Framework for Adherence Research and Translation: A Blueprint for the Next Ten Years

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Office of Behavior and Social Sciences Research
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The Office of Behavior and Social Science Research (OBSSR) is part of the Office of the Director at the National Institutes of Health, with responsibility to coordinate, prioritize, identify gaps, and encourage activity by Institutes and Centers at NIH.

A PubMed search identified >44,000 hits in the literature associated with adherence, yet despite that foundation, there seems to be little movement in the field. That suggests possible issues with regard to translation, dissemination, education, and development of quality measures to move research findings forward into standard clinical practice. The meeting was called to focus on these issues, shape priorities, and form an action agenda.

Research Presentations

Brian Haynes: Adherence is the extent to which a person's behavior (in terms of taking medications, following a diet, modifying habits of attending clinics) coincides with medical or health advice. It is equivalent to compliance. Concordance is a different concept where there is a consensual agreement between patient and practitioner about which activities they are willing to perform.

The number of efficacious self-administered treatments has increased, expanding the patient's role as an active participant in the regimen. And an aging population has increased the overall burden of disease, particularly chronic disease. However, the gap between how healthy people could be and their actual health status has widened over the last twenty years, in large part because of the issue of adherence.

While the efficacy of the intervention is important, the behavior of adherence itself also appears to have an independent beneficial effect on health outcomes. The downside of this dynamic is that strong compliance can intensify negative or toxic effects associated with a therapy.

Dr. Haynes used an example of treating a patient with type 2 diabetes, dyslipidemia, and hypertension. The standard approach is to change diet (reducing calories, fat and salt), increase exercise, add multiple medications, and self-monitor glucose and blood pressure. He urged those who prescribe such a regimen to first try it themselves so that they understand how difficult it is to follow. It is no surprise that compliance is difficult.

A Cochrane Review from 1979 found significant non-adherence rates:

Task	Non-Adherence Rate
Screening in community	35%-90%
Referral from screening	50%-65%
Staying in care	31%-66%
Follow-up appointments	16%-84%
Medications	31%-58%
Weight loss	29%-100%
Smoking cessation	71%-96%

A Cochran Review of interventions to improve adherence to medications, conducted by Dr. Haynes and colleagues, will become available in April 2008. It found that most did not improve adherence or patient outcomes. Many studies were small and perhaps were underpowered to detect a benefit; of short duration; did not include clinical outcomes; and did not measure durability of effect once the intervention was stopped. He said single interventions by themselves likely will not have a significant effect, but when combined there may an additive or synergistic effect.

Measurement of adherence is difficult: "Simple measures are not very accurate; accurate measures are not very simple." Many of the interventions do not translate well into clinical practice. Physicians often believe they can predict which patients will comply with the regimen, but research has shown that there are no good demographic predictors of that.

Dr. Haynes listed problems with adherence research:

- Fragmented – each field discovers anew the problem of adherence, then reinvents approaches to it
- Weak – most are poorly conducted
- Noncumulative –do not build on earlier research and try to move the field forward
- Unimaginative – relying upon pamphlets, logic, and "scaring the patient to death"
- Impractical – cannot be rolled out into wider practice
- Atheoretical

His prescription for future research includes:

- Measurement research
- Fundamental research to better understand the determinates
- Incremental research to better deal with existing regimens
- Encouragement of innovations that reduce treatment burdens on the patient
- Dual target research that includes
    - Both practitioners and patients
    - Both quality of prescribing and adherence

"Physicians do not understand that they don't know what their patients are doing."

A recent international panel made recommendations[1] for advancing adherence. They include:

- Simple, feasible interventions for both clinicians and patients
- Improving theories/development through conjoint efforts of medical, pharmaceutical, social, and technical scientists
- Involving patient groups
- Focusing efforts on non-adherent patients
- Focusing theory development on improving adherence rather than explaining it

Ira S. Ockene: The Pharmacist-assisted Compliance Trial (PACT) sought to improve patient adherence to lipid-lowering medications through a pharmacist-mediated program. Patients were randomized to intervention and control groups, while compliance was measured through pharmacy refill records. There was no difference between the two groups (88% vs. 90% respectively), primarily because compliance was so high.

Issues that arose during the course of the study included:

- The catheterization laboratory had a high volume of patients while the study only needed a few per day
- The chaotic environment and rapid discharge posed challenges to recruitment
- Sedation became standard of care during the course of the study
- Difficulty in recruiting adequate numbers of minorities and women
- HIPPA came into force and one pharmacy refused to supply refill records
- Selection bias toward younger, more alert, more cooperate patients
- Not a single response from physicians

A discussant cited recent research has shown that when it came to questions of drug efficacy, patients trust doctors (75%) and pharmacists (65%) the most; all other sources (nurses, Internet, etc.) were significantly lower (≤25%). On issues of cost, the ranking of pharmacists and physicians flipped, while that of the other players remained similarly low. He urged that physicians be trained to more effectively discuss use of regimens.

Dr. Ockene reinforced the message that while prevention is important, it seldom is urgent, and so often gets less attention from a busy physician during a visit. It is important to create systemic defaults that remind and reinforce the use of prevention or adherence messages.

Michael D. Murray: Hypertension patients were stratified into those with uncomplicated and complicated disease under the rationale that side effects of the medicine might inhibit compliance among the former group, while the symptoms of hypertension experienced by the later might serve as a reminder and increase compliance with the regimen. Uncomplicated patients were older and had more education, but the groups were otherwise similar.

Each stratum was randomly assigned to receive standard care or additional special messages and literature from trained participating pharmacists at an Indianapolis hospital. Patients were actively followed for 12 months with active intervention, then a follow-up evaluation 6 months after the last intervention.

A patient-centered aspect of the study was that participants negotiated with their provider when they would to take their medication within the context of their daily activity.

The literature was a simplified version of what traditionally is handed out with a drug. High literacy patients preferred the more information–dense original material to the simplified version. They also received information on diet and exercise.

The print materials had a theme of medication as a lifeline and used visual images of a sailboat, life preserver, and a shark as a reminder of what might happen with poor adherence. The study population consisted predominately of low income minorities. Some conference members wondered if the metaphors were culturally appropriate for the location and population and if the materila had been vetted by focus groups of the targeted population.

All participants were given access to a special clinic pharmacy where the service lines were shorter than at the standard pharmacy. That may help to explain the heightened clinical responses seen in the control group.

The study found no overall effect of the intervention on adherence between the two arms. There was a positive effect on systolic blood pressure, with the intervention arm showing a 7-9mm greater decline.

One curious finding of the study was that the intervention did have a positive effect on the adherence of white participants, though not on African Americans, perhaps because of the relevance of the literature. The clinical effect initially persisted once the intervention was stopped but soon drifted back toward the baseline. While there may be an educational component to a program; Dr. Murray believes that adherence is largely an ongoing management issue.

After accounting for the cost of the intervention ($205/patient), there was a net savings of $1400 per patient enrolled in the intervention, due primarily to reduced emergency and hospital visits.

There was extended discussion on the possible effect of systems issues on adherence, particularly co-payments among low income patient populations. Studies on compensation to increase adherence currently are underway.

Jacqueline Dunbar-Jacob: The study recruited patients on medication for each of the comorbid conditions of diabetes, hypertension, and hyperlipodemia, with the goal of improving adherence to their regimens. Entry criteria had to be modified when it became

apparent that a significant portion of providers in the study area were not following treatment guidelines for management of hyperlipodemia. So, while the study team could identify patients with all three conditions, few of them were on medication for hyperlipodemia. The study protocol was modified to focus on the first two conditions.

Participants were recruited from community medical practices and disease-oriented mailing lists [*Might the later group not constitute a more active and compliant segment of the patient population, and hence over-sample them?*] A baseline evaluation determined that about one-third were "good adherers" who were ≥80% adherent to their medications. They were tracked separately to gain a better understanding of this patient subset.

The remaining participants (N = 267) had <80% adherence for at least one of the drugs being monitored. They were randomized into intervention or control groups. They were 40% male, with a broad range of age and income (though the means of both were close to the national averages), and had had diabetes (~10 years) and hypertension (~ 13 years) for some time.

What was most striking about the cohort was the complexity of their disease; they were managing an average of 7 comorbidities, with a range of 1 to 20 diagnosed diseases. The number of prescribed medications ran parallel and in addition, patients on average took 2 additional over the counter medications.

Baseline rates of adherence were 88.1% (hypertension), 82.7% (cholesterol), and 81.7% (diabetes), leading Dr. Dunbar-Jacob to conclude that adherence to one drug regimen does not necessarily predict adherence to another. Multivariate analysis found a trend to increased nonadherence as the number of comorbidities and medications increased, but that relationship was not linear. The complexity and restrictions of the regimens [such as food] were more important factors affecting adherence than were the total number of pills taken. Depression was a predictor of adherence, though it varied between diseases.

Paul Colson: The Tuberculosis Adherence Partnership Alliance Study, conducted out of Harlem Hospital, is looking at peer educators to increase adherence to the nine-month self-administered regimen used to treat latent tuberculosis infection. Compliance ranges from 30% to 60% in clinical settings. Factors contributing to that include the lack of active symptoms of infection; a long duration of treatment; sensitivity issues with the tubercular skin test; and little knowledge of patient perceptions and social/behavioral factors in treating tuberculosis.

The study compared current practice of self-administered treatment with an intervention that included one-on-one peer support and access to a health educator over the nine-month regimen. Some 56% of the control group complete treatment, compared to 61% of the intervention group, which was not statistically significant. However, other tuberculosis patients at the Hospital, who were not enrolled in the study, had a treatment completion rate of only 44%. It suggests that the added attention of participating in a

trial, even though one did not receive the intervention, may have had a significant effect on compliance. The only variable that proved predictive of adherence was age (>40 years).

Instructions for Discussions

Margaret A. Chesney: The goal of the breakout groups was to generate optimal next research steps on adherence that can be taken across the NIH Institutes and Centers. It was not to simple identify key questions but to go beyond that to how those issues might be approached. Discussion was to address difficulties in getting adherence research proposals through study sections as well as what might be important to say to CSRs to facilitate more complicated, creative research designs.

She reviewed the questions for discussion (see Appendix A):

- What should be our **Focus**?
- What are the **Challenges**?
- What are some promising **Solutions** to the challenges and barriers to adherence?

Adherence was proposed as a theme for a trans-NIH Roadmap initiative but it did not generate sufficient interest. Dr. Chesney believes the advocates did not create a sense of urgency about the proposal. She reviewed how in the 1970s a focus on high blood pressure resulted in the first generation of compliance studies and concern with adherence to HIV medications brought a second generation of studies. She urged participants to identify "grand challenges" that might generate a sense of urgency and stimulate the next generation of research on adherence.

Participants then broke into four small discussion groups, rotating among them on an assigned basis for each of the questions posed. A reporter from each group reported back at the end of the session. Key points from those discussions follows.

Question #1: What should be the *Focus*?

There was general support for a broad definition of adherence that is evidence-based. Availability and access to appropriate care on a timely basis is the framework for adherence without which all other issues become moot. Research should include:

- Prevention of the acquisition of disease and maintenance of health according to medical and public health guidelines
- Medications
- Self-management of diet and exercise
- Trust and mistrust
    - Perceptions of efficacy of the intervention
- Negotiation processes: how negotiations, concurrence, compliance, and adherence play out
- Context, structural, and systemic issues that may interact and affect

    - Providers
    - Patients
    - Clinical environment
    - Social activities
- Structural and policy implications: short and long term issues in changing behavior as exemplified by use of seatbelts and smoking cessation
- Behavior as an ongoing issue that blurs the border between prevention and treatment
- Packaging adherence as procedure, to better "sell" resreach to NIH and others

Current gaps include:

- Development of efficacious interventions
- Cost-effectiveness and sustainability: should be factors in trial design and evaluation
- Identify similarities across disease silos for common lessons
- Priority on improving measures
    - Adherence assessment
    - Engagement and retention in care
    - At the social level, such as through claims data
- Determinates of adherence, beyond the individual patient, to better shape the intervention to the situation
    - Provider influences
    - Characteristics of the regimen
    - Clinic systems and designs
    - Social context
- Deconstruct successful interventions to better understand what parts work with what patients
- Methods to identify who needs help with adherence
    - Translate that into clinical practice
    - Make it applicable to all members of the healthcare team
- What must be in place to "get there" through continuing education

Key discussions

The WHO requires that a healthcare provider make the recommendation to trigger a question of adherence. However, the consensus of the meeting was that participation of a healthcare provider is not necessary for an adherence event to occur, so long as it is evidence-based. The framing of the issue and questions may well depend upon the audience and context of the discussion. (Riley)

The difference between intentional and non-intentional adherence should be made explicit, studied, and reported in clinical trials data. A certain percentage of patients make informed decisions to take actions outside of the recommended guidelines; "We have to be respectful of that." As the IOM report points out, a patient's decisions are based upon a body of values that are broader than medical guidelines.

An example was offered of a patient who cleanses here body with blueberry juice, and also stops her antiretroviral medications on the weekend, because she does not want the toxins to build up. "She is very adherent, but not to what we would want her to do. Understanding how she can be motivated and adherent to her regimen is important, even thought we would define her as nonadherent." (Kalichman)

"We're looking at the patient as a problem, not as a person." We have focused on what we want and not what they want. There is a need to better identify what the patient has agreed to do, versus what we have recommended they do." (Kalichman)

The model of adherence research often has focused on the physician performing the adherence intervention, when if fact all aspects of healthcare delivery need to be taken into account.

At the same time, there is a huge element of "clinical inertia" in terms of physicians adopting evolving standards of care, and that cannot be ignored – adherence to a substandard regimen will yield substandard clinical outcomes. But, given issues of patient trust, and leadership within the healthcare setting, the physician must be involved with the process to some degree.

The physician needs to have a better understanding of where a patient is in terms of willingness to change and adhere at a particular point in time. Better, more appropriate tools need to be developed to apply at the appropriate time, rather than trying to force the patient to comply with a standardized intervention.

Information sources such as the Internet should be thought of as a sort of "physician extenders" that can be better utilized, so long as they are evidence-based. Are Internet or telephone interventions better or worse than a group program? (Chesney)

Treatment expectancies have an impact on adherence, there is a value to it.

One paper found that half of the interventions prescribed by physicians do not conform to current treatment guidelines. AHRQ has done work on physician adherence to treatment guidelines.

Psychologists have extensively studied adherence and personality models. It is important to not duplicate these efforts. It may be useful to synthesize it through a meta-analysis, then move from description to studies to interventions. (Haynes)

It is important to deconstruct complex interventions to understand the contribution of each component within particular subsets of patients, but that takes additional time and money. Prioritizing adherence likely will vary from individual to individual, depending on comorbidities and other interventions. (Murray)

The potential for "payoff" of highly successful research should be a factor in prioritizing research. That calculation may be based upon a projection of benefits to patients and the

healthcare system if successfully implemented, as well as the foundation of existing research and the validity of the methodology to be employed in such studies.

Question #2: What are the *Challenges*?

- Increasing language and cultural diversity within the US
    - It is a two-way street involving both consumers and providers as increasing numbers of US healthcare workers are foreign born
- Web-based information: quality is uneven
- Aging population
    - Cognitive deficits
    - Comorbidities and polypharmacy
- Emerging infectious diseases such as SARS and West Nile Virus
- Climate change
- Shift from acute to chronic disease treatment
- Complexities of managing comorbidities
- Long-term maintenance, apart from initial adherence
- Health literacy: a broad distribution from high to low
- Substance abuse: will it change in terms of variety and extent?
- Increasing cost of treatment: will it contribute to adherence or detract?
- Youth population and nonadherence even while chronic diseases related to obesity increase
- Mobile electronic health records: a challenge and opportunity
- Globalization: learning more from other countries and sharing what we know
- Patient trust and push back as they become more knowledgeable and empowered
- Implementing changes as the standard of care evolves
- Methodology
    - Flexible and adaptive designs of studies beyond the RCT
    - Handling complexity and individual patient needs without making a study impractically large
    - Tailoring interventions, perhaps with re-randomization during a study
    - Training in statistical design and analysis
    - Recruiting diverse participants that are representative of the disease burden being studied
    - Selection bias in enrolling study participants
    - How to identify potential nonadherers early in a study and tailor care
    - Privacy issues as a possible impediment to adherence research
        - Can one measure it
        - Would one even be allowed to measure it
- Funding
    - Too much emphasis on RFPs
    - Need mixed method qualitative research
    - Operations research
    - Use of secondary data
    - Effectiveness studies

    - Difficulty funding long-term studies that run beyond the 5-year grant cycle
    - Public-private partnerships
- Genetic/genomic revolution and the evolving personalization of medicine as a possible wedge for adherence research—regardless how the intervention changes, adherence will remain a central issue
- Need to be more strategic about uncertainties of levels of research funding, emerging technologies, and healthcare policy
- Complementary and alternative therapies
- NIH culture as a behavioral factor
- Health disparities
- Setting priorities among competing demands
- Incorporation of information technologies
    - Electronic medical records
    - Patient knowledge and empowerment
    - Harness for adherence research and implementation
- Changing environment of healthcare delivery from disease-centered to patient-centered care through personalized medicine may raise a conceptual barrier
    - Pay for performance
    - Availability of real time data and its portability
    - Integration of systems and challenges of polypharmacy
    - Privacy
- Veterans from Iraq with complex issues that will spill over from the VA
- Incorporation of mental health issues into traditional disease management
- Who is the right person to deliver care
- Designing a system to maximize adherence
- Challenge of getting payers and insurers involved

Key discussions

The "worried well" will become an increasing problem as 90% of adults probably have a marker of elevated weight, blood pressure, cholesterol, or other conditions. Genomics will only accelerate the problem as research increasingly identifies genes associated with increased risk for developing particular morbidities.

"I think there are people who, if given a choice at age 20 to live happily, eat what you want, smoke what you want and die at 55, or would you like to worry from this point on, would chose the former. We need to recognize this as a challenge." (Ockene)

Often research is conducted at one level and is not connected to inform policy or clinical practice. NIH probably needs to do a better job at setting priorities for funding things that will have a broader impact, not simply ask an interesting scientific question. (Bosco)

Standardization should include nomenclature, standards, methods, measures, and even how the data is entered into IT data fields so that studies can be compared and the raw data combined into meta-analysis.

A recent IOM report *What Works in Health Care* sets out a national program for setting standards, criteria, and a common language for evidence review, synthesis, and the development of clinical guidelines. Leverage sould be used to encourage persons to use these standards. One of the goals is to build or rebuild trust in public sources of information.

The systems of a particular facility can have an influence on adherence outcomes, so a study may have to involve facilities with different systems approaches in order to be more representative of clinical practice. This has size and cost implications

Adherence researchers need to be at the table when electronic health records are developed. The link between treatment and clinical outcomes cannot be conclusively established without a record of adherence; gross pharmacy records may not suffice. (Riley)

A consensus meeting around adherence is needed to inform people on the state of the science and move toward a more standardized approach, including methodological ways of dealing with complexity in care and trials. A similar meeting to develop guidance on STDs as a biological endpoint proved to be very useful for NIMH study sections dealing with HIV interventions. (Kalichman)

Safety is an under-discussed issue, particularly when dealing with controversial issues.

Question #3: What are some of the promising *Solutions* to the challenges and barriers to adherence?

- Physicians and patients don't talk much about adherence: A simply worded question as part of a standard interview checklist might be useful
- Complexity of the regimen appears to influence adherence
    - Frequency, timing, and restrictions such as food appear to have a greater impact than total pill burden
    - Compliance is roughly similar across diseases and conditions
    - Socio-demographic factors are not strong predators of adherence
- Self-reporting has its limitations, but there may be ways to strengthen its validity
- Build upon what already has been shown to be effective
- Test incentives that might reinforce compliance
- Shift focus of research from single morbidities to complex comorbidities that more closely reflect the situation of clinical practice
- Opt-out rather than opt-in strategies that change the defaults for systems and individuals
- Public awareness and education campaigns that reinforce change in individual behavior
- Importance of translating research findings into standard of care guidelines that are implemented at the clinic level
- Better recruitment of diverse and representative populations to recruitment studies

- Information technologies
    - Ensure that adherence information is captured in electronic medical records
    - Tap the experience with electronic medical records by leading organizations such as the Department of Veterans Affairs and Kaiser Permanente
    - Mine existing databases for a better understanding of adherence
- Systematically learn from the experience of other health research and interventions, such as smoking cessation, that have combined basic research with elements of public, physician, and patient interventions
- Focus on the top ten causes of morbidity/mortality
    - Identify behavioral and quality issues
    - Secondary data analysis
- Consensus conference on adherence standards
- Study section with adherence expertise
- Need for high level support for a campaign, and a "star" to lead a public awareness campaign
- Finesse "turf" issues within the research and healthcare communities to build a common effort towards adherence
- Team approach appears to be more effective than a single practitioner at increasing adherence
- Substance abuse, depression, and stress are major risk factors for poor adherence; addressing these issues should be part of the overall effort to increase adherence
- Follow up action is required to monitor and reinforce adherence
- Make better use of the chronic illness model toward self-administration of interventions
    - Investigate the utility of patient training in self-administration skills
    - Interventions should be patient-centered but involve the entire healthcare team
- Adherence research should be integrated into clinical trials
- Successful interventions will not be integrated into clinical practice unless they are paid for, therefore, cost-effectiveness must be demonstrated to third party payers
- Develop a political constituency at NIH and HHS that supports adherence
- Frame adherence as primary to health—without adherence there is no health
- The substantial amount data on what does not work needs to be synthesized and serve as a cornerstone for future research
- Adherence is multi-factorial, the literature shows that combination strategies tend to be the ones that work – often the effect of single interventions is marginal but a combination can be additive or synergistic and achieve significance
- Community-based research should be the primary focus
- The most important factor in clinical outcomes often is simply getting people into care, all else follows that
- Little is known about the importance of threshold adherence, which likely is disease/intervention specific – i.e. early HIV regimens often had a short half-life and low barriers to resistance, thus demanding >90-95% adherence to prevent the

emergence of resistant virus; other disease interventions may be more tolerant of lapses in adherence
- Integrate research into existing networks supported by NIH and use them as a platform for adherence studies

Key discussions

A common theme was the need to step back and look more broadly at systems in order to make progress. That includes partnerships with other Institutes at NIH and with external groups that may include industry, insurers, and healthcare delivery groups. (Carey)

Simply wagging a finger and admonishing a patient for poor adherence has limited effectiveness. Physicians need a tool kit of guidance and messages on adherence to use in an ongoing dialog with patients.

One should not underestimate the issue of clinical inertia in terms of implementing what has already demonstrated efficacy.

It may be possible to build a political constituency for adherence by highlighting studies that have proven cost-effective in delivering interventions.

Appendix A

BREAKOUT GROUP DISCUSSION QUESTIONS

Framework for Adherence Research and Translation: A Blueprint for the Next 10 Years

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Following are the questions for breakout group discussion:

1. What should be our **FOCUS**?

    - Broadly conceived, "adherence" could apply to any behavior including personal self-care, self-initiated prevention efforts, or personal improvement efforts. How should the field define and limit the focus of adherence research, and by what basis should this be done?
    - What are key understudied areas (gaps) in adherence research to date?

2. What are the **CHALLENGES**?

    - What are the major societal, cultural, demographic, health-care or other challenges that will emerge in the next 10 years that would require a renewed public health effort to improve adherence to preventive and treatment regimens?
    - What key methodological barriers must adherence overcome to meaningfully advance the science of adherent behavior?

3. What are some promising **SOLUTIONS** to the challenges and barriers to adherence?

    - Based on prior research, what is currently known about adherence, in terms of predictors, barriers, and strategies to increase adherence, both within and across diseases that could potentially be translated into practice?
    - What new directions and innovative approaches might the next generation of adherence research undertake to advance our understanding of and ability to improve adherence?
    - What rationales and strategies can be employed to elevate the area of adherence research as an NIH and DHHS priority?

[1] Van Dulmen et al. *BMC Health Services Research 2008, 8:47 doi:10.1186/1472-6963-8-47*