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Medication Adherence: Landscape, Strategies, and Evaluation Methods

Washington, DC | December 10, 2019

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Executive Summary

Medication adherence—the extent to which patients take medications as prescribed in agreement with their health care providers—is essential for ensuring the safe and effective use of therapies to prevent and treat disease. Although the prevalence of medication non-adherence varies by disease and condition, increased adherence can improve health and reduce economic burden due to health conditions. Numerous strategies, including innovative tools and technologies, are used to assess and enhance medication adherence, with variable success. On December 10, 2019, the Duke-Robert J. Margolis, MD, Center for Health Policy at Duke University, under a cooperative agreement with the U.S. Food and Drug Administration (FDA), convened a public meeting to explore the state of the science of clinical research evaluating adherence to FDA-regulated medical products. **This meeting summary presents key takeaways from the discussion and serves as a reference for stakeholders interested in understanding the state of the science related to medication adherence.**

The meeting's four sessions addressed (i) barriers to medication adherence, (ii) interventions to track and improve adherence, (iii) measures of adherence, and (iv) study designs to evaluate interventions intended to track adherence, improve adherence, or improve clinical outcomes secondary to increased adherence. In session one, discussion focused on the many factors contributing to medication non-adherence. Session two discussed trends in interventions to track and improve medication adherence. Session three covered methods and measures to evaluate medication adherence. Session four explored study designs for evaluating adherence interventions (including randomized controlled trials and pragmatic trials) and design features for assessing a causal link between interventions and adherence outcomes, as well as interventions and clinical outcomes. The following key takeaways emerged from the meeting discussion:

1. Medication adherence can be evaluated at the individual and population levels. Interventions tailored to the individual level can directly address the barriers experienced by each patient.

2. Numerous medication adherence interventions exist, including innovative technologies, but challenges remain when evaluating and translating the impact of interventions to routine clinical settings. These challenges involve study design considerations, including criteria for subject selection and measures of adherence.

3. Medication adherence encompasses a wide range of behaviors, and using standardized terminology is therefore essential to understanding the impact of interventions on medication adherence and clinical outcomes. The appropriateness of measurements of medication adherence will depend on the medication-taking behavior being studied. Clinically acceptable adherence thresholds will vary depending on the disease or condition as well as medication characteristics (e.g., drug forgiveness). Accordingly, considering only one threshold for adherence (e.g., 80%) to evaluate treatment benefit may not be appropriate.

4. When conducting adherence intervention studies, features of pragmatic clinical trials may be useful. For example, trials can be designed to enroll at-risk patients and assess clinically relevant outcomes over longer study periods, to identify durable effects.

Public Meeting Summary

Introduction and Overview of Medication Adherence

Medication adherence—the extent to which patients take medications as prescribed in agreement with their health care providers—is essential for ensuring the safe and effective use of therapies to prevent and treat disease. Adherence is a function of complex and dynamic behaviors influenced by an array of factors related to patients, providers, and health care systems. Such factors include, but are not limited to, treatment regimen complexity and cost, health literacy, and the extent and effectiveness of communication between patients and health care providers. Optimal medication adherence can improve health outcomes for individual patients and can also improve population-level health by reducing health care utilization, infectious disease transmission, and drug resistance.

On December 10, 2019, the Duke-Robert J. Margolis, MD, Center for Health Policy at Duke University, under a cooperative agreement with the U.S. Food and Drug Administration (FDA), convened a public meeting to explore the state of the science of medication adherence research with FDA-regulated products. Specific topics of discussion included:

(a) the landscape of interventions intended to track or improve medication adherence and clinical outcomes secondary to improved medication adherence;
(b) methods of measuring medication adherence; and,
(c) study designs to evaluate interventions intended to improve adherence, with or without an impact on relevant clinical outcomes.

This paper summarizes the public meeting, presents key takeaways, and serves as a reference to stakeholders interested in understanding the state of the science related to medication adherence.

Key concepts and terms

The meeting began with an overview of medication adherence including key concepts and terminology.

In 2003, the World Health Organization defined adherence as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider."[1] This concept of deviation from prescribed medication was originally described as "compliance." Discussion at the meeting noted that the term "adherence" has replaced compliance, given that compliance implies patient passivity rather than active agreement with the recommendations from the health care provider.

Another term that has been used to describe medication-taking behavior is concordance. Concordance implies agreement, trust, and harmony between patient and doctor regarding treatment, and acknowledges the patient as a decision-maker. Professional empathy is a cornerstone of this component.[2]

To describe the complex nature of adherence and the range of behaviors it encompasses, academic groups have developed taxonomies related to medication adherence. One such taxonomy, developed by the Ascertaining Barriers for Compliance (ABC) project,[3] breaks down adherence behavior by identifying four attributes:

- initiation: starting a recommended medication
- implementation: executing the prescribed dosage as scheduled

- persistence: length of time between initiation and discontinuation
- discontinuation: stopping a recommended medication

While reviewing taxonomies and key terms, an important distinction was raised regarding the difference between a single patient and a patient population. Generally, and although health care system-level policies may impact different patients in different ways, adherence was discussed from the perspective of a single patient's behavior.

Session I: Key Barriers to Effective Medication Adherence

The first session considered key barriers to effective medication adherence, particularly related to chronic medications. Such barriers can arise at the level of patients, health care providers, or health care systems; specific challenges can include complex treatment regimens, comorbid conditions (e.g., depression), ineffective communication between clinicians and patients, costs of medications, and limited health literacy.

Factors that contribute to medication non-adherence

Non-adherence is driven by a range of factors and is not simply a matter of patients forgetting to take their medication. Research has demonstrated that patient forgetfulness drives only (approximately) 30% of non-adherence[4] and cannot be reliably predicted by any single demographic characteristic.[5]

Stakeholders throughout the session proposed frameworks and structures to characterize barriers to adherence. One categorization separated barriers into unintentional barriers (including forgetfulness, work schedules, access, confusion, and work restriction) and intentional barriers (including mistrust, fear of side effects, lack of belief in efficacy, fear of dependency, lack of desire, and altruism). Another stakeholder discussed classifying barriers according to six "adherence phenotypes," characterized by cognitive, psychological, medical, regimen, social, and economic factors.

Identifying factors contributing to non-adherence is important because each patient may have unique reasons motiving their non-adherence. Understanding these factors and a patient's individual context may influence the type of intervention delivered. For example, it may not be effective to send daily text message reminders to patients who cannot afford to fill prescriptions. Understanding the range of barriers to adherence might also explain why interventions tested in large randomized controlled trials (RCTs), such as HeartStrong[6] and REMIND[7], did not improve adherence. Although these interventions were potentially helpful to patients whose non-adherence could be attributed to forgetfulness, the interventions may have been ineffective for patients whose non-adherence was not caused by a need for reminders. This example underscores the point that an effective intervention should address the underlying factor of non-adherence in individual patients.

Lack of trust as a barrier to adherence

Discussion put particular emphasis on the role of trust between the patient and health care provider as a key component of adherence. Historically, some providers may have shamed patients for not taking medications as prescribed. In addition, video interviews of patients (played during the session) indicated that doctors' yes-or-no questions did not allow patients to explore nuances of their medication-taking behavior. Patients reported not taking medications because they did not fully understand the health benefits. Talking with providers about their confusion helped these patients better understand their

medications and alleviated some of their concerns. When patients trust their health care providers, patients may be more forthcoming about their concerns.

Educating providers about barriers to adherence and creating time for providers to have open conversations with patients about their medications can help build trust. A patient advocate shared an anecdote about a medication that caused undesired side effects. When the patient had a provider who did not listen to his concerns, the patient discontinued the medication. When the patient found a provider willing to address the side-effects, the patient remained adherent. The advocate emphasized that sometimes non-adherence occurs because products fail patients.

Lack of motivation as a barrier to adherence

Barriers to adherence were also discussed with regard to behavioral economics, which posits that people do not always make choices in their own best interest, and gaps exist between a person's intention and behavior. These gaps may be a result of "present bias," a core cognitive bias where a person's behavior is motivated by instant and tangible gratification and not by what the person rationally knows is beneficial for them. Present bias potentially explains why patients are more likely to be adherent to stimulants than to other types of medications (e.g., chronic disease medications); the patient perceives an immediate benefit from taking the stimulant but not from a medication with long-term protective effects. A related concept to present bias is "hyperbolic discounting," referring to the idea that when assessing the costs and benefits of a behavior, people consider future outcomes less important than present outcomes.

Several examples were discussed regarding how to address motivational barriers using behavioral economic principles. Interventions are being developed in which patients are paid upfront to download an app to their mobile phones and take pictures of their medication in their hands each day. These financial incentives can help motivate patients to be adherent and form habits for taking their long-term medications.

Health care systems-level barriers to adherence

Although many of the barriers to adherence may be unique to individual patients, barriers can also occur at a health care systems level. Pharmacy deserts (locations where there are limited pharmacies), refill asynchronization, and poor care coordination were identified as health care systems-level barriers that make it more difficult for patients to adhere to their prescribed medication regimens.

Both pharmacy deserts and a lack of refill synchronization increase patient burden for picking up prescriptions. Pharmacy deserts make it difficult for patients to fill prescriptions, particularly in areas where patients do not have access to reliable transportation. Patients taking multiple medications often do not have their prescription refills synchronized to the same day of the month, thus increasing the burden of picking up refills. Additionally, some medications for chronic conditions are only dispensed 30 days at a time. Allowing a larger quantity of medication to be dispensed at one time, and to be dispensed at the same time for all chronic medications a patient is taking, would decrease the burden of frequently picking up medications.

Stakeholders emphasized that the entire health care team—physicians, nurses, and pharmacists—is responsible for medication adherence, but that coordinating patient care and educating patients can be challenging. Pharmacists are well-positioned to interact with patients and answer questions about medications, but time constraints arising from other core responsibilities (e.g., filling the prescriptions), and lack of access to a patient's health information limit pharmacists' ability to address medication

adherence. Care coordination is particularly challenging in the case of polypharmacy; patients are prescribed medications from different specialists, without a plan for how to manage all their concomitant prescriptions. Also, patients can receive medications from multiple pharmacies—such as community, mail-order, and specialty pharmacies—contributing to the complexity of care coordination.

Considerations at the level of the health care systems also impact strategies to address barriers to medication adherence. Regulations regarding prescriptions and pharmacies vary between states, making it difficult to implement large-scale policy changes. Challenges also exist regarding the funding of adherence research. Stakeholders called for additional real-world adherence implementation research, but noted that the traditional, multi-year academic grant-award process does not readily support such studies.

Session II: Interventions to Track and/or Improve Medication Adherence

Discussion considered the current landscape of existing interventions and explored developments to track or improve medication adherence. Many approaches have been employed to improve adherence of FDA-regulated products, including patient education, reminders, simplifying medication regimens (e.g., switching to single pill combination therapies), and cognitive behavioral therapy. Recent advances have involved technological approaches, including sensors that detect pill ingestion or administration of medication, and mobile applications that provide reminders and tailored feedback about medication use.

Current trends in medication adherence interventions

Patient perspectives and cultural competency

Understanding the needs of specific patients is crucial when designing interventions to improve adherence and, as such, this issue was discussed in different contexts throughout the session. Many interventional approaches exist; a key feature of all approaches hinges on identifying needs and barriers to non-adherence on an individual or sub-population level. The interventions discussed included patient-driven medication regimens, culturally sensitive engagement, and behavior-oriented interventions.

Patient-driven medication regimens—including medication therapy management, refill synchronization, changes to medical product formulations (e.g., extended release pills), changes to the route of administration (e.g., patches, chewable tablets), and combination therapies—were highlighted as current strategies to reduce medication-taking burden. In this context, patient-focused drug development was also discussed as an important tool that might be employed throughout the drug development process, to acknowledge patient preferences surrounding medication-taking behaviors.

Interventions focused on cultural competence and engaging patient communities—especially for hard-to-reach populations—was another topic of discussion. An example provided was the Health Advocates In-Reach and Research (HAIR) program administered through the University of Maryland Center for Health Equity, which partnered with barbershops to convey health information to African American men in a community setting. The HAIR effort included bringing pharmacists to barbershops to address questions and concerns about medications. A key feature of success for this type of intervention is the trust established by engaging patients outside of the health care system, in settings where they might feel more comfortable receiving information about medications.

Case studies of adherence interventions

Adherence to blood pressure, cholesterol, and oral diabetes drugs became part of Medicare Advantage and Part D plan star ratings in 2011. In these measures, adherence is a binary outcome: a patient is considered adherent if, during a calendar year, they have a proportion of days covered (PDC) of 80% and filled their prescription in two or more months. With this new incentive to improve adherence, health plans began hiring companies, such as RxAnte, to develop and deploy interventions intended to promote adherence.

RxAnte shared data on the effectiveness of four interventions that were deployed. The first intervention involved licensed pharmacists calling 16,644 patients identified as being at risk of being non-adherent, and then answering patient questions. After conducting a difference-in-difference analysis,[a] RxAnte reported a 7.4% "lift" in adherence. The second intervention, involving interactive voice response calls ("robocalls") with refill reminders, was deployed to 91,829 patients with higher predicted likelihood of being adherent at baseline, and resulted in a 3.4% increase in adherence rates. The third intervention involved financial incentives to physicians to improve adherence in 253,011 patients. Even in the most engaged group of physicians, a modest 4.5% increase in adherence rates was found. Similarly, in another study involving financial incentives to pharmacies, the maximum adherence improvement for any disease area was 2% in a highly engaged pharmacy compared to a moderately engaged pharmacy. RxAnte hypothesized that some of its interventions were not as impactful as anticipated because they did not account for differences in adherence barriers. The interventions were more successful for patients experiencing certain barriers (e.g., transportation, cost, forgetfulness, confusion) compared to others (e.g., side effects, changes in dosage).

Results of a trial involving financial incentives to 1,503 patients and 238 primary care providers, sponsored by the University of Pennsylvania, were also discussed. The trial had four arms: control, patient incentives, physician incentives, and shared incentives at half-value (i.e., 50% each). A statistically significant difference in low-density lipoprotein cholesterol (LDL-C) reduction was found only in the shared incentive group when compared to the control group. Even though both groups had smaller incentives, researchers contributed the finding that using shared financial incentives between providers and patients was necessary to shift motivations and drive change because adherence involves behaviors by both parties—doctors prescribing medications and patients taking the medication.[8]

Other patient-focused approaches, based on behavioral economic principles, to address individual patient needs were considered during the discussion, including:

- Regret lottery: Every day, a lottery is held to determine which patient receives a monetary reward. If a patient's number is drawn on a particular day, they receive the reward only if they performed the behavior (i.e., took their medication) the previous day. This design uses feelings of loss and regret to incentivize adherence.
- Deposit contracts: This approach takes at least two forms. In one, patients deposit money and get the money back (along with an additional bonus) if they are adherent. In another, patients receive money upfront and can keep the full amount if they reach a goal. Both forms rely on the tendency for people to display "loss aversion" (i.e., be unwilling to lose money).

[a] When conducting the difference-in-difference analysis, RxAnte compared the difference in the *predicted* adherence level for two groups (patients who were reached and receptive to the intervention and patients who were not reached) with the difference in the *year-end* adherence levels for the two groups.

- Social incentives: Family members receive text message reminders about the patient's non-adherence; the family members can then contact patients, providing additional accountability.

Current challenges when implementing and testing interventions

Despite recent innovations in medication adherence interventions, challenges remain when translating the interventions to routine clinical settings. Although some of these issues are rooted in study design, stakeholders focused on implementation challenges, including subject selection, measurement, implementation, and impact.

Implementing interventions in the "wrong" patient population was identified as a reason an intervention may fail. Several trials were discussed that further underscored the reasons for these failures, including recruitment of patient populations that may already have a high baseline of adherence. Stakeholders highlighted the need for trial enrichment that targets patient populations who may have a lower adherence rate, to ensure that appropriate populations are being studied. Another challenge is the "white-coat" or "Hawthorne" effect.[9] It can be challenging to accurately measure adherence during trials, given that patients feel obligated to take the medications when they are being watched and monitored. As one scenario, interventions such as electronic pill bottles, if given to patients in a control arm of a trial when assessing other interventions to improve adherence, can have an effect of making the control arm more adherent.

Given the complexity and range of medication-taking behaviors, interventions must be scalable to larger populations and durable over an extended period to demonstrate a meaningful effect. This process can be challenging, and opportunities to leverage implementation science were raised as a way to promote the adoption and integration of evidence-based practices, interventions, and policies into routine health care and public health settings. Some adherence interventions may have only a small quantitative impact, such as increasing the number of adherent patients by 5%, yet in highly prevalent, chronic conditions, 5% may be considered a meaningful improvement. Gathering robust population-level data on adherence will help better-characterize the clinical impact of changes in adherence rate.

Session III: Measuring and Evaluating Medication Adherence

The third session discussed measurements of medication adherence, potential best practices across different conditions, and how measurements assess the impact of adherence improvements on clinical outcomes. Methods for measuring adherence vary in their accuracy and the ease with which they can be assessed. Direct measures of adherence, such as observing patients ingesting medication, can be more accurate, but may not be feasible for use in studies with large populations. Indirect measures of adherence, such as patient self-reporting, can overestimate levels of adherence.

Medication adherence terminology

Stakeholders emphasized the importance of identifying the medication-taking behavior of interest when measuring or evaluating adherence. Currently, multiple taxonomies and varying definitions of these terms exist, which makes assessing literature reviews and understanding the current state of science challenging. Using precise, consistent terminology can provide relevant context around the intervention employed and generate more meaningful results. The meeting discussion focused on selected components of medication-taking behaviors, as articulated in the ABC taxonomy[3] mentioned previously: initiation (starting a recommended medication); implementation (executing the drug-dosing regimen); persistence (length of time between initiation and discontinuation); and discontinuation (stopping a

recommended medication). Other taxonomies of adherence may also be considered for use in this context.

Commonly used measures of adherence or non-adherence

Researchers typically categorize measures of medication adherence as objective or subjective, depending on the underlying data source. Objective measures often rely on data generated from health system encounters, such as direct observations of the patient during medication administration, pharmacy dispensation derived from claims data, and clinical data in the patient's health record such as biomarkers, drug levels, or drug metabolite levels. Subjective measures include patient self-reports of medication-taking behaviors.

Although numerous measures of medication adherence exist, no single measure is considered optimal. For example, an examination of National Institutes of Health (NIH) grants designed to study adherence behavior funded from fiscal year 2017 to fiscal year 2019 found that many studies included multiple measurements of adherence, and that measures involving self-report and electronic-monitoring, such as Medication Event Monitoring System (MEMS) caps, were used most commonly. Objective measures of adherence were discussed as possibly more accurate than patient self-reports, but such measures are often more expensive and potentially challenging to employ in real-world settings; in addition, some drugs do not yet have well-studied biomarkers to assess adherence.

Stakeholders also emphasized that the appropriateness of an adherence measurement approach depends in part on the medication-taking behavior being studied. For example, findings from a survey of adherence researchers regarding approaches to measuring non-adherence behaviors showed that the most commonly rated approach deemed "at least somewhat suitable" or better for detecting when patients do not fill their initial prescription was prescription-fill data. In contrast, compared to other measurement approaches, electronic-monitoring was most often rated "at least somewhat suitable" or better for measuring missed doses.[10] Also, the appropriateness of measures of medication adherence may vary depending on the study design. In the conduct of clinical trials, one stakeholder recommended the use of electronic monitoring to assess all components of medication adherence according to the ABC taxonomy. For studies conducted in a routine clinical setting, the same stakeholder recommended that electronic monitoring assess implementation while prescription fill data assess initiation and persistence.

A portion of the discussion focused specifically on calculated measures of medication adherence involving prescription fill data: medication possession ratio (MPR) and proportion of days covered (PDC). These measures leverage an existing data source (pharmacy claims data), do not rely on the existence of biomarkers, and can be applied in the case of polypharmacy. MPR is the number of days of supply that the patient has in a particular time period, divided by the number of days in the time period. PDC is similar to MPR but considers the number of days that are "covered" in a given time period—a day is considered covered if a patient has the drug on hand. Of note, PDC is used by Centers for Medicare and Medicaid Services (CMS) quality rating system that directly reimburses care services rendered to improve medication adherence.

Despite the widespread use of MPR and PDC in adherence research, adherence measures derived from prescription fill data have limitations. For example, prescription fill data do not comprehensively capture medication adherence, because the corresponding information does not indicate whether the patient took the dispensed medication as prescribed. In addition, pharmacy claims data can be fragmented and are not always provided to researchers in a timely manner. One stakeholder provided an anecdote of

spending upwards of 30 minutes on calls to determine whether a prescription had been filled given the partial information available in the patient's record. Finally, claims data do not always link the medication dispensed for a patient's specific diagnoses. For example, beta-blockers are indicated for the treatment of multiple conditions, including hypertension, heart failure, and irregular heart rhythm. Without additional information, it may be difficult to categorize the reason a patient was prescribed beta-blockers, making analysis of condition-specific adherence difficult.

To address data delays and fragmentation, stakeholders are increasingly incorporating digital health data captured by mobile devices and other smart technologies. For example, adherence can be monitored in real-time through data captured by electronic pill bottles that record the time and date each time the bottle is opened and closed, or by data captured by sensors ingested with the medication. These new technologies may provide more objective measures of adherence, but they are not without implementation challenges. For example, researchers face difficulties with the large volume of data generated and with integration into existing analyses.

Thresholds to assess the effectiveness of medication adherence interventions

Another key topic centered on identifying an appropriate level of adherence to assess the effectiveness of an intervention. Although many studies use 80% as a threshold indicative of adherence, speakers suggested that appropriate thresholds depend on the therapeutic area of interest and medication characteristics. The optimal threshold for adherence can therefore differ across medication classes as well as individual patients. For example, the level of adherence needed to optimize virologic and clinical outcomes for treatment of human immunodeficiency virus (HIV) infection was at one point considered to be 95% or greater. As antiretroviral therapies have grown more potent, new studies report the threshold to be approximately 80%.[11] Similarly, new drugs coming to the market might lack baseline information on adherence. More data should be collected during the drug development process to help set appropriate thresholds and parameters for assessing adherence.

One characteristic effecting appropriate adherence thresholds is drug "forgiveness," which is the difference between the duration of action and the prescribed dosing interval. In other words, drug forgiveness reflects the extent to which medication-taking behavior can deviate from prescribed therapy regimen without causing negative clinical consequences (e.g., loss of effectiveness, emergence of drug resistance, toxicity). The degree of forgiveness will vary depending on the pharmacokinetic and pharmacodynamic properties of the drug (e.g., half-life). For example, an acceptable deviation for drug A is missing two consecutive doses, whereas a patient may only miss one dose of drug B before a detectable clinical consequence occurs.

Thus, some stakeholders suggested that a single threshold may never be sufficiently precise, given the range of medication-taking behaviors and potential impact on calculating the threshold. For example, patients with a composite adherence of 80% might still miss doses regularly, stop taking the medication for a period of time, or take the drug every day but at different times of day. For twice daily pills, patients might miss their morning dose, and then take two doses at once in the afternoon to compensate. These behaviors may result in an adherence rate of 80% by some measures, but the individual patterns of behavior and resulting clinical outcomes will likely vary.

Strategies to improve the measurement of medication adherence

In the case of polypharmacy, defining a clear study outcome is crucial to effectively measuring medication adherence. Adherence might be measured as adherence to a single medication, all

medications for a particular disease, or all medications taken by a patient. Researchers should clarify the measurements of interest at the start of the study and clearly report their choice in resulting publications.

Stakeholders discussed data linkage, a process of bringing information from different sources together about the same person or entity, as an area of opportunity to improve the measurement of adherence. Data linkages could support more comprehensive and robust datasets to assess medication adherence. One stakeholder discussed ongoing work at the National Cancer Institute to link pharmacy claims with registry data from Surveillance, Epidemiology, and End Results (SEER) Program, an authoritative source of information on cancer incidence and survival in the United States. The contextual information from SEER might facilitate identification of clinically acceptable adherence thresholds for oncologic disease areas.

Other technological trends that might change how medication adherence is measured involve electronic health record functionality. One stakeholder mentioned a new health record functionality that can automatically calculate PDC using both claims and electronic health record data. This new feature allows for more up-to-date calculations of measures of adherence and dovetails with digital health data trends.

Session IV: Study Designs to Evaluate Tracking, Improvement in Medication Adherence, and Impact on Clinical Outcomes

The final session discussed details of study designs—either in current use or being proposed—to evaluate tools and technologies intended to track or improve medication adherence and clinical outcomes secondary to increased adherence. Traditional randomized controlled trials might not capture representative patterns of non-adherence that occur in the real world due to homogenous study populations and enhanced monitoring that can lead to "white coat adherence." Pragmatic clinical trials or observational studies represent additional methodological approaches for generating real-world evidence on adherence, but such designs are also not without challenges.

Current research evaluating adherence interventions

In discussing existing research on adherence interventions, one speaker cited systematic reviews and meta-analyses as demonstrating a need for more and better-designed studies of interventions. A 2014 Cochrane review, for example, identified 17 RCTs with low bias; among the 17 trials, only 5 showed improvements regarding both level of adherence (e.g., self-report, pill count) and patient outcomes (e.g., intraocular pressure, viral load, global assessment of functioning scale).[12] A 2016 meta-analysis of text-message interventions found that such interventions improved adherence, but the trials were of short duration and generally relied on self-reports of adherence.[13] Given this current state of information, stakeholders emphasized the importance of designing studies tailored to address the complexity of medication adherence behaviors and the need to utilize different types of study designs.

Study design considerations to assess medication adherence interventions

RCTs are a critical part of evidence generation and can establish efficacy under ideal conditions. RCTs also serve as a cornerstone of the evidentiary standard FDA applies in regulatory decision-making and provide baseline information on adherence characteristics of the study population, which can further inform post-market research.

Traditional RCTs, however, have limitations when applied to the study of adherence. Medication adherence behaviors are dynamic and change over time; therefore, solely relying on short-duration

RCTs might not accurately depict whether the intervention's impact is meaningful. Additionally, because of the need to tightly monitor RCTs, it can be challenging to enroll sufficient numbers of participants to power a study and obtain statistically meaningful results. This last point is even more relevant in studies of chronic diseases, where improvements in adherence can be incremental and may require very large sample sizes.

Many stakeholders stated that medication adherence is an ideal use case for real-world study designs, such as clinical trials with pragmatic elements. Such trials are generally viewed as randomized trial designs that occur within health care settings, minimize exclusion criteria, use different comparators, and tailor intervention delivery. Stakeholders from the NIH Adherence Research Network, a consortium of institutes and centers that provide leadership, vision, and support to advance adherence research funded by NIH, emphasized growing interest in the research community to develop pragmatic study designs.

One stakeholder framed real-world study features of pragmatic clinical trials using the PRECIS-2 tool, which describes different domains of a study regarding pragmatism.[14] These domains include eligibility, recruitment, setting, organization, flexibility (of delivery and adherence), follow-up, primary outcome, and primary analysis. Stakeholders considered how studies evaluating medication adherence interventions could be designed in a manner that incorporates real-world features of pragmatic trials to support methodological rigor and robust results.

Stakeholders recommended reducing the number of exclusion criteria in studies evaluating medication adherence interventions to allow the enrollment of patients with more comorbidities, thus increasing the generalizability of results. Stakeholders also suggested that recruiting and enrolling patients at higher risk for non-adherence could serve as an "enrichment strategy" to identify clinically meaningful results and to avoid ceiling effects.[b]

Researchers should also select a clinically meaningful follow-up period. The goal of adherence interventions is to demonstrate a long-term, durable improvement in adherence. Trials that only track patients for a relatively short duration—a time period will vary based on the condition involved—may show transient improvements which subsequently diminish. For example, a six-week follow-up period may not be sufficient to study adherence for a chronic disease.

To sufficiently power studies, many stakeholders suggested cluster randomization. Cluster randomization is defined as the unit of randomization beyond the patient. In such trials, the unit of randomization could be the provider, clinic department, or entire hospital system.

Using an intent-to-treat analysis plan may help account for real-world applications of adherence interventions. Intent-to-treat plans analyze patients in the group that they were randomized to, rather than considering the ultimate treatment the patient received (or did not receive). This analysis structure may be particularly useful when studying adherence interventions, because patients might be offered interventions that they subsequently do not use.

Finally, stakeholders noted that improving adherence without improving patient outcomes may not represent a useful goal. For example, the ultimate goal of an intervention to improve adherence to HIV treatment should be to improve a patient's viral load, not merely to improve the number of pills taken as prescribed. Although prior evidence, such as a clinical trial, may indicate that a medication is effective

[b] A ceiling effect refers to the idea that, if the maximum level of adherence is 100%, a patient who has 90% adherence at the start of a trial, for example, is limited in how much their adherence can improve.

in a study population, it may not allow us to predict whether efforts to improve adherence will result in a meaningful improvement in patient outcomes.

Two case studies of adherence intervention study design

During this session, two case studies were presented to highlight the key considerations made when designing adherence interventions.

Propeller Health designs digital sensors for patients who use inhalers to treat respiratory conditions, such as asthma or chronic obstructive pulmonary disease (COPD). The sensors measure inhaler use and synchronize with a mobile phone app to provide feedback to patients. As relevant background information, the adherence rates for inhaled medications are reported to be 10-40%—a range lower than for oral medications.[15]

Propeller Health tested its interventions in multiple trials and shared lessons learned during the session. They reflected that null studies of adherence often were low-powered, selected low-risk or already adherent patients, and did not provide adequate follow-up time. Considerations for trial design include: clearly articulating the study question and goals; having well-defined interventions, comparators, and outcomes; selecting the appropriate population; and using a longer study duration for chronic conditions.

Proteus Digital Health creates "digital medicines"—edible sensors (ingestion event markers) encapsulated with medications. When a patient ingests the medicine, a wearable patch can record the event and pass the data, via Bluetooth, to a patient's mobile app and a provider's web interface.

Proteus designed the intervention to address problems in the "pharmacotherapy feedback loop." Unlike in a traditional hospital setting, patients in the real world are responsible for taking their medication and reporting their success or challenges back to providers. Proteus noted that computer designers do not blame users for not understanding products, but rather design products that users understand. Analogously, digital medicines are designed to help patients use medications and do not blame patients for non-adherence.

In deploying various types of trials, Proteus studied its intervention in both a controlled research setting and in the real world. One study of tuberculosis patients compared directly observed therapy to wirelessly observed therapy, and the results suggested that the wirelessly observed therapy was superior to directly observed therapy in supporting confirmed daily adherence and was also preferred by patients.[16] To further evaluate their intervention, Proteus is using real-world data to examine the durability of adherence improvement and emphasizes the importance of selecting patients at high risk of non-adherence in trials of adherence.

Considerations for future research

Throughout the discussion, key considerations were identified to help improve and advance adherence trials, including intervention selection, study design, outcome definition, result reporting, and ethics.

Trends in trial designs were discussed, such as cluster randomization, stepped-wedge trials, adherence intervention "dosing" trials, N-of-1 designs, micro-randomized trials, and the use of the Continuous Evaluation of Evolving Behavioral Intervention Technologies (CEEBIT) framework. Speakers also discussed the value of using trajectory modeling, a technique that can help predict future adherence or non-adherence. Modeling is particularly valuable because adherence is not a one-time event.

Future research might also employ different trial designs to evaluate adherence interventions for already approved drugs and pre-market drugs. For pre-market drugs, one speaker proposed a trial design where efficacy and adherence might be evaluated simultaneously, in a multi-arm study. If issues with adherence were discovered in the course of the trial, the speaker suggested a paradigm in which the drug might be approved along with a set of adherence risk management strategies.

The discussion also covered other study design considerations. First, the use of incentives can help engage difficult-to-recruit patients. Such patients are likely those who are non-adherent or have poor clinical outcomes, and thus would benefit the most from an intervention. Current incentives to rapidly complete trials push investigators to recruiting the patients who are easiest to reach. Second, a variety of experts should be engaged when designing trials for interventions. Just as a trial would not proceed without first creating a statistical analysis plan, researchers should consult with implementation science experts, as well as patients, who will be the ultimate users of interventions. Third, quicker access to data from sources, such as CMS, pharmacy benefit managers, or pharmacies, will increase the pace of research. Finally, studies should aim to have both statistically meaningful and clinically meaningful results. Clinically meaningful thresholds may be difficult to determine, however, and additional research might be needed specifically in this area.

When designing and discussing trials, researchers should use clear and precise definitions of adherence. Reporting a "30% improvement in adherence," for example, does not fully capture the complex behavior that is adherence. Using consistent, specific terms, such as initiation, implementation, and persistence, will help specify how interventions address different components of adherence. Similarly, when considering the impact of interventions, stratifying results by adherence component may help clarify impact of specific medication-taking behaviors on clinical outcomes. To that end, trials should be reproducible; many journals do not allow space for publishing entire protocols, but the open sharing of trial details can aid in the development of new studies.

Finally, the discussion turned to ethics, with some speakers wondering if some pragmatic trial designs raise concerns regarding informed consent. Other speakers shared examples of minimal risk research, where the requirement to obtain informed consent was waived because doing so (and alerting the patient to the presence of an intervention) would undermine the validity of the study. Ethical issues, and the potential involvement of ethicists, should be considered in the development of medication adherence studies.

Key Conclusions and Takeaways

This meeting explored the state of the science of clinical research evaluating medication adherence involving FDA-regulated products. Key takeaways emerged from the meeting regarding barriers to adherence, the need for standardized terminology, how the appropriateness of medication adherence measures and adherence thresholds will vary, as well as study design considerations:

1. Medication adherence can be evaluated at the individual and population levels. Interventions tailored to the individual level can directly address the barriers experienced by each patient.

2. Numerous medication adherence interventions exist, including innovative technologies, but challenges remain when evaluating and translating the impact of interventions to routine clinical settings. These challenges involve study design considerations, including criteria for subject selection and measures of adherence.

3. Medication adherence encompasses a wide range of behaviors, and using standardized terminology is therefore essential to understanding the impact of interventions on medication adherence and clinical outcomes. The appropriateness of measurements of medication adherence will depend on the medication-taking behavior being studied. Clinically acceptable adherence thresholds will vary depending on the disease or condition as well as medication characteristics (e.g., drug forgiveness). Accordingly, considering only one threshold for adherence (e.g., 80%) to evaluate treatment benefit may not be appropriate.

4. When conducting adherence intervention studies, features of pragmatic clinical trials may be useful. For example, trials can be designed to enroll at-risk patients and assess clinically relevant outcomes over longer study periods, to identify durable effects.

References

1. World Health Organization. *Adherence to Long-Term Therapies: Evidence for action.* 2003. 92 4 154599 2.
2. Johnell K, Lindstrom M, Sundquist J, Eriksson C, Merlo J. Individual characteristics, area social participation, and primary non-concordance with medication: a multilevel analysis. *BMC Public Health.* 2006;6:52.
3. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol.* 2012;73(5):691-705.
4. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353(5):487-497.
5. McHorney CA. The Adherence Estimator: a brief, proximal screener for patient propensity to adhere to prescription medications for chronic disease. *Curr Med Res Opin.* 2009;25(1):215-238.
6. Volpp KG, Troxel AB, Mehta SJ, et al. Effect of Electronic Reminders, Financial Incentives, and Social Support on Outcomes After Myocardial Infarction: The HeartStrong Randomized Clinical Trial. *JAMA Intern Med.* 2017;177(8):1093-1101.
7. Choudhry NK, Krumme AA, Ercole PM, et al. Effect of Reminder Devices on Medication Adherence: The REMIND Randomized Clinical Trial. *JAMA Intern Med.* 2017;177(5):624-631.
8. Asch DA, Troxel AB, Stewart WF, et al. Effect of Financial Incentives to Physicians, Patients, or Both on Lipid Levels: A Randomized Clinical Trial. *JAMA.* 2015;314(18):1926-1935.
9. Wickström G, Bendix T. The "Hawthorne effect" - what did the original Hawthorne studies actually show? *Scandinavian Journal of Work, Environment & Health.* 2000;26(4):363-367.
10. Kronish IM, Thorpe CT, Voils CI. Measuring the multiple domains of medication nonadherence: findings from a Delphi survey of adherence experts. *Transl Behav Med.* 2019.
11. Bezabhe WM, Chalmers L, Bereznicki LR, Peterson GM. Adherence to Antiretroviral Therapy and Virologic Failure: A Meta-Analysis. *Medicine (Baltimore).* 2016;95(15):e3361.
12. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev.* 2014(11):CD000011.
13. Thakkar J, Kurup R, Laba TL, et al. Mobile Telephone Text Messaging for Medication Adherence in Chronic Disease: A Meta-analysis. *JAMA Intern Med.* 2016;176(3):340-349.
14. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ.* 2015;350:h2147.
15. Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax.* 2008;63(9):831-838.
16. Browne SH, Umlauf A, Tucker AJ, et al. Wirelessly observed therapy compared to directly observed therapy to confirm and support tuberculosis treatment adherence: A randomized controlled trial. *PLoS Med.* 2019;16(10):e1002891.