CLINICAL LEADER

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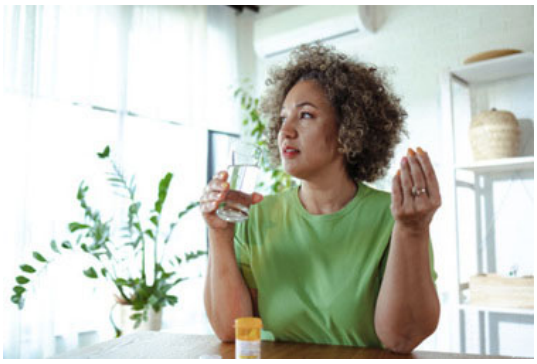
Understanding The Effects Of Non-Adherence To Treatment In Clinical Trials

By Aad R. Liefveld, team member of the BEAMER project



Despite the often-devastating negative effects nonadherence to treatment can have on society and the many benefits of helping patients optimize their adherence behavior, the speed and efforts organizations are putting into improving adherence are lower than expected.

To better understand and improve adherence behavior, the BEAMER[1] project (grant agreement number 101034369) was initiated by the Innovative Medicines Initiative 2 Joint Undertaking (IMI2)[2], a public-private partnership between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA)[3] under the Horizon 2020 program, and IMI associated partner Link2Trials.

With this two-part series of articles, I hope to clarify why it makes sense to adopt and implement already available innovative solutions to improve adherence behavior today, and not tomorrow. In part one, I will identify the severity of the issue, as it concerns both public health and pharmaceutical company finances and describe the conditions that contribute to nonadherence to treatment. In part two, I will explore the benefits of adherence to treatment for patients, payers, and regulators, as well as offer ways to improve adherence behavior now.

Billions Of Reasons To Improve Adherence

Adherence to treatment is the process in which the patient engages in a health, technology, or medication-enabled treatment, which was discussed and agreed upon together with a healthcare professional. Adherence includes meeting the following conditions that are relevant to the treatment[4]:

1. Taking prescribed medication correctly at the minimum clinical threshold agreed upon, including initiation, dosage, and persistence; and
2. Carrying out recommended health behaviors such as attending follow-up appointments and/or implementing lifestyle changes (e.g., avoiding certain foods or engaging in specific exercise), at the minimum clinical threshold agreed upon.

Nonadherence is related to 200,000 premature deaths yearly in the EU[5], which causes patients to suffer and places a significant burden on healthcare systems. The annual costs in Europe of avoidable hospitalizations, emergency care, and adult outpatient visits are assessed at 125 billion euros and similar figures exist for other regions in the world.

According to a 2018 study[6], the medical costs of "prescription drug-related morbidity and mortality from non-optimized medication therapy" is estimated at between $495 billion and $673 billion each year for the U.S. healthcare system. This includes the direct costs of treating complications from nonadherence, such as hospitalizations, emergency room visits, and physician visits, as well as the indirect costs of lost productivity and premature death.

For example, a 2012 study[7] found that medication nonadherence in diabetes is associated with a 37% lower pharmacy cost and a 7% lower outpatient cost but also with a 41% higher inpatient cost. Similarly, a 2011 study[8] found that patients with heart disease who were nonadherent to their medication were two times more likely to be hospitalized than those who were adherent.

These numbers are about healthcare costs, but when we include the economic and other costs of sick days, it is obvious that the overall societal costs are even higher. In 2010, the European Foundation for the Improvement of Living and Working Conditions estimated the cost of absence from work at 2.5%[9] of the GDP per year, equaling $392 billion when extrapolated based on 2019 figures. For that same year, the Integrated Benefits Institute estimated the annual cost for the U.S. of poor health in the workplace at $575 billion[10]!

Improving adherence to treatment can help reduce the need for more expensive care, such as hospitalizations and emergency room visits. When patients follow their treatment as prescribed, they are more likely to control their chronic conditions and avoid complications. This can lead to significant savings for patients, the healthcare system, and our society.

Nonadherence Also Happens In Clinical Trials

When talking about adherence, the focus is usually on clinical care, as it is a less controlled and often more complex situation (multi-condition and polypharmacy), but avoidable nonadherent behavior also exists in clinical trials. Across all conditions and depending on the stage of the condition and the type of trial, the early dropout (an extreme form of nonadherence) rate is substantial and can be as high as 30%[11]. At the same time, almost 70%[12] of the protocol deviations in clinical trials can potentially be linked to patient behavior.

When patients do not take their medications as prescribed it can make it difficult, if not impossible, to assess the true efficacy and safety of the treatment being studied[13, 14, 15]. Poor adherence to treatment can lead to various problems in clinical trials, including:

- If patients are not taking their medication as prescribed, they are less likely to experience the benefits of the treatment. This can lead to an underestimation of the treatment's true efficacy and effectiveness.
- If patients are not taking their medication as prescribed, they are less likely to experience the side effects of the treatment. This can lead to an overestimation of the treatment's true safety.
- If adherence to treatment is not carefully monitored, it can be difficult to interpret the results, which will influence the statistical power of the trial. For example, if a treatment is more effective than the control arm, but adherence to treatment is lower in the treatment arm, it can be difficult to determine whether the difference in efficacy is due to the treatment itself or to the difference in adherence.

Clinical trials involve patients, and their behavior is essential to the outcome of clinical trials. For this reason, it is important that the trial staff take steps to keep patient adherence to treatment as high as possible and monitor patient behavior closely throughout the trial.

Clinical Trials At Risk Of Low Adherence To Treatment

Not every clinical trial is at risk of low adherence, but it is likely it will surface in:

- Trials with complex medication regimens
- Trials with long-term treatment durations
- Trials with high-cost medications
- Trials with medications that have side effects
- Trials with participants who have low motivation to adhere to treatment
- Trials with adjuvant treatments where the condition has been treated successfully and patients are only at risk of recurrence

For example, a trial of a new drug for HIV treatment that requires patients to take multiple pills per day and has a high risk of side effects is more likely to have low adherence to treatment than a trial of a new drug for the common cold that requires patients to take one pill per day and has few side effects.

Other factors that can increase the risk of low adherence to treatment in clinical trials include:

- Lack of meaningful communication between trial staff and participants
- Cultural differences
- Language barriers
- Lack of transportation to trial visits
- Lack of financial aid for copayments and other costs of treatment

The Effects Of Nonadherence In Clinical Trials

The effects of nonadherence in clinical trials can include:

- Increased costs of recruiting and retaining participants:
  - When patients are nonadherent, they may need to be replaced in the trial, which can increase the cost of recruitment and retention.
- Increased costs of conducting the trial:
  - Nonadherence can lead to longer trial durations and higher data collection costs.
  - To mitigate the risks of nonadherence, trials tend to overenroll, leading to higher costs.

- Reduced statistical power:
  - Nonadherence can reduce the statistical power of the trial, making it more difficult to detect meaningful differences between the treatment and control groups.
- Increased risk of misleading results:
  - Nonadherence can lead to misleading results, making it difficult to draw accurate conclusions about the safety and efficacy of the treatment being studied.

While the first two may seem high, they can be managed and contained. However, the last two are much more worrying.

The effects and risks of reduced statistical power and misleading results in clinical trials can be exceedingly high. The costs caused by reduced statistical power and misleading results in clinical trials will vary depending on the trial in question. However, they can be significant, both in terms of financial resources and human health.

Reduced statistical power means that a trial is less likely to detect a true difference between the treatment and control groups, even if one exists. This can lead to the trial concluding that the treatment is not effective, when in fact it is.

When a trial's findings are not accurate due to nonadherence, other factors, or chance, it can lead to misleading results and the trial may conclude that the treatment is effective or safe, when in fact it is not.

Reduced statistical power and misleading results in clinical trials also influence the costs related to:

- Wasted resources:
  - Clinical trials are expensive and time-consuming to conduct. When a trial produces misleading results, the resources invested in the trial are wasted.
- Delayed development of new treatments:
  - When a trial fails to detect a true difference between the treatment and control groups, it can delay the development of a new and potentially beneficial treatment.
- Harm to patients:
  - If a trial concludes that a treatment is safe and effective, when in fact it is not, patients may be harmed by following that treatment.

The above can lead to much higher costs than foreseen for the affected clinical trials, and it is important to take steps to ensure that trials are well-designed and properly conducted. This includes calculating the appropriate sample size and using rigorous statistical methods to analyze the data. It is also important to monitor adherence to treatment closely and to report the results of the trial in a transparent and correct manner.

In part two of this series on patient adherence, discover the upsides to better patient adherence in clinical trials and practice, as well as the perks of better adherence for regulators and payers and tips for improving adherence in your next trial.

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About The Author:

Aad R. Liefveld is a member of the BEAMER project team and a member of the advisory board at Link2Trials. He has over 30 years of management experience across multiple industries and is a strong advocate of patient centricity and patient experience. Together with Prof. Dr. Sjaak Bloem (Nyenrode Business University), Aad has developed the Adherence Risk Management Services for Link2Trials to improve patient adherence behavior during clinical trials.

For more information, follow the BEAMER project on LinkedIn.