Review of Adherence Measures for Use in Phase IV Studies and Recommendations for a New Standardized Generic Measure

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Background
Medication adherence is a frequently-evaluated endpoint in Phase 3 clinical trials of experimental medication. However, adherence data drawn from these settings holds questionable external validity for four primary reasons:

1. The definition of adherence: The WHO (2003) defines adherence as the extent to which a person’s behaviour corresponds with recommendations from a health care provider. This definition implies active, voluntary, and collaborative patient involvement. However, within most clinical trials, a participant is expected to passively follow a medication regimen.
2. A protocol-driven environment: A clinical trial is strictly driven and governed by a protocol. Titration, medication holidays, and variable dosing are not allowed by virtue of the study. However, they are common strategies in clinical practice to improve adherence.
3. A self-selecting population: The population who agrees to participate in a clinical trial is usually motivated, do not have strong treatment preferences, and fit (often times) narrowly-stated inclusion criteria.
4. The impact on other endpoints: Adherence data alone is potentially interesting but is of little use in the absence of reasons for non-adherence which provide context and inform strategies for improvement. Adherence-related factors can rarely be comprehensively understood within a clinical trial environment without impacting on the primary objectives of the study.

From humanistic, clinical, and economic perspectives, it is important to understand whether medications are used as intended and in line with empirically-defined guidance in clinical practice once the medication has garnered marketing authorization. This literature review appraises the adherence metrics that have been used for evaluating adherence in prospective and retrospective research occurring under “real-world” conditions (Phase IV studies).

Methods
Eligibility for the latter search included self-report measures of adherence behaviors or adherence beliefs hypothesized to impact adherence (provider- or proxy-reported measures excluded). The measure had to be developed specifically for adherence screening, segmentation, or prediction for use in clinical practice or research. Articles were excluded if they were simple adaptation articles (e.g., when a measure was adapted by adding or deleting items) or subsequent re-validation articles (e.g., re-validation of a measure in a language other than that of the original measure). A total of 708 articles were identified of which 48 meet search criteria. An additional 22 measures were identified from a search of the reference lists of the 48 eligible articles for a total of 70 unique self-report measures of adherence.

We critically appraised these adherence measures for use in prospective and retrospective Phase IV studies (e.g., trials, pragmatic and observational studies).

Results

Drug concentration assays can be a relatively sensitive measure, but they are intrusive, invasive, costly, and do not account for intra- and inter-individual pharmacokinetic variation. Adherence metrics using pharmacy claims (e.g., PDC, MPR) are only feasible in closed health care systems, and the data is often not available in real-time. Medication event monitoring systems can be sensitive but are intrusive, expensive, and not widely available. Pill counts can be time consuming, labor intensive, and are subject to gaming by patients. Clinician impression over-estimates adherence relative to other metrics. Patient self-report can be quick, simple, practical, and inexpensive. However, they may overestimate adherence and be vulnerable to social-desirability influences.

We identified 70 unique self-report measures of adherence:

1. 3% were published in the 1980’s, 10% in the 1990’s, 58% from 2000-2009, and 29% from 2010 onward.
2. 26% were generic and the remainder were disease specific.
3. The most common disease-specific measures were for hypertension (23% of all disease-specific measures), HIV (21%), mental conditions (12%), and diabetes (10%).
4. Instrument length ranged from one to 78 items.
5. 34% only measured adherence behaviors, 37% only measured beliefs and attitudes, and 29% measured both.

Recommendations

A new adherence measure should:

1. Be generic – standardization of content would allow for the assessment of adherence behaviors and beliefs between and across therapies.
2. Be reported by the patient – this is the only metric that allows for an understanding of the why as well as the what of non-adherence.
3. Have a minimum set of adherence concepts (behaviors and beliefs) that apply across therapeutic areas.
4. Be developed with patient input (concept elicitation) and verified as to its comprehension and relevance using cognitive interviewing.
5. Be brief and have demonstrated reliability and validity, particularly predictive validity. Its sensitivity and specificity should be clinically and statistically acceptable.