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Enhancing adherence in clinical research

William N. Robiner*

Health Psychology, Department of Medicine, University of Minnesota Medical School, Mayo Mail Code 295, 420 Delaware Street, Southeast, Minneapolis, MN 55455-0392, United States

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Abstract

This article presents overviews of adherence or compliance in clinical care and research, focusing on the need to enhance research adherence. The scope of the clinical research enterprise and costs of conducting clinical research are summarized. Costs associated with suboptimal adherence in clinical care and research also are addressed, along with their implications for enhancing adherence. Methodological problems and statistical challenges (including intent-to-treat) associated with poor adherence are reviewed. Addressing social factors, regimen characteristics, behavioral patterns, and systems issues can affect adherence. Strategies for enhancing adherence in clinical research subjects, including pre-randomization screening, behavioral and educational interventions, monitoring, and enhancing subjects' status and contingencies for adhering are discussed. Integrating adherence-enhancing strategies throughout research phases, from pre-randomization screening during recruitment to endpoint, has the potential to improve the quality and outcome of research while limiting costs.

Keywords: Adherence; Clinical research; Clinical care

1. Enhancing adherence in clinical research

In a society that looks to its doctors, scientific community, government, private sector, and health care system for ever-better drugs and technology, there is an imperative for treatments to withstand rigorous

* Tel.: +1 612 624 1479; fax: +1 612 899 8925.
E-mail address: robin005@umn.edu.

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scientific scrutiny. Enhancing the nation's public health depends, in part, on a cost-effective system for evaluating therapeutic and diagnostic innovations. Health care professionals and patients look to such advances to reduce morbidity and mortality, help manage illness, and promote a range of health and quality of life outcomes. The current *zeitgeist* of evidence-based medicine depends on the ability of researchers to derive conclusions based on well-designed and efficiently conducted scientific studies. This article presents overviews of clinical and research adherence, summarizes the scope and costs of clinical research, and focuses on the need to enhance subjects' adherence in clinical research and approaches for addressing it.

2. Adherence

The degree to which patients and research subjects act in accordance with the advice or instructions of their health care provider or researchers is termed "adherence" or "compliance" [1,2]. These terms are commonly used interchangeably, albeit the former terminology may be preferred because of its more positive connotations. In both clinical practice and research, adherence to regimens is a challenge [3]. As former U.S. Surgeon General, C. Everett Koop remarked at a 1984 conference on patient compliance, "Drugs don't work if you don't take them" [4].

In clinical practice, the primary negative outcome of poor adherence is at a micro-level: the risk of poorer health outcomes for the individual such as increased morbidity (e.g., toxicity, exacerbation, disease progression), decreased quality of life, or mortality across a spectrum of conditions [5,6]. Poor adherence can interrupt or complicate care and increase costs. There also can be macro-level effects (e.g., poor adherence contributing to drug-resistance undermining the efficacy of interventions throughout the population [7]; transmission of human immunodeficiency virus (HIV) associated with improper use of condoms). Poor adherence has been characterized as the most common cause of unsatisfactory response to medication [8]. Haynes and Dantes [9] caution that, "No practitioner or researcher can afford to assume that patients or participants will follow prescribed treatments or follow-up procedures. Indeed the opposite must be expected and planned for." (p. 13).

2.1. Adherence problems in clinical practice

Although adherence to treatment regimens is a prerequisite for clinical care [1], it is often inconsistent. Early estimates of nonadherence in ambulatory patients range from 20% to 82% [10]. More recent estimates are that 50–65% of outpatients do *not* adhere to prescribed medication regimens [11,12,13]. Dunbar, Erlen et al.'s [14] review revealed ≤50% adherence rates for medication-taking (objectively documented with electronic monitoring) for chronic disorders, including: asthma, cardiac disease, diabetes, hypertension, psychiatric disorders (i.e., depression and schizophrenia), rheumatoid arthritis, seizure disorders, and ankylosing spondylitis. An American Association of Retired Persons (AARP) survey revealed that 21% of respondents failed to fill initial prescriptions at least once [15]. A Boston Consulting Group [16] survey projected that millions of Americans fail to comply with prescribed drug regimens every year. As concerning as the trends for medication-taking are, adherence to other medical advice (e.g., weight loss, diet, exercise, smoking cessation) is likely even worse [17].

Numerous factors influence patients' adherence [18]. The literature is contradictory regarding the effects of age, gender, socio-demographic factors, and personality on adherence [17,19]. Psychological phenomena (e.g., depression, anxiety, personality) have been identified as risk factors for non-adherence,

though findings about their impact have not been uniform [20,21]. Other factors affecting adherence include: Severity and chronicity of health problems; complexity of treatment regimens (e.g., frequency of dosing); comorbid conditions; adverse effect profile; and drug–drug interactions. The relationship between patients and providers has been posited to be of utmost importance in affecting adherence [22].

Despite individual variation in adherence, there is no evidence of either an "adherent personality" or a "non-adherent personality" [23]. Indeed, it is probably more fitting to view adherence as a continuous rather than dichotomous variable due to the inherent difficulties measuring adherence, heterogeneous definitions and categorization criteria, and individuals' temporal variation in adhering [24]. Also, individuals may vary in terms of their adherence to specific components of medical regimens. This is evidenced by low correlations of adherence estimates among specific aspects of diabetes regimens [25]. The causes of non-adherence are complex, multivaried, and probably vary among people. The Boston Consulting Group [16] estimates that passive processes may account for only a relatively small proportion of non-adherence (e.g., 24% of patients attribute their non-adherence to forgetting). Active choices *not* to take medications as directed may reflect concern about side effects (20%), costs (17%), the desire to exert personal control by making one's own decisions (i.e., do not think they need the drug [14%]), or be related to access problems (10%) [16]. Improper adherence also may stem from misunderstanding of regimens or underlying conditions, disbelief, denial, family disorganization, psychosocial problems, problematic communication with health care teams, and systems factors.

The biological impact of poor adherence may be affected by numerous factors. These include individual physiology, the pattern of poor adherence [26], the severity and pathophysiology of the disorder, as well as specific medication's pharmacokinetics which determine how "forgiving" it may be if taken inconsistently [27]. The clinical sequelae of poor adherence are far-reaching. For example, as many as half of drug "failures" for hypertension may result from poor adherence [28]. As many as 700,000 pregnancies in the U.S. may stem from problematic adherence to oral contraceptive regimens [29]. Despite the life-threatening clinical risks for transplant recipients, including graft loss and death, poor medication adherence is a limiting factor for transplant health outcomes [30,31]. Schweizer et al. [32] estimated that non-adherence accounted for 25% of graft failures. Poor adherence to antiviral drugs confounds treatment of HIV [33].

2.2. Costs of inadequate adherence in healthcare

The economic costs of non-adherence are staggering. Estimates of healthcare costs associated with inadequate adherence (e.g., more diagnostic tests and treatment, unnecessary therapies, increased dosages, more frequent clinic visits and monitoring, hospital admissions, nursing home care) and lost productivity may approach US$100 billion annually [16,34]. Sullivan et al. [35] estimated that as many as 1.94 million (5.5% of) hospital admissions could be attributed to poor adherence with drug therapy. Extrapolating their finding to the hospital admission rates of that era suggested that nearly 2 million hospitalizations, or US$8.5 billion (in 1986 dollars), or 1.7% of the nation's total healthcare bill could be related to poor adherence. They surmise that some admissions could be prevented by improved adherence. They estimated that poor adherence resulted in US$17–25 billion in indirect costs (i.e., productivity loss, wage loss, opportunity costs, premature mortality).

Other researchers have unearthed similarly troubling trends [14]. Medication adherence problems (e.g., failure to fill prescriptions) resulted in approximately half of geriatric drug-related emergency department [36] and hospital admissions [37,38]. In one hospital, 38% of all inpatient care costs for

diabetic ketoacidosis were estimated to be precipitated by poor adherence [39]. Extrapolating that data to estimates of the US$27.28 billion of U.S. inpatient care for diabetes in 1997 [40] suggests poor adherence for diabetes regimens generates billions of dollars of potentially avoidable healthcare costs annually. Across the spectrum of health conditions, the impact of non-adherence, including direct and indirect costs, for patients, families, employers, the healthcare system, and society, is enormous.

2.3. Adherence problems in research regimens

The challenges of non-adherence in clinical practice have considerable relevance for conducting research because of the corresponding impact of psychological, behavioral, and systems factors. Subjects' willingness to volunteer for studies of the effects of investigational agents [41] and diligence in following prescribed protocols are fundamental to clinical research. However, once enrolled in clinical studies, some subjects incompletely execute their charge [42]. There are two primary types of adherence in research. "Follow-up adherence" refers to fulfilling the scheduled sequence of assessment measures within planned time windows (e.g., keeping follow-up clinic visits, undergoing laboratory tests) until reaching endpoint [43,44]. For example, in the Diabetes Control and Complications Trial (DCCT), 99% of patients completed the study and >95% of scheduled examinations were completed [45].

"Regimen adherence" or "protocol adherence" refers to pursuing the assigned regimen consistently (e.g., keeping to schedule in taking medication at the specified dose). There may be multiple components of adherence (e.g., prescribed medication-taking schedules, maintenance of diet or exercise regimens, self-monitoring, meeting objective biological targets, such as maintaining low glycosylated hemoglobin) [45]. In the DCCT, the mean time in the assigned treatment was 97%. However, while follow-up adherence was impressive, only 44% of intensively treated subjects achieved the target HbA_{1c} goals. Other aspects of research adherence can include avoiding concomitant treatments and cooperating with other procedures [42].

Regimen adherence problems can involve both errors of omission (e.g., forgetting to take a medication, delaying a dose, under-dosing), and commission (e.g., over-medicating, taking the wrong medication). Adherence problems can be random or non-random (e.g., covariates of illness severity, treatment effects, or length of time in study [i.e., study fatigue]), transitory or long-term, or attributable to other factors with implications for data analysis and interpretation [46].

The absence of definitions and standards for satisfactory compliance within research are methodological shortcomings [47]. A convention in biomedical research known as the "80% rule" has been used as an operational, albeit problematic, criterion for regimen adherence [48]. Scientific journals are reluctant to publish articles with lower adherence rates [49]. This general adherence threshold has been supported by some research, such as Sackett et al.'s [50] study of anti-hypertension medications which revealed that exposure to 80% of the protocol's medications was necessary to reveal beneficial effects.

Although research subjects have generally been considered to adhere better than clinical patients [27], the continuum of research adherence is heterogeneous, ranging from extremely conscientious and cooperative subjects at one end, to partial adherers, and dropouts at the other extreme. Lasagna and Hutt [51] estimate that 25–50% of research subjects are not adherent. In a review of 10 Veterans Affairs studies, Collins et al. identified dropout rates as high as 50% in two studies, and greater than 20% in another five studies [52]. Mean adherence rates in clinical trials for appointment keeping, short-term medication-taking, and long-term medication-taking have been estimated to be 39%, 62%, and 63% respectively for prevention trials and 78%, 78%, and 59% for treatment trials [3,53]. Longer-term studies

have reported worse adherence than short-term studies [54,55]. A 2002 CenterWatch review of IRB records of 25,855 subjects who consented to participate in U.S. industry-sponsored studies revealed that only 74% completed their trials [56].

In 1999, of the estimated 2.8 million individuals who were screened for industry-sponsored research, only 7% enrolled, and 5% completed the trials. This reflects a 29% loss accounted for, at least partially, by non-adherence [57]. In other words, of the 196,000 subjects enrolled in industry-sponsored studies, approximately 56,000 did not complete the studies.

Although investigators seek to recruit subjects who will sustain adherence to study protocols, adherence can falter for many reasons. Diverse factors related to trial protocols can affect retention rates in clinical trials, such as: staff–subject interactions; subjects' characteristics, behaviors, and relationships with others; and organizational and environmental factors [44,58,59]. For example, in the Lipid Research Clinic-Coronary Primary Prevention Trial (LRC-CPPT) study, although 19–22% of dropouts were related to adverse drug effects, and 11–20% were related to somatic problems, the majority (58–69%) were attributed to psychosocial problems [53]. This underscores the need to understand and address psychosocial and other adherence-limiting factors more seriously when conducting research investigations.

3. The clinical research enterprise

A brief overview of the clinical research enterprise is provided in the next sections to illuminate the context and scope of adherence problems in research. Clinical research generally evaluates the effects of drugs, vaccines, blood and tissue products, surgical techniques, radiation, new methods (e.g., gene therapy), and other therapies (e.g., psychotherapy, occupational therapy) and of combined treatments, in preventing, diagnosing, and treating conditions. Prospective, controlled, randomized clinical trials are generally considered to be the premier means for evaluating medications, medical devices, surgical procedures, and other healthcare regimens. Such studies are critical to the mission of the National Institutes of Health (NIH) and other governmental and private research organizations, as well as to the pharmaceutical, medical device, and biotechnology industries [23]. Scientists, healthcare professionals, universities, hospitals pharmaceutical companies, research organizations, and a complex of regulatory entities, such as institutional review boards and the Food and Drug Administration (FDA), serve key roles in research.

Promising drugs and other therapies may become subject to investigation on human subjects after years of laboratory and animal studies. The system is comprised of a graded series of investigations that focus on specific aspects of agents' effects, as presented in Table 1, and that address a range of health matters, as presented in Table 2. Phase I studies, the first research on human beings, are concerned with establishing whether agents are safe for use with humans. For approximately 70% of investigational agents that reach this phase of testing, basic safety usually is demonstrated. Phase II studies next evaluate effectiveness. These are typically double-blind comparisons between either (a) the new agent and a placebo or another drug used to treat the condition, or (b) of a previously approved agent for a new purpose (e.g., an antidepressant for use in treating anxiety). Approximately one-third of agents pass through Phase I and Phase II trials. The third phase of human research involves more extensive evaluation, with comparisons of the relative effectiveness of agents with other treatments. Approximately 70–90% of such studies yield positive results, reaching the threshold of eligibility for FDA approval through the Center for Drug Evaluation and Research (CDER).

Table 1
Phases of clinical trials

Phase	Objective	Questions	Length of study/approach	Typical number of subjects
I	Safety	How is drug absorbed, metabolized, excreted? What are its short-term adverse effects? How should it be administered (e.g., p.o., i.v., i.m.), dosing, frequency? How long does it act?	Typically several months	20–100; as low as 12; May include healthy or affected subjects
II	Effectiveness and safety	What are the short-term effects of the agent on the specific condition, short-term risks, and side-effects?	Several months to a few years. Often randomized clinical trials	100–300 or 500 subjects with the disease or condition
III	Expanded Studies of benefits, effectiveness, dosing, and safety	How does the agent compare with other accepted treatments? What is the incidence of adverse effects, interactions; or side-effects? How should drug be labeled?	Several years. Usually randomized, double-blinded clinical trials.	1000–3000 or 5000
IV	Post-marketing Long-term safety, effectiveness and impact on quality of life	What are its risks, benefits, and optimal use? What is its cost effectiveness relative to other treatments? How do intended populations use it?	Variable	

Typically, the FDA requires two randomized, controlled trials providing evidence of safety and efficacy for drugs.

3.1. Scope of clinical research

The U.S. clinical research enterprise is vast. In 2001, NIH awarded 12,710 clinical research awards, spending US$6.279 billion, which accounted for 37.4% of NIH's extramural total research dollars [60]. The pharmaceutical industry, the National Institutes of Health, along with other federal agencies and private organizations, sponsor an estimated 9,300 clinical studies according to the website sponsored by the National Library of Medicine (www.ClinicalTrials.gov).

To illustrate the magnitude of clinical research for a single group of diseases, approximately 1700 oncology trials were conducted in association with the National Cancer Institute (NCI) in 2002. Non-governmental groups, such as the American Cancer Society and the Susan Komen foundation supported 45 clinical studies. Between 1997 and 2001, more than 25,000 cancer patients were enrolled annually in NCI treatment trials, with 2300 patients in intramural trials at NCI alone. According to the NCI website, an estimated 2.5% of adult cancer patients participate in some type of clinical investigation. The Pharmaceutical Research and Manufacturers of America (PhRMA) estimated that in 2001 there were 402 drugs under evaluation for the treatment of cancer, involving 170 pharmaceutical and biotechnology companies [61].

3.2. Costs of research and drug development

Because clinical research is complex, cumbersome, painstaking, and involves so many people and entities, it is extraordinarily expensive. PhRMA estimated that the drug industry invested US$30.3 billion in research and development (R&D) in 2001 [61]. This amounted to 59% more than the US$19.1 billion pharmaceutical firms' spent on promotional activities (e.g., advertising) that year. An Office of Technology Policy report of the National Science Foundation and U.S. Department of Commerce [62] ranked medical substance and device companies second among eight industrial sectors in terms of how much U.S. corporations spent on R&D in 1997. Clinical research spending in 2001 for medical device and biotechnology companies cost an estimated US$1.675 billion [57]. Major brand pharmaceutical companies spent an average of approximately 13% of their budgets on R&D in 2001 reflecting a 59% increase since 1997 [63]. One driver for such robust R&D investment is that branded products face limited legal windows of economic protection as intellectual property before becoming subject to stiff competition from generic pharmaceuticals.

The Tufts Center for the Study of Drug Development estimates that pharmaceutical companies typically spend US$802 million bringing each new medication to market in a 10–15-year process [64]. In 1991, in response to urgent demands for new HIV treatments, the FDA accelerated the drug-approval process. The FDA estimates the drug development cycle has shortened considerably [63]. Drug development rigorously ascertaining the properties and effects of agents and eliminates those that are unsafe or ineffective. It is a public health filter in that most molecular entities never reach the market. Only 0.1% of chemical compounds emerge from preclinical laboratory testing to studies involving humans. Of these, only 20% proceed to the market [61]. Consequently, R&D expenses contribute substantively to the costs of prescription medications.

The economic impact of successful drug development is immense. The results of each study can yield enormous economic stakes, as exemplified in the recent ImClone Systems scandal involving Martha Stewart and Samuel Waksal. Spending on prescription drugs in 2002 was estimated to be US$162 billion [65]. In relative terms, medications account for the third largest segment of national health costs. Moreover, prescription drug costs are the most rapidly expanding type of national health expenditure, accounting for about 10% of nation's health bill. The percentage of healthcare dollars spent on medications is expected to rise to 14.2% by 2010. Taking depression as an example of the costs associated with one disorder, medications account for increasing proportions of costs: US$10.4 billion in 2000, or 12.5% of the total

Table 2
Types of trials

Type	Objective
Prevention	Evaluates approaches to preventing disease onset or recurrence (e.g., medicines, vitamins, vaccines, minerals, or lifestyle changes).
Screening	Evaluates methods for detecting certain diseases or health conditions (e.g., virtual colonoscopy, PSA)
Diagnosis	Evaluates tests (e.g., blood test, imaging study) or procedures (e.g., colonoscopy) for diagnosing specific diseases or conditions.
Treatment	Evaluates treatments (e.g., devices, medicines, surgery, radiation), and combinations of treatments
Quality of Life (or Supportive Care)	Evaluates approaches to enhance patient comfort and quality of life for individuals with a chronic or life-threatening illness.

economic burden of this disorder, up from 2.4% a decade earlier [66]. As pharmacologic treatment options increase across the universe of diseases and disorders, costs attributable to medications may mount inexorably. These trends highlight the need to conduct drug research cost-effectively (Table 2).

4. Effects of problematic adherence on clinical research

The scientific importance of adherence within clinical trials cannot be overestimated [67]. In addition to the effect of adherence problems on their own health, research subjects' intentional or inadvertent non-adherence, and deviations in protocol (e.g., pregnancy or intolerance of assigned treatment) may threaten researchers' ability to complete investigations. Temporary or permanent withdrawal from studies also jeopardizes studies [68]. Problematic adherence may jeopardize some subjects' health, lengthen studies, necessitate larger subject samples to achieve adequate statistical power, and it inflates the cost of completing studies. Such concerns suggest that adherence arguably deserves to be added to the list of challenges facing the national clinical research enterprise recently compiled by the Clinical Research Roundtable at the Institute of Medicine [41]. Inadequate adherence threatens studies' validity, confounds researchers' ability to derive scientific conclusions and complicates statistical analyses. Whether or not adherence per se is a primary study outcome, its contribution to the success of clinical trials is essential.

4.1. Analytic/statistical challenges associated with problematic adherence

Subjects' adherence has profound implications for the statistical power for detecting differences among treatment arms in clinical investigations. Adherence to research regimens within allocated treatment arms is a prerequisite for the statistical comparisons underlying studies' research design. Inadequate adherence (i.e., behavioral variation) contributes to statistical variance and increases the risk of type II errors. It may lead to erroneous conclusions that either no differences can be identified between or among treatments, that a treatment is ineffective, or to overestimates of drug dosing [51]. The latter ultimately can result in otherwise avoidable adverse reactions associated with excessive dosing. Poor adherence has been estimated to limit the statistical power of a study as a square of the proportion of adherent subjects [69]. Studies can be more powerful statistically with smaller numbers of adherent subjects than with larger numbers of participants whose adherence is problematic [70].

Missing data is pervasive in randomized controlled trials (RCTs). Hollis and Campbell's [71] review of 249 RCTs published in four top medical journals in 1997 revealed that 119 (48%) compensated for missing data by incorporating intention to treat (ITT) analyses. Most (75%) of the studies were affected by missing data related to primary outcome variables. The need for ITT arises from multiple sources (e.g., subjects' drop-out, cross-over, and death), but problematic adherence is a major factor. ITT analyses include all subjects, whether or not they (a) actually received the treatment to which they were allocated, or (b) deviated or withdrew from the study. ITT analyses are intended to avoid overvaluing differences between or among treatments that may occur if subjects who generate missing data are excluded from studies. Unfortunately, for a fixed sample size, decreasing the likelihood of Type I errors increases the risk of Type II errors. There are several ITT analytic methods (e.g., Last Observation Carried Forward [LOCF] regression) [72]. ITT analyses are predicated on missing data issuing from random events, even though this is not necessarily a valid assumption. Ultimately, the choice of analyses may be controversial, with some statisticians believing that efficacy analyses based on data from only

cooperative subjects is more accurate than including all participants, regardless of their adherence, following the ITT model [73].

The severity of problems caused by missing data varies based on factors, such as the frequency (e.g., rate of inactivity or drop-out), magnitude of treatment effects, homogeneity of adherence rates and clinical attributes across treatment groups, and the factors that contribute to it [74]. Unfortunately, the choice of statistical method, such as principled (e.g., multiple imputation) or naïve (complete cases analysis, linear extrapolation, predicted mean and hot decking), of dealing with dropouts' data can significantly influence results [74,75]. Ultimately, the less consistently subjects adhere during a study, the less clear the conclusions can be. Thus, the more complete a data set can be based on consistently adhering subjects for the full duration of a study, the smaller the potential variance resulting from statistical artifact potentially associated with ITT methods.

4.2. Clinical outcomes and adherence in research

Adherence appears to be a factor in individual outcomes in clinical trials [76]. Better outcomes have been identified for subjects with good adherence to treatment regimens than with poor adherence in studies of cardiac disease [77], cancer [78], and psychiatric disorders [79,80]. Hughes et al's [27] review of 22 clinical investigations revealed that as adherence decreases, so do treatment benefits. In addition, since studies may be prolonged due to non-adherence, the more adherent subjects are, the shorter the period for which any subjects may need to be exposed to regimens that ultimately are found to be inferior.

4.3. Adherence costs in research

The costs associated with undertaking studies stem from multiple sources (e.g., investigator and consultants' time and support, tests, materials, drugs or devices, infrastructure, computers, subject incentives and treatments, monitoring compliance, auditing by sponsoring entities). Some research costs are fixed (e.g., space, computers), but others may be affected by adherence-related variables, such as sample size, length of study, number of tests performed and pills provided, as well as the costs of undertaking adherence-enhancing activities (e.g., phone contacts). The Pharmaceutical Interventions Working Group [81] estimated the costs of monitoring each elderly subject's pharmacologic adherence in clinical trials to be somewhere between US$11 and US$75 per month. Albeit the actual costs of suboptimal adherence across the entire clinical enterprise is not known, there is little doubt that problematic adherence contributes substantially to the cost of conducting research [8].

Recognition of the potential for inadequate adherence increases sample size necessary to evaluate research hypotheses [82], lengthening investigations, adding additional trial centers, and requiring additional staff time to address nonadherence [58,83]. For example, an expectation of 20% non-adherence factored into the sample size requirements above the number of subjects identified by power analyses, will increase costs associated with recruiting, screening, and running them. More specifically, a study with a 20% non-compliance rate, with a power of .95 to reveal differences at the .05 level may need as many as 50% more subjects than if the study participants achieved 100% adherence [84]. Goldsmith [85] calculated that for an antihypertensive study specifying (α=.05; β=.05; δ=10 mm Hg) based on a 100% adherent sample (n=23), reductions in adherence to 90%, 80%, 70%, 60%, or 50%,

would require respective sample size increases of 5 (21%), 12 (52%), 22 (96%), 38 (165%), and 65 (283%) subjects.

Non-adherence can result in other types of research costs. Contending with non-adherence is demoralizing to staff: It can contribute to staff burnout and turnover. In the worst case, non-adherence can lead to aborting a study. Such costs ultimately increase the expenses of bringing technological innovation into healthcare as industry sponsors seek to recoup R&D costs when establishing pricing for new treatments.

Although, the cost effectiveness ratio of medications is generally presumed to decrease with poor adherence, the relationship between adherence and the cost of medications is complex. Hughes et al.'s [27] analysis revealed eight studies demonstrating that higher drug regimen costs were associated with lower adherence, whereas seven studies revealed the reverse. In the case of expensive, but relatively inefficacious treatments, poor adherence (e.g., early discontinuation) may in fact yield cost-savings [86].

It is possible to derive gross estimate of the effects of nonadherence on research. Since studies strive for adherence $\geq$80%, using Goldsmith's [85] data, a 52% increase in sample size might be needed. If the 196,000 subjects participating in industry-sponsored studies include a theoretical 20% who do not adhere, it might theoretically be possible to conduct the research and achieve comparable results (in terms of efficacy if not management) on a sample somewhere between 156,800 (i.e., 80% of 196,000) and 128,800, representing 65.7% of the actual number (based on Goldsmith's estimate). Theoretically, the benefits associated with *not* running the 39,200 to 67,200 subjects with problematic adherence could net major time savings for staff and reduced duration of studies, site and staff reductions, and lower per-subject expenses. Were it possible to achieve an ideal of 100% adherence, significant reductions in overall research costs might be realized.

Although the proportion of overall research costs associated with incomplete protocol or follow-up adherence (e.g., drop-out), as well as the actual dollar amounts are unknown, the magnitude of pharmaceutical R&D costs cited earlier, suggests that potential savings of billions of dollars annually could be realized were it possible to improve adherence across the totality of studies underway. Theoretically, more accurate estimates could be derived through models that consider per-subject costs, length of studies, scaled down recruitment of smaller samples, robustness of effects, and other factors that influence investigational costs. Whereas adherence problems and enhancement efforts do not account for the main costs of conducting individual studies, the costs are not trivial when considered across the nation's research enterprise.

5. Enhancing adherence in clinical research

The adverse effects and costs of subject adherence for clinical research reveal a compelling need for more effective techniques for promoting, sustaining, and evaluating subject adherence through all research phases. The selection of subjects who understand study burdens and are willing to commit to regimens is a critical up-front step in promoting research adherence [87]. This requires a combination of effective screening to exclude subjects who might reasonably be identified as at risk for non-adherence based on histories of poor adherence with treatments, inconsistency with medical care (e.g., lateness or missed appointments), problematic communication, or ambivalence about participating. It also entails effective communication about trial participation (e.g., informed consent, accepting random allocation, importance of adherence) [87].

5.1. Pre-randomization screening

A preventative approach for promoting adherence in effectiveness studies is recruitment screening to identify potential subjects at risk for compromised adherence. The purpose of prerandomization screening is to predict subjects' level of adherence so that those likely to cooperate enroll while those at risk for adherence problems are either screened out or targeted for intensive adherence-promoting interventions [88].

Two pre-randomization approaches have been used primarily. The "run-in" is a behavioral methodology that places potential subjects on a prescribed regimen for a specified period to assess their fidelity in following a proxy regimen. The premise is that short-term adherence during prerandomization can predict long-term adherence after enrollment. Run-ins are usually single-blind, and may use placebos and pill counts. In the Physicians' Health Study (PHS), the run-in resulted in an estimated 20–41% increase in power, and 34% decrease in sample size [89], yielding considerable cost-savings.

A second pre-randomization screening approach is test-dosing. Potential subjects are given a small dose of active agent for a few days prior to randomization. Test-dosing identifies those who may have difficulty tolerating adverse medication effects. It identifies candidates for exclusion based on their individual biological responses to specific agents. The validity, sensitivity, and specificity of run-in and test-dosing procedures, while promising, are controversial [90].

A third potential approach to prerandomization screening could involve evaluating other types of behavioral and psychosocial data based on variables that are empirically related to adherence (e.g., anxiety, depression, motivation, barriers to participation). Whereas pre-randomization screening approaches are appropriate for efficacy trials designed to evaluate whether agents are effective, they are not suitable for management trials that address the impact of interventions on broader populations. The benefit of prerandomization screening is the potential to enhance the power of studies, thereby increasing the likelihood of finding bona fide group differences, while circumventing avoidable costs that ultimately would be associated with screened-out candidates' poor adherence.

5.2. Adherence enhancement

The second primary approach for promoting adherence is to integrate adherence-enhancing strategies into research (see Table 3). Adherence-enhancing efforts can be multifactoral, addressing health, social, research, and logistical matters, including assisting subjects to surmount participation barriers. Coordinated efforts to address target adherence behaviors directly (e.g., medication-taking), by involving principal investigators, trial coordinators, behavioral scientist consultants, other staff, auditors, and people in subjects' social network present multiple opportunities to promote adherence [91]. Russell [92] developed a counseling process to promote adherence based on 11 steps and an adherence documentation checklist for addressing common adherence problems. Adherence-promoting interventions integrate education, cueing to remind subjects to fulfill regimen demands, and contingent reinforcement for adherent behaviors (i.e., operant conditioning) [93]. In addition, simplifying medication regimens, enhancing social support, and intervening early when adherence problems emerge may facilitate adherence. For some drugs, it may be possible to incorporate drug delivery systems that are relatively more resistant to non-adherence (e.g., patches) earlier in the drug development process.

A recent meta-analysis of interventions for promoting clinical adherence yielded heterogeneous results, but nevertheless provides some hope for integrating strategies into future clinical research [94].

Table 3
Adherence enhancement strategies in clinical research

Recruitment
Spend adequate time providing informed consent and getting to know subject
Explain the disorder, protocol, medication/device, side-effects, interactions
Explain participants' roles, need for and importance of randomization and adherence
Explore, motivation, expectations, views of research, tolerance of randomization, history of research participation; history of discipline in self-care
Set clear, mutually acceptable goals and assess understanding
Use adherence run-in, or other techniques prior to randomization to screen for adherence and exclude potential poor adherers
Balance staff objectives in recruitment between enrolling largest number of subjects possible and limiting enrollment to those with reasonable likelihood of adhering to allow study to provide interpretable results

Healthcare
Promote contact with other treating professionals and garner their support for subject to participate
Provide health-related and research-related information
Promote referrals as necessary to other health professionals to support optimal healthcare, including mental health support
Address emotional aspects of disease and research participation

Social aspects
Promote positive, collaborative relationships between subjects and members of research team
Provide social support
  Maintain frequent phone contact, email, clinic visits
  Send birthday and anniversary cards, trial newsletter
Provide positive feedback for regimen and follow-up adherence
  Social reinforcement and other reinforcers
Involve family members, or other support network to promote involvement in research when necessary, consider family therapy referral

Regimen characteristics
Goal setting: develop clear and realistic expectations
Streamline protocol
  Minimize dosing frequency, number of pills, risk of side effects
  Minimize uncomfortable and unpleasant aspects of protocol
  Ensure materials are readable, conveniently packaged
Tailoring: develop regimen that can be realistically integrated with patients' other daily activities
Optimize clinical regimen to minimize adverse effects
Reduce negative consequences associated with regimen
Enhance healthcare access and promote treatment of comorbid conditions and addressing psychosocial factors

Logistical support
Schedule appointments at convenient times and in convenient locations; minimize waiting times
Provide free parking, baby-sitting, support with transportation and lodging (if needed)
Provide compensation for missed work, travel reimbursement
Promote access to relevant technology (e.g., use of Internet, email)
Provide reminders of regimen and importance of sustaining adherence throughout

Adherence
Dedicate resources to promoting adherence (e.g., incorporate staff and consultants with expertise in adherence, encourage staff professional development, such as negotiating around adherence, understanding motivations for and types of non-adherence, as well as ethical issues in research and adherence)

Table 3 (*continued*)

Adherence (*continued*)
Devise adherence plan as part of study design, including protocol for addressing non-adherence
Promote collaboration between subjects and research staff
Provide feedback about how well subjects are adhering to protocol or achieving target goals whenever possible
Promote candid, non-judgmental discussion of adherence, including barriers, facilitators, and personal challenges
Anticipate adherence challenges and address them proactively (teach skills necessary for to organize behaviors the underlie adherence, time management, stress management)
Monitor adherence (e.g., pill counts, Medication Event Monitoring System (MEMS) caps, journal, logs, assays, use of tracer substances, self-monitoring and self-report, collateral reports); direct observation (i.e., supervised therapy/dispensing)
Use multiple methods of assessing adherence, including, but not limited to self report
Incorporate behavioral techniques and problem-solving to enhance adherence
Practical strategies to promote consistent pill-taking (e.g., pairing medication-taking with routine life events)
Use prompts (e.g., pill boxes, reminder letters, telephone calls, emails, Internet)
Provide positive reinforcement (i.e., social reinforcement, incentives) for good adherence whenever possible (e.g., at clinic visits, inter-visit communications)
Model adherent behavior (e.g., show subject other subjects successfully following regimen
Intervene early and as often as necessary when adherence problems emerge (e.g., call if an appointment is missed); discuss barriers to adherence
Increase frequency of visits if adherence becomes problematic
Decrease visit frequency if adherence is sustained
Use behavioral contracts when necessary
Address factors, as possible, that indirectly may affect adherence (e.g., refer for mental health treatment or social services if depression appears to be a factor undermining adherence)
Systems
Promote research on enhancing adherence
Increase funding within clinical research awards to support adherence-enhancing efforts

Adapted from Refs. [8,18,42,84,87,92,104].

Comprehensive interventions addressing cognitive, behavioral and affective components were more successful than single-focus approaches. A second recent review concluded that although efforts to promote adherence to medication regimens tend to be complex and labor-intensive, they are not consistently effective [95]. Only modest benefits were found, even for the most effective adherence-enhancing interventions.

5.3. Monitoring adherence

A third critical component for clinical research is evaluating subjects' adherence to assigned regimens [22]. Monitoring enables adherence-enhancing efforts to be targeted to those who need it most, and allows for analysis of the effect of adherence on the outcomes of the research [96]. Despite the need to evaluate research adherence, there are neither consensus on standards for quantifying or defining adherence, nor completely accurate methodologies for measuring it [24]. For example, day-to-day consistency of medication taking may be measured in some studies, whereas the total quantity of an agent taken over a longer period may be analysed in others, neglecting the daily variation pattern [88]. Albeit different patterns of medication-taking may yield differential clinical outcomes, measurements may not always capture critical information.

Several methodologies have been employed. In pharmacological studies, markers (e.g., inert molecules, radioactive substances, stable isotopes, pharmacological substances with relatively long half-lives, such as low dose Phenobarbital; digoxin) may be used, coformulated with study preparations (including placebo) to quantify exposure to agent. Another approach incorporates monitoring systems such as the Medication Event Monitor System (MEMS) marketed by the Aprex division of Advanced Analytical Research on Drug Exposure (AARDEX), using microchips embedded in drug vial caps to identify when vials are opened [97]. The approach is predicated on the presumption that medication is taken only through the monitored vial and that each vial opening indicates medication was actually taken. Nevertheless, such monitoring probably yield more accurate estimates of adherence than patient report, which has been estimated to identify only 25–50% of non-adherence subjects [98]. Even systematic pill counts, which are more sensitive than patient reports, likely miss about 10% of non-adherence [99], and may be undermined by pill dumping [22].

5.4. Cultural change and expanding the benefits of adherence and research participation

Our expanding understanding of mechanisms for intervening in clinical conditions contributes to the growing need for research study participants [41]. Whereas the behavioral approaches described above may be employed to enhance subjects' efforts to adhere to regimens, broader approaches also seem warranted. Cultural or social psychological changes designed to augment research subjects' status and motivation may enhance recruitment and adherence. Historically, subjects have been viewed as volunteers or "guinea pigs" passively incorporated within studies. Recently, subjects have been described as "customers" whose satisfaction needs to be considered [100]. Such perspectives fail to fully appreciate each subject's critical contribution to the success of the research studies in which they participate and their importance in helping to fulfill the nation's research agenda. Subjects' participation generally goes unheralded, and their risk-taking, willingness to tolerate uncertainty, altruism and sacrifices (e.g., time, exposure to discomfort and unproven therapies) are largely unrecognized. Despite evolving research safeguards, subjects assume risks that can be as life-threatening as those facing other groups (e.g., military and emergency response personnel) whose actions on others' behalf are more readily recognized. Efforts to elevate subjects' status may make participation more attractive and intensify their psychological commitment to study participation and adherence.

Within studies, subjects agree to comply with multiple daily regimen demands (e.g., repeated medications or device use), potentially for years. On a day-to-day basis, some subjects' spend more time engaged in activities in support of investigational objectives than the research personnel who are remunerated for their roles in the research. Subjects' responsibility in following research protocols justifies affording greater recognition of their altruistic roles.

In addition, an argument can be advanced to reward subjects' efforts commensurate with their contributions and risk assumption, by providing more compelling incentives for participating and adhering to protocols. Given the extensive resources already expended by pharmaceutical and device companies on R&D, and their interest in promoting use of effective interventions, incentives (e.g., drug discount coupons following participation) could be offered contingently based on externally verified protocol adherence. This would be akin to how insurance companies provide incentives to enrollees who behave in ways that limit their liability (e.g., lower premiums for non-smokers). It would also reinforce subjects' personal awareness of the broader stakes in achieving studies' scientific objectives and of the goals they share with researchers and sponsoring entities.

Similarly, given the government's interest in promoting R&D and the public health, and in making the research enterprise more cost-effective, it might be possible to offer incentives (e.g., tax deductions or credits; grants akin to the GI bill, subsidies for healthcare or prescriptions) to subjects who adhere closely with regimens in government-sponsored research. Clearly, infrastructure, logistical, legal, attitudinal, and ethical (e.g., privacy, autonomy) [101] challenges would need to be surmounted if this type of approach were to be considered. Such efforts would more fully recognize subjects' courage and commitment in partnering with investigators and sponsors in securing answers to research questions. These broader strategies are consistent with approaches discussed earlier for providing incentives to reward subjects for good adherence [87].

6. Concluding remarks

Subjects' inconsistent adherence to clinical research regimens is a vexing problem that merits further attention. It continues to be a limiting factor to the success and efficiency of clinical trials. Enrollment and completion failures have been considered primary factors delaying drug development [100]. In general, problematic adherence is likely to increase healthcare costs because it decreases the efficacy of treatment and increases the likelihood of treatment failure [102]. By draining resources, including funds and researchers' attention and energy away from their primary focus, problematic adherence retards scientific inquiry and the advancement of knowledge. From a public health perspective, problematic research adherence slows the translation of discoveries into clinical settings where they can realize their potential. Poor adherence contributes to the expense of drugs and ultimately of healthcare, and may needlessly prevent safe and therapeutic compounds from ever reaching patients who might benefit.

Drawing attention to these concerns is intended to pique research sponsors' interest and galvanize researchers' efforts in promoting adherence. This includes supporting research on predicting, promoting, and evaluating research adherence. A broader aspect entails increasing subjects' cognizance of the greater good that comes from their participation and the critical responsibility they assume (i.e., to other subjects and future patients) in advancing scientific innovation. The need to devise better strategies for helping subjects to develop and sustain commitment to adherence in investigative protocols is clear. Ethical considerations in promoting adherence and pursuing research objectives also need to be fully recognized and upheld by stakeholders [103]. Decreasing the prevalence of problematic adherence can promote clinical outcomes, facilitate scientific progress, and mitigate some costs of discovery. The adverse clinical effects of poor adherence, as well as the collective, burgeoning costs of healthcare, poor adherence, and research, heighten the priority for achieving better adherence in clinical research.

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