

COMPLIANCE AND ADHERENCE

Marketplace challenges and solutions



1 THE IMPACT OF POOR ADHERENCE ON CLINICAL TRIALS

THE EFFECT OF CLINICAL TRIAL ADHERENCE ON THE PHARMACEUTICAL INDUSTRY

The level of patient adherence in a clinical trial will have an effect on the outcome of the trial because of the direct influence adherence has on the perception of a drug's efficacy. Simply stated, if patients do not adhere to the trial regimen, it will appear as if the drug is not effective. In turn, the outcome of a clinical trial (the perceived effectiveness of a drug) dictates whether or not the drug will be approved for use as well as the dosing recommendation of a medication when it arrives in the market. This can result in the rejection of a drug that could actually be effective in the market, the approval of a drug that will not be effective under recommended use, under- or over-dosing in the general population, and ineffective treatment of disease in the general population. Therefore, patient adherence in clinical trials affects the overall pharmaceutical market from both a revenue perspective and a patient health/safety perspective.

Poor adherence results in inaccurate data

A consistently high level of adherence is necessary in order to prove that the differences in treatment outcomes are related to the treatment, not to variations in adherence.¹ If the patients in a study participate at varying rates of adherence, the perceived results of the drug's effectiveness will not be consistent.

Partial compliance in clinical trials is common, which creates problems when estimating the magnitude and variability of the effect of the medication.² Any variability that is observed may in fact be a result of the medication's effectiveness, but it may also be a result of inconsistent adherence across the study sample. Without perfect adherence to the trial regimen, it is impossible to tell whether the varying effects are to be expected when using the drug, or whether the effects vary because patients are not taking their medication. Broad variability may result in the need to repeat the trial, or even in the prevention of the drug's market entry.

Inadequate adherence can damage the validity and statistical power of a study¹ and lead to a false-negative decision.³ One of the most important contributors to the variance of reported drug response is nonadherence. Nonadherence can lead to both underestimates of drug response and overestimates of dosage requirements.⁴ Again, if the study cannot claim validity and reliability, the drug may not be approved for use in the market. Additionally, incorrect estimates of dosing requirements may result in the drug entering the market with incorrect dosing recommendations.

The impact of poor adherence on clinical trials is illustrated in Figure 1, as published in Hasford's *Design and Analysis of Clinical Trials of Compliance*.

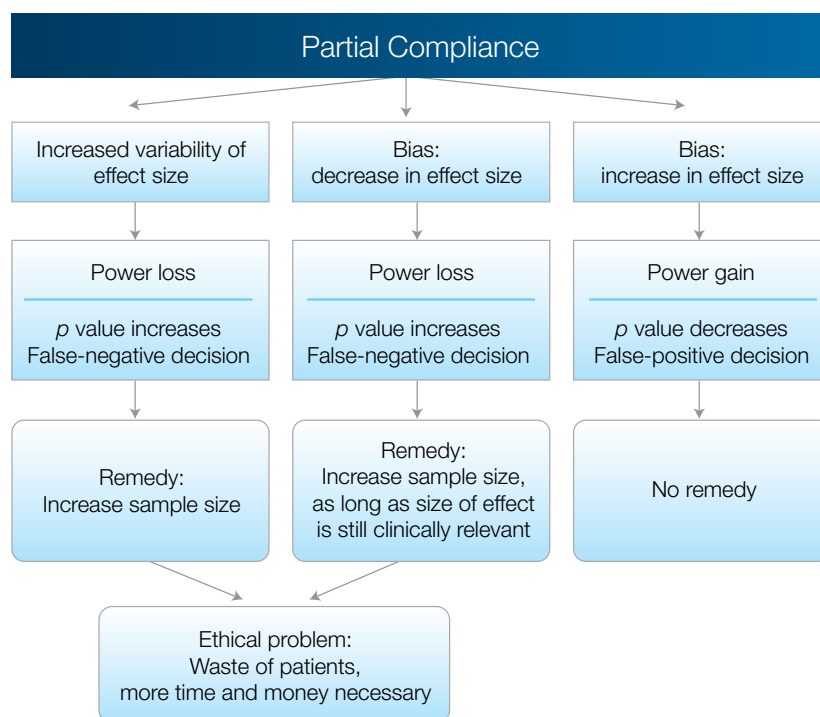


Figure 1. Impact of adherence on clinical trials³

Inaccurate data can result in unexpected outcomes in the market

1. Impact on revenue

It has been estimated that pharmaceutical companies spend from \$802 million⁵ to one billion dollars⁹ bringing one drug to market over 10–15 years. The high cost of research and development contributes to the high cost of prescription medications in the market.⁵ The high cost of some medications creates a barrier to adherence in the market, causing patients to forego treatment. This barrier can result in lost revenues for pharmaceutical companies and pharmacies, higher costs for payers, and increased risk of complications for the patient. Estimates of the pharmaceutical industry's lost revenues due to unfilled prescriptions are close to \$70 billion in the U.S. alone.⁶

The ability of poor adherence to slow or even prevent a drug's arrival to market will also have an effect across the value chain. Poor adherence results in low confidence in efficacy and slows the speed of bringing a drug to market, where the drug is needed and useful. Poor adherence in clinical trials may lead to an incorrect perception that a drug is ineffective and therefore may also prevent useful drugs from reaching the market altogether.¹

The inaccurate data that results from imperfect adherence leads to a misrepresentation of the effectiveness of the drug. Incorrect perception of a drug's efficacy or dosing requirements can continue to create difficulties once the drug has been approved for use in the market. For example, 22% of the drugs entering the market between 1980 and 1999 required significant post-launch dose-adjustments, which is a result of poor understanding of dose effect following a clinical trial.⁷ Drugs are also at risk of being pulled from the market when unexpected effects are seen among a large-scale group.⁸ Pharmaceutical manufacturers are then unable to recover the investment they made in the development of the drug.

Improving adherence in clinical trials will impact revenue through cost savings due to smaller, shorter trials. Estimates of the cost to bring one drug to market are nearly one billion dollars, and a factor in the growth of this number is the increase in the number of patients included in clinical trials.⁹

Improved adherence in trials could reduce cost through reducing the number of participants necessary in a study.^{10,1} A study of a small group of consistently adherent participants has greater statistical power than a study of a larger participant base who are not reliably adherent. In order to achieve 95% confidence in a study with 20% nonadherence, the study would have to increase the number of participants by 50% over the size of a 100% adherent group. This can be illustrated through the findings of an antihypertensive study with 95% confidence based on 100% adherence among a sample of 23 patients. In order to maintain this statistical power at lower levels of adherence, the sample size would need to increase as follows:⁵

The benefits of running a study with fewer people would be staff and site reductions, study duration reductions and lower cost-per-participant. Based on the known costs of drug development, savings due to adherence could be in the billions of dollars.¹

It has been estimated that the cost of monitoring patient adherence is \$11–\$75 per patient, per month. This cost is less than the cost of conducting a second trial to verify the effectiveness of a single medication.^{5,10}

| Rate of adherence | Necessary sample size increase | Percent increase |
|-------------------|--------------------------------|------------------|
| 90% | 5 | 21% |
| 80% | 12 | 52% |
| 70% | 22 | 96% |
| 60% | 38 | 165% |
| 50% | 65 | 283% |

2. Impact on health of patients

The problem of nonadherence creates a need for larger sample sizes in clinical trials in order to achieve validity. Increasing the sample size of a study population not only raises the cost of the study, it also puts more patients at risk by exposing them to a potentially inferior treatment.³ Because a small population of adherent patients is as reliable as a large population of patients with poor adherence, manufacturers should strive to maintain a high level of adherence in trials in order to minimize the population and to reduce the number of participants that are put at risk.

Overestimation of dosing requirements results from underestimating the efficacy of the drug, which occurs due to the presence of nonadherent patients in the sample.¹² The overestimation of drug dosing requirements may then lead to excessive dosing and adverse effects among the general population once the drug is approved for use in the market.¹

Additionally, drug toxicity may be underestimated due to nonadherence. The information contained on medication labels is included based on the data received from the clinical trial. If this data is inaccurate, the results seen and/or felt by patients will not be consistent with the information on the label.^{12,8} A lack of results will cause patients to discontinue treatment. Excessive dosing can harm patients by increasing side effects, while under-dosing will not effectively manage the patient's condition. Under-dosing may also lead to adverse effects due to the spread of drug-resistant mutations of bacteria and viruses.²

ADHERENCE TO TREATMENT IN CLINICAL TRIALS IS POOR

The problem of poor adherence in clinical trials was recognized as early as 1957, when Dixon *et al.* reported that the results of their trial of oral chemotherapy medication were “probably built on very unsure foundations.” Dixon went on to say that “However carefully they were controlled statistically and scientifically, the results may have been vitiated by inadequate consumption of prescribed drugs.”³

Approximately 25–50% of research participants are not adherent. Mean adherence rates to specific activities in clinical trials are as follows: appointment keeping, 39%; short-term medication taking, 62%; long-term medication taking, 63%.¹

Nonadherence can take on one of, or a combination of, four different forms:⁸

- Taking more medicine than prescribed
- Taking less medicine than prescribed
- Taking medication at time of day or time intervals other than prescribed
- Taking medication in conditions other than prescribed (with or without meals, etc.)

REASONS FOR POOR ADHERENCE IN CLINICAL TRIALS

The typical reasons for nonadherence in clinical trials are similar to the reasons that patients do not adhere to treatment in the general population. Patients’ decisions are driven by a range of needs, from functional needs such as reduced costs, to emotional needs, such as inspiration and motivation. These needs are illustrated in Figure 2.

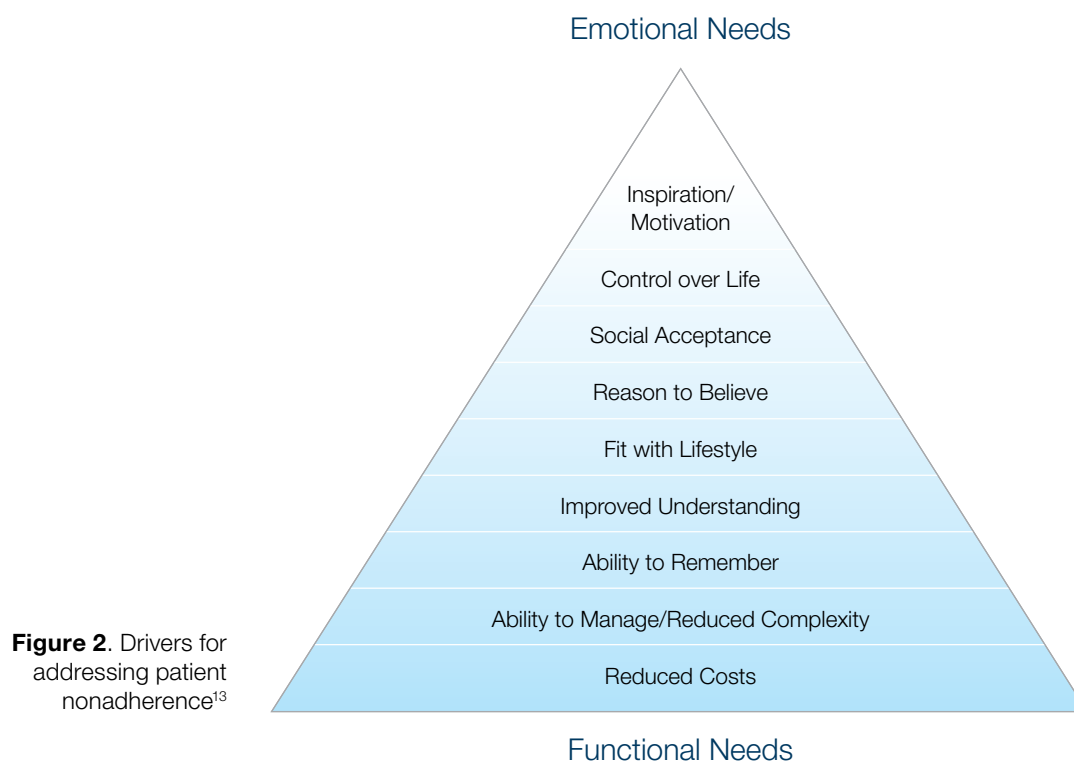


Figure 2. Drivers for addressing patient nonadherence¹³

The reasons and drivers for patient nonadherence in clinical trials are listed below in relation to patient needs.

- Lack of social support¹
- Negative external influences¹⁴
- Patient confidence in physician¹⁵
- Poor relationships with trial staff¹⁴
- Effectiveness/noticeable improvement⁸
- Unrealistic protocol demands¹⁴
- Fear of adverse effects²
- Lack of understanding of the importance of adherence⁸
- Type of disease¹⁵
- Profession¹⁵
- Income¹⁵
- Education level¹⁵
- Complex treatment regimens^{1,15}
- Multiple medications¹⁵
- Logistical challenges, such as lack of transportation¹⁴

Emotional



Functional

Emotional drivers, such as a lack of social support or poor confidence in the physician, tend to influence intentional nonadherence. For example, in a clinical trial a patient may believe (correctly or incorrectly) that he is receiving a placebo, lose the reason to believe that there is a personal benefit for continuing treatment, and decide to stop taking the scheduled dose. Additionally, friends and family may discourage a patient from participating in a clinical trial for fear of the negative effects of a trial drug.

Functional drivers, such as ability to remember and complexity, tend to influence unintentional nonadherence. Many patients may simply forget to take a scheduled dose, or they may forget specific dosing instructions such as time of day or mealtime instructions.

2 DESCRIPTION OF THE SOLUTION

BLISTER PACKAGING IS A SOLUTION FOR POOR ADHERENCE

A potential solution to the problem of nonadherence in clinical trials is a paperboard case that houses a fold-over inner blister card designed specifically to improve adherence. Blister packaging addresses key drivers of nonadherence, including complexity, ability to remember, improved understanding, fit with lifestyle and social acceptance.

The outer paperboard case encloses the pill blister and makes the medication easier to manage than a vial. Opening the outer package and dispensing medication from the blister can be performed by an adult with ease.

The blister package fits nearly any patient's lifestyle because it is easy to use and easy to transport, and the outer paperboard case is more attractive than a typical pill container.

In addition to addressing basic drivers of patient adherence, the blister package is available in varying levels of child resistance, including F1. The blister package also meets senior-friendly testing protocols.

The blister package is low cost and easily scalable, further adding to cost savings for stakeholders.

Calendaring

The calendar blister indicates by date and/or time which medications should be taken. The package serves as a visual aid, making it easier for the patient to remember when to take their medication and recognize whether or not they have taken a scheduled dose. This unit dose format, allowing the patient to view the correct dose or timing, makes blisters an effective adherence tool.²

Many study participants are accustomed to and prefer pill organizers over pill bottles. These patients will remove all of the pills from the bottle (even if it is electronically monitored) and transfer them to an organizer in order to keep track of dosing.¹⁵ Unlike a pill organizer box that the patient loads himself, the prepackaged blister provides reassurance that the right medications are contained within. The combination of the blister's seal and the outer carton also protects the integrity of the medications and prevents spilling, resulting in fewer lost doses.

Education/communication on package

In addition to the instructional area on the blister itself, the paperboard case also contains a great deal of billboard and communication space, aiding in patient understanding of the regimen. In addition to providing dosing instructions, the space can be used to reinforce why full participation in the trial is important and impactful. A large, fold-out panel displays all relevant information and ensures that detailed instructions stay with the package. This, combined with the portability of the package, makes transporting both medication and instructions easy for the patient, decreasing the likelihood of missed doses.

An instructional leaflet in a blister package is a value-added feature.² Clinicians have had success with the detailed instructions included with oral contraceptives. It has been recommended that all chronic-use medications should adopt this type of informational addition to the packaging in order to mitigate the widespread problem of nonadherence.⁸

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- ⁶ Datamonitor
- ⁷ Kenna, L. & Sheiner, L. (2004). Estimating treatment effect in the presence of non-compliance measured with error: precision and robustness of data analysis methods. *Statistics in Medicine*, 23, 3561-3580.
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- ¹⁵ Metry, J. (1999). Measuring compliance in clinical trials and ambulatory care. In J. Metry & U.A. Meyer (Eds.), *Drug Regimen Compliance: Issues in Clinical Trial and Patient Management* (pp.23-40). Chichester, West Sussex: John Wiley & Sons.