiple baseline approaches. In addition, a number of novel approaches have been used to incorporate preferences and/or mimic real-world decisions, e.g. the equipoise stratified randomization approach used in STAR*D (Lavori, Rush, Wisniewski, 2001; Rush et al., 2004).

Advances in the design and statistical analyses of clinical trials are necessary for, and grow from, practical clinical trials. The science of public health clinical trials has had to develop rapidly to meet new challenges (see Piantodosi, 2005), and there is a central role of the methodologist in each of the NIMH-funded trials. Estimating treatment effects in observational, non-random studies requires statistical approaches that are different from the typical intent-to-treat analyses seen in efficacy trials. The non-randomness of missing data is a central concern in pooling effects from multiple sites and intervention arms, and sophisticated approaches to making inferences about missing data are necessary (Rubin, 1976). If the treatment assignment is non-random, such as in observational trials, propensity scores have been used to evaluate treatment effects in observational studies (Rosenbaum & Rubin, 1983). Furthermore, as the questions shifted toward what treatment works for which patients, the need is increased for statistical methods to address moderation and mediation (see Kraemer, Wilson, Fairburn, & Agras, 2002).

**Outcomes**

The effectiveness researcher has the particular challenge of making study assessments as brief and minimally impactful on the participants, while extending assessment beyond the disease state to multi-dimensional outcomes involving function, disability, and quality of life (Norquist et al., 1999; Stroup & Appelbaum, 2006). For example, the European CUtLASS trial has as its primary outcome quality of life, rather than symptom resolution. Given the recency of the completion of the NIMH trials, most of the first reports on outcomes of these interventions have dealt with the effectiveness of interventions in relation to remission of symptoms. In CATIE, among the first major outcome papers published dealt with the comparison of study medications in terms of time to all-cause discontinuation (Lieberman et al., 2005). Instead of describing the effectiveness in treating the symptoms of schizophrenia, the results of papers indicated that each of the medications was associated with high rates of discontinuation. Therefore, the CATIE study described the behaviour of clinicians in the real world, which may ultimately be more important to stakeholders than which of the medications works under the best of circumstances.

Given their emphasis on clinically meaningful results, effectiveness trials generally include data on costs. Considerations about cost are among the primary reasons, for example, why psycho-social interventions that are empirically validated are not implemented in clinical settings. The CATIE study evaluated cost-effectiveness of the antipsychotic medications in Phase I, and found large discrepancies between atypical and typical forms of antipsychotic (with higher costs in the atypical arms) (Rosenheck et al., 2006). Assessing cost effectiveness is facilitated through the development of standardized utility measures that are tied to clinical outcomes, as used in the CUtLASS study (Jones et al., 2006).

**Safety and ethical considerations**

In practical trials, the delivery of the intervention and the status of the participants is further from the control of the study coordinators. Participant safety emerges as a primary concern in effectiveness trials. Compared to the prototypical efficacy trial, participants may have more medical comorbidities and a higher risk of suicide. In addition, clinicians may be less trained than in efficacy trials, and assessments may be gathered from remote means (e.g. interactive voice response) to facilitate processing data from thousands of patients. In particular, monitoring algorithms that provide
alerts to clinicians at the time that suicidal ideation is identified must be developed a priori to handle suicidal patients, with a rapid response (Nierenberg et al., 2004).

Another ethical consideration that arises prior to study onset is the consent process. Typical consent forms that explain the procedures, risks, and benefits of a study to a lay person may not be sufficient to ensure adequate understanding, particularly among patients whose psychiatric disorder diminishes their capacity to consent to research. Methods to enhance consenting, such as decisional capacity assessment, repetition of content, and multimedia or PowerPoint consent procedures may be necessary (Dunn et al., 2002; Stroup et al., 2005). In severe mental illness, decisional capacity cannot be assumed to be a stable characteristic, just as psychiatric symptoms change in severity. Decisional capacity may indeed become impaired, placing the researcher in the quandary of whether to continue to allow that participant to continue. ‘Subject advocates’ or consent monitors may be used to ensure that participation was in the participant’s best interests (Stroup & Appelbaum, 2006).

Data management
In a trial that includes thousands of participants, with each ‘case’ associated with bundles of documents, integrated centralized data management and inter-site communication is an enormously important task. There also needs to be efficient methods for reporting, and automation in scanning incoming data for errors. There is increasing use of web-based data management and communication systems (Wisniewski et al., 2004). This kind of system can also be useful in training and certifying raters to conduct standardized assessments, limiting inter-site differences in reliability of measures (Kobak, Engelhardt, & Lipsitz 2006). In particular, these centralized web-based systems can reduce staff workload, and in an ideal world could be adapted to enhance the practice setting’s data management once the study is completed.

It is common in multi-site trials that sites drop out due to failure to recruit targets, personnel changes, or waning investment of site PIs. When there is great variability between sites, interpretation of results becomes a problem at the conclusion of the study (Kraemer & Robinson, 2005). Site variability may blur the results and reduce the power to address the aims of the study. Beyond the monitoring provided by coordinating centre continuing review and external data and safety monitoring boards, some effectiveness trials may take a proactive quality assurance approach to tracking performance in individual sites (Warden et al., 2005).

Training, funding, and breaking from tradition
A final but important barrier to effectiveness research has to do with the researchers themselves. As noted by Tunis et al. (2003), there is a lack of researchers trained in public health orientated trials, and at least a perception of limited funding available for effectiveness research. Drug companies, with some notable exceptions, see Phase IV research as an opportunity to expand the indications of a particular medication versus understanding for whom treatments work best. Most journals and grant reviewers base their evaluation of completed or proposed research in accordance with efficacy. The CONSORT guidelines, as pointed out by Glasgow, assess 21 characteristics that are inherent to internal validity and one to external validity (Glasgow et al., 2006). Clearly, the orientation towards public health trials will require a shift in emphasis of the clinical research community, as well as increased training of junior investigators in subjects such as community-based participatory research.

The NIMH practical trials
The National Institute of Mental Health initiated a set of large-scale public health orientated trials in nearly 10,000 adults with schizophrenia, Alzheimer’s disease (Clinical Antipsychotic Trials of Intervention Effectiveness or CATIE), treatment resistant depression (Systematic Treatment Alternatives to Relieve Depression or STAR*D), or bipolar disorder (Systematic Treatment Enhancement Program for Bipolar Disorder or STEP-BD). The designs of those trials have been described in peer-reviewed journals (Rush et al., 2004; Sachs et al., 2003; Schneider et al., 2003; Stroup et al., 2003) and the initial findings have been published in major, high impact journals (Lieberman et al., 2005; Nierenberg et al., 2006; Perlis et al., 2006; Rush et al., 2006; Trivedi et al., 2006). Publications or results from the trials continue to be produced at a steady volume.

Overall, much has been learned from these trials. In general, the trials show that a personalized approach to treatment is important and that there is considerable need for new treatment approaches. The trials have demonstrated that there is a different and productive way to approach research in therapeutics, an approach that focuses on long-term outcomes of functional significance in large and representative samples in typical clinical settings. The trials showed that it is useful to try to duplicate certain approaches to standard clinical practice such as incorporating patient and clinician preferences and experiences in the selection of treatments.
On the other hand, the trials showed the advantages, unusual in routine practice, of measurement-based approaches to treatment that support aggressive approaches to dosing and duration of treatment and that standardize approaches to patient and family education. Finally, the trials addressed the economic barriers that are confronted by many persons as they seek treatment.

The trials had innovative approaches to the inclusion of non-traditional settings for clinical research and specified the role of the academic health centre with respect to protocol design, study operations, and data analysis. The collaboration of the pharmaceutical industry was critical in the trials, and each of the studies demonstrated that there is a positive role for well-constructed government industry academic collaborations. Pharmaceutical companies committed substantial resources to these trials by providing medications at no cost. At the same time, the companies agreed to have a strictly hands-off role with respect to the design of the studies, their operations, or the interpretation of the data. Potential conflicts of interest were scrupulously evaluated and standards for ethical and responsible conduct of research exceeded those typically established for academic investigators.

Overall, the trials showed that it is possible to design and carry out studies that patients, their families, and the clinicians that care for them will all find valuable. Additionally, the studies showed that such public health orientated trials could have results that policy makers and the general public find useful and important.

At the same time, the trials showed that when studies include representative patients in typical clinical settings that serious adverse events and negative outcomes are possible. In these trials there were deaths from general causes and a small number of suicides, some unintended overdoses, hospitalizations, and accidents. The trials showed that these outcomes could be minimized by using proactive, aggressive risk-management strategies (Nierenberg et al., 2004) in these studies in which there had been scrupulous attention to the assessment of capacity to consent and fully voluntary informed consent for every component of the protocol.

Large-scale trials such as these provide important platforms for specific studies. Each of these trials had a process for the inclusion of ‘ancillary studies’ in all the trials, for example, participants were offered the opportunity to provide a blood sample to be used for pharmacogenetic and biomarker studies. These genetic materials have been placed in an NIMH-supported repository and will be made available for public use along with all the clinical data from the trials. Additional specific studies were developed in each of the trials and the results are now being reported (for example, Perlick et al., 2006; Weissman et al., 2006).

Much more remains to be learned from the data from these trials, including the moderators of treatment response and the results of ancillary studies. But no set of trials can answer all questions, and each of these trials has highlighted the need for new treatments and new approaches to treatment sequencing. In particular, the studies indicate that residual symptoms remain problematic for many patients and the field needs better approaches to these. Fundamental questions such as optimal duration of treatment remain unanswered, as does the need to optimize treatment adherence and overall quality improvement. Finally, approaches to disease prevention and prophylaxis are yet to be developed for mental disorders.

As for the NIMH trials, the basic structure of these trials is being maintained and the content and focus of future trials will address the questions that emerged from the first wave of findings. As medicine evolves from a curative to a pre-emptive approach (Zerhouni, 2006), the methodologies developed in these trials will inform the emerging systems of healthcare that will be tailored to this new paradigm.

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References


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