Interventions to Improve Medication Adherence

Current Evidence and Future Directions

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Tamara Navarro, MSc

on behalf of the Patient Adherence Review team at the Health Information Research Unit
1. The importance of improving medication adherence

2. Cochrane systematic review update - Methods
   _Tamara Navarro_

3. Cochrane systematic review update – Main results

4. Risk of bias in adherence intervention RCTs

5. Recommendations & Future directions
What is Medication Adherence?

The extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider.

- World Health Organization, 2003

“Adherence to medications” is the process by which patients take their medications as prescribed, further divided into three quantifiable phases: “Initiation”, “Implementation” and “Discontinuation”

- The Ascertaining Barriers for Compliance project – Final Report 2012 (www.ABCproject.eu)
The Increasing Importance of Adherence

- Increasing number of self-administered treatments
- Surging burden of chronic diseases
- Increasing shift from in-patient care to community care
- Our ability to help patients adhering has not kept pace
- Thus, the gap between potential and actual patient health has widened
**Good Adherence Saves Lives**

### Beneficial drug therapy

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Mortality (good)</th>
<th>Mortality (poor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug Project Research Group 1980 (^w1)</td>
<td>106/708</td>
<td>88/357</td>
</tr>
<tr>
<td>Wei et al 2002 (^w5)</td>
<td>14/272</td>
<td>14/155</td>
</tr>
<tr>
<td>Cotter et al 2004 (^w6)</td>
<td>1/52</td>
<td>1/12</td>
</tr>
<tr>
<td>β blocker heart attack trial (men) 1990 (^w2)</td>
<td>14/1009</td>
<td>3/72</td>
</tr>
<tr>
<td>β blocker heart attack trial (women) 1993 (^w3)</td>
<td>11/242</td>
<td>2/23</td>
</tr>
<tr>
<td>Wei et al 2004 (^w7)</td>
<td>24/226</td>
<td>26/160</td>
</tr>
<tr>
<td>Canadian amiodarone myocardial infarction arrhythmia trial 1999 (^w8)</td>
<td>33/445</td>
<td>19/128</td>
</tr>
<tr>
<td>San Andres Rebollo et al 2004 (^w9)</td>
<td>69/197</td>
<td>300/753</td>
</tr>
<tr>
<td>Cohn et al 2002 (^w10)</td>
<td>8/585</td>
<td>2/41</td>
</tr>
<tr>
<td>Garcia de Olalla et al 2002 (^w11)</td>
<td>156/831</td>
<td>105/388</td>
</tr>
<tr>
<td>Grimwade et al 2005 (^w12)</td>
<td>12/743</td>
<td>27/545</td>
</tr>
<tr>
<td>Hogg et al 2002 (^w13)</td>
<td>62/955</td>
<td>44/327</td>
</tr>
<tr>
<td>Paterson et al 2000 (^w14)</td>
<td>0/23</td>
<td>1/58</td>
</tr>
<tr>
<td>Wood et al 2003 (^w15)</td>
<td>117/1067</td>
<td>76/355</td>
</tr>
<tr>
<td>Physicians health study 1994 (^w16)</td>
<td>89/6608</td>
<td>102/4396</td>
</tr>
<tr>
<td>West of Scotland prevention study 1997 (^w17)</td>
<td>66/2435</td>
<td>40/867</td>
</tr>
<tr>
<td>Howell et al 2004 (^w19)</td>
<td>24/654</td>
<td>14/215</td>
</tr>
<tr>
<td>Miura et al 2001 (^w20)</td>
<td>17/218</td>
<td>32/213</td>
</tr>
<tr>
<td>Dobbels et al 2004 (^w21)</td>
<td>9/84</td>
<td>2/17</td>
</tr>
</tbody>
</table>

Total (95% CI): 17,354 (good adherence), 9,082 (poor adherence)

Test for heterogeneity: χ²=14.34, df=18, P=0.71, I²=0%

Test for overall effect: z=10.54, P<0.0001

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*Simpson et al, BMJ, June 2006*
### Importance of Adherence in General

<table>
<thead>
<tr>
<th>Study</th>
<th>Good adherence to drug therapy</th>
<th>Poor adherence to drug therapy</th>
<th>Odds ratio (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug Project Research Group 1980 ^w1</td>
<td>274/1813</td>
<td>249/882</td>
<td>27.53</td>
<td>0.45 (0.37 to 0.55)</td>
<td></td>
</tr>
<tr>
<td>β blocker heart attack trial (men) 1990 ^w2</td>
<td>31/1037</td>
<td>4/57</td>
<td>5.11</td>
<td>0.41 (0.14 to 1.20)</td>
<td></td>
</tr>
<tr>
<td>β blocker heart attack trial (women) 1993 ^w3</td>
<td>15/219</td>
<td>4/21</td>
<td>4.20</td>
<td>0.31 (0.09 to 1.05)</td>
<td></td>
</tr>
<tr>
<td>Canadian amiodarone myocardial infarction study 1988 ^w4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrhythmia suppression study 1988 ^w5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physicians Health Study 1992 ^w6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>West of Scotland prevention study 1997 ^w7</td>
<td>95/2420</td>
<td>40/873</td>
<td>19.54</td>
<td>0.85 (0.58 to 1.24)</td>
<td></td>
</tr>
<tr>
<td>University Group Diabetes Project 1970 ^w8</td>
<td>11/143</td>
<td>10/62</td>
<td>6.69</td>
<td>0.43 (0.17 to 1.08)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>13,429</td>
<td>6,204</td>
<td>100.00</td>
<td>0.56 (0.43 to 0.74)</td>
<td></td>
</tr>
<tr>
<td>Total events: 581 (good adherence), 415 (poor adherence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 14.34$, df = 7 (P = 0.05), I^2 = 51.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 4.23$, P &lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Association between adherence to placebo and mortality

Simpson et al, BMJ, June 2006

“healthy adhererer effect”

Mortality

CVD outcomes

Figure 2
Risk estimates for the association between statin non-adherence and mortality outcomes according to adherence, discontinuation and persistence studies.

Figure 3
Risk estimates for the association between statin non-adherence and cardiovascular disease outcomes according to adherence, discontinuation and persistence studies. Abbreviations are as follows: AMI, acute myocardial infarction; CAD, coronary artery disease; CHF, chronic heart failure; CVA, cerebrovascular accident; CVD, cardiovascular disease; HD, haemorrhagic disease; YTE, venous thromboembolism.
## Adherence to Unsafe Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Good adherence to drug therapy</th>
<th>Poor adherence to drug therapy</th>
<th>Odds ratio (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harmful drug therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrhythmia suppression trial 1996</td>
<td>23/505</td>
<td>0/69</td>
<td>13.34</td>
<td>6.77</td>
<td>(0.41 to 112.72)</td>
</tr>
<tr>
<td>University Group Diabetes Project 1970</td>
<td>26/151</td>
<td>4/53</td>
<td>86.66</td>
<td>2.55</td>
<td>(0.85 to 7.68)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>656</td>
<td>122</td>
<td>100.00</td>
<td>2.90</td>
<td>(1.04 to 8.11)</td>
</tr>
<tr>
<td>Total events: 49 (good adherence), 4 (poor adherence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=0.43$, df=1, P=0.51, $I^2=0\%$

Test for overall effect: $z=2.03$, P=0.04

*Simpson et al, BMJ, June 2006*
## What Are Adherence Levels in Practice?

<table>
<thead>
<tr>
<th>TASK</th>
<th>NON- ADHERENCE RATES*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening in community</td>
<td>35%-90%</td>
</tr>
<tr>
<td>Referral from screening</td>
<td>50%-65%</td>
</tr>
<tr>
<td>Staying in care</td>
<td>31%-66%</td>
</tr>
<tr>
<td>Follow-up appointments</td>
<td>16%-84%</td>
</tr>
<tr>
<td>Medications</td>
<td>31%-58%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>29%-100%</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>71%-96%</td>
</tr>
</tbody>
</table>

* Sackett and Snow, 1979

→ In individuals, adherence ranges from 0% to >100%
History of the PAR Review

• 1996 Update
  – 13 studies (2 acute; 11 chronic)

• 2002 Update
  – 33 studies (3 acute; 30 chronic)

• 2005 Update
  – 57 studies (8 acute; 49 chronic)

• 2008 Update
  – 78 studies (9 acute; 69 chronic)
Why Update?

Previous update (2008)
• No clear evidence of effective interventions
• Poor quality of trials

Expected changes
• 50 new RCTs (based on trend)
• Innovative interventions & technologies
• Improved study quality
Interventions to Improve Medication Adherence

Cochrane Systematic Review Update

Primary Objective

To assess the effects of interventions intended to enhance patient adherence to prescribed medications for medical conditions, on both medication adherence and clinical outcomes.
Electronic System

Web-based database management system to facilitate screening, data extraction, adjudication of disagreements, author review and confirmation of data, production of data tables, and production of data files for future research:
Selection Criteria (1)

Types of Studies
• RCTs with unconfounded tests of interventions

Types of Participants
• Patients who are prescribed medications for medical (including psychiatric) disorders
• Excluded: studies targeting patients with addictions

Types of Interventions
• An intervention that serves to affect patients’ adherence to self-administered prescribed medication
Types of Outcome Measures

• At least one adherence measure, AND
• At least one clinical outcome, AND
• Adequate follow-up:
  ➢ >80% follow-up in all treatment groups
  ➢ Long-term regimens with initial positive findings had to have at least a 6 month follow-up period
Search Methods

• Studies from 2008 update were assessed for carry-over

• We updated searches on 11 January 2013:
  ➢ *The Cochrane Library*, including CENTRAL (via
  ➢ MEDLINE, EMBASE, PsycINFO (all via Ovid)
  ➢ CINAHL (via EBSCO)
  ➢ Sociological Abstracts (via ProQuest)

• Bibliographies in articles on patient adherence, and contacted authors of relevant original and review articles

→ 1<sup>st</sup> and 2<sup>nd</sup> screening in duplicate; disagreements resolved by adjudicator
Data Extraction Methods

• Data extracted in duplicate; disagreements resolved by adjudicator

• Similar data as previous update, with addition of:

• Cochrane Risk of Bias

• Information on theoretical background and tailoring of interventions
31,813 records identified through database searching
154 additional records identified through other sources

28,312 records after duplicates removed

28,312 records screened
24,639 records excluded

1664 full-text articles excluded, with reasons:
Not a RCT = 764
< 80% follow-up = 299
Not an adherence study/no adherence intervention = 197
No adherence measure = 135
No patient outcome = 92
Patient not prescribed a medication for a medical disorder = 28
Cannot access data/study/author = 26
Confounded study = 10
No between-group comparisons = 7
Not prescribed self administered medication = 4
Missing information about the intervention = 1
Analysis compromised = 1

1673 full-text articles assessed for eligibility

162 studies included in qualitative synthesis = 109 from this update + T3 from the previous review

8 studies included in quantitative synthesis (meta-analysis)
Included Studies

5 studies from the 2008 update were excluded after detailed review

- 2 did not address self-administered medications,
- 1 had <80% follow-up,
- 1 had no clinical outcome data,
- 1 was confounded

Total of 182 RCTs included

→ 109 new RCTs since 2008 – growth of 150%

Location*

- 80 from high-income countries (44 from USA)
- 17 from middle-income countries
- 5 from low-income countries
- 7 from unknown geographic locations

Targeted conditions
• HIV/AIDS (36)
• Psychiatric disorders (29)
• COPD (27)
• Cardiovascular disease or risk (21)
• Hypertension (17)
• Diabetes (16)
• Other (36)

Complexity of targeted regimen
• The majority of new RCTs (67/109) targeted >1 medication
• 27 RCTs targeted 1 medication
• 15 RCTs targeted unknown number of medications
Cautionary Tale

ANY medical condition included, to:
• Get a complete overview of the research field
• Account for the fact that adherence problems are often comparable
• Not exclude multi-morbidity

Large variety in:
• Study settings
• Clinical conditions
• Recruitment methods
• Treatment regimens
• Intervention types
• Adherence measures
• Clinical outcome measures

→ Insufficient common ground for quantifying differences between groups or estimating pooled effect sizes
ANY medical condition included, to:
• Get a complete overview of the research field
• Account for the fact that adherence problems are often comparable
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Large variety in:
• Study settings
• Clinical conditions
• Treatment regimens
• Intervention types
• Adherence measures
• Clinical outcome measures

ABC final report
Only RCTs measuring adherence with MEMS: $I^2 = 98.88\%$
How to Analyze Heterogeneous Results?

Summary
- text
- tabular

Vote counting / Combining p-values
- text
- tabular
- harvest plots
- effect direction plots

Summary of effect estimates
- descriptive statistics (non parametric)
- box and whisker plots

Meta-analysis
- meta-analysis
- predictive intervals
- forest plots

Exploring heterogeneity
- sub-group analysis
- meta-regression
- graphical approaches
Risk of Bias

Considering the large heterogeneity among RCTs, we chose to focus on RCTs with the lowest risk of bias, for:

- Random sequence generation
- Concealment of treatment allocation
- Blinding the assessment of the primary clinical outcome

→ 17 RCTs had a low RoB; 7 from previous update, 10 new

- Cochrane ‘Risk of Bias’ tool (Higgins 2011)
- Manuscript text (and author feedback) typically provided insufficient details to determine some RoB measures
RCTs with Lowest Risk of Bias

4 RCTs also had a low RoB for measuring adherence
Gray 2012        Chung 2011
Solomon 2012     Haynes 1976

13 RCTs had high/unknown RoB for measuring adherence
Ellis 2012        Wu 2006
Farooq 2011       Weber 2004
Morgado 2011      Laporte 2003
Lester 2010       Stevens 2002
Martins 2009      Nazareth 2001
Simoni 2009       Walley 2001
Simoni 2007
Methods

- **Participants:** 27 patients with new ocular hypertension or open-angle glaucoma
- **Intervention:**
  - Delivered by a glaucoma trained nurse
  - Assessment of patient needs, beliefs, and potential solutions
  - Devise a 1 year individualized care plan
  - Planning five face-to-face / phone follow-up contacts for reassessment
- **Control:** care as usual
- **Adherence measurement:** pharmacist report (low RoB)
- **Clinical outcomes:** intraocular pressure & care changes (routine medical charts)
- **Timelines:** intervention during 12 months, no intervention at months 12-24

Results

- **At 12 months:** Intervention more patients with 100% refill, no differences clinical outcomes
- **At 24 months:** Control had increased fluctuation of intraocular pressure and care changes
- Differences at 24 months due to chance?
Methods
• **Participants:** 2097 low-income older adults who were initiating osteoporosis medication
• **Intervention:**
  ✓ 7 informational mailings addressing osteoporosis
  ✓ 8 phone counseling sessions by health educators using motivational interviewing
• **Control:** only 7 informational mailings addressing osteoporosis
• **Adherence measure:** medication possession ratio, using pharmacy claims data (low RoB)
• **Clinical outcomes:** self-reported fractures or falls
• **Timelines:** 1 year follow-up

Results
• No difference in adherence and clinical outcomes
• 113-day time lag between identifying eligible patients and making the first phone call
• Interventions were generally **complex**, trying to overcome multiple barriers to adherence

• Primarily involved **enhanced support** from family, peers, or allied health professionals

• Of these 17 RCTs:
  ✓ 5 improved both adherence and clinical outcomes
  ✓ 3 improved only adherence outcomes
  ✓ 1 improved only clinical outcome
  ✓ 8 did not improve adherence or clinical outcomes

• This was a similar success rate to that found in the 21 newly included studies in the 2008 update (Haynes 2008)
Required Advances
Why We Need Advances

• Lack of convincing evidence for consistent, reliable, and potentially practical and cost-effective interventions

• Only modest reduction of Risk of Bias in the 35 year publication timespan in the cumulative review
  
  *Pearson correlation 0.156, 2-tailed p=0.035*

• Despite a growth in the number of adherence RCTs and a slight improvement in study methodology, largely the same methodological drawbacks endure

• The adherence research field is slow to catch up with the increasing availability of self-administered medications and technological innovations

<table>
<thead>
<tr>
<th>Psychosocial category</th>
<th>N of studies</th>
<th>Quality</th>
<th>Longitudinal association</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Beliefs and cognitions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. About medication and treatment</td>
<td>9</td>
<td>All low</td>
<td>2 x yes 3 x no</td>
<td>No association</td>
</tr>
<tr>
<td>II. About illness</td>
<td>3</td>
<td>All low</td>
<td>3 x no</td>
<td>(limited evidence)</td>
</tr>
<tr>
<td>III. Self-efficacy and locus of control</td>
<td>10</td>
<td>All low</td>
<td>1 x yes 9 x no</td>
<td>No association</td>
</tr>
<tr>
<td>B. Coping styles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. Task-oriented</td>
<td>4</td>
<td>All low</td>
<td>4 x no</td>
<td>No association</td>
</tr>
<tr>
<td>II. Emotion-oriented</td>
<td>6</td>
<td>All low</td>
<td>1 x yes 5 x no</td>
<td>No association</td>
</tr>
<tr>
<td>C. Social influences and social support</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. Regarding medical caregiver</td>
<td>5</td>
<td>All low</td>
<td>1 x yes 4 x no</td>
<td>No association</td>
</tr>
<tr>
<td>II. Regarding friends and family</td>
<td>6</td>
<td>All low</td>
<td>1 x yes 5 x no</td>
<td>No association</td>
</tr>
<tr>
<td>III. In general</td>
<td>14</td>
<td>All low</td>
<td>14 x no</td>
<td>No association</td>
</tr>
<tr>
<td>D. Personality traits</td>
<td>8</td>
<td>All low</td>
<td>1 x yes 7 x no</td>
<td>No association</td>
</tr>
<tr>
<td>E. Psychosocial well-being</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. Mood state</td>
<td>21</td>
<td>All low</td>
<td>3 x yes 18 x no</td>
<td>No association</td>
</tr>
<tr>
<td>II. Perceived stress/stressors</td>
<td>8</td>
<td>All low</td>
<td>2 x yes 6 x no</td>
<td>No association</td>
</tr>
</tbody>
</table>


- Multiple determinants, many inconsistencies

→ Low adherence is **very hard to predict**
Of the 109 new RCTs
- Only 11 (10%) enrolled patients based on their baseline adherence
- 52 did not consider adherence status for enrollment
- 46 studies did not provide sufficient details to determine whether they considered adherence status for enrollment
- Of 56 RCTs (51%) measuring baseline adherence, only 11 reported results based on baseline adherence status
- Baseline adherence measurement possible?
  - 71 (65%) targeted patients who were already on the medication
  - 38 (35%) targeted newly starting patients
    (proxy: adherence to other med, prior visit attendance?)

‘Run-in’ period before randomization to identify NON-adherent participants?
### Table 2. Categorization of features of patient recruitment methods into scale scores based on whether that feature is absent (no), uncertain absent or present (uncertain), and present (yes)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score 0 (no)</th>
<th>Score 1 (uncertain)</th>
<th>Score 2 (yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonadherent patients selected</td>
<td>No (no mention of past adherence in any capacity, assume both adherent and nonadherent patients recruited)</td>
<td>Indeterminate (eg, only included patients with high blood pressure or patients who had that physiologic state possibly due to a lack of adherence in the past but not explicitly stated that adherence was measured before selection)</td>
<td>Yes (adherence was measured before study inclusion, and only those with low adherence were included in the study, or those with low adherence to begin with are separately reported)</td>
</tr>
<tr>
<td>Representativeness of sample (number recruited/number screened who met eligibility criteria)</td>
<td>Number of patients asked to join is much greater than sample size (&gt;2:1 nonenrolled to enrolled)</td>
<td>Does not report number of patients asked before reaching sample size</td>
<td>The number of patients asked to join is similar to sample size (≤2:1 nonenrolled to enrolled)</td>
</tr>
<tr>
<td>Results reported based on baseline adherence</td>
<td>Baseline adherence was not measured</td>
<td>Baseline adherence measured, but results were not reported according to initial adherence level</td>
<td>Yes, results were reported based on baseline adherence level or if only nonadherent patients are recruited, if intention-to-treat analysis is followed</td>
</tr>
</tbody>
</table>
In the 109 new RCTs
• Overall 163 measures of adherence were included
• The median overall quality of these measures was 4 on a scale from 0 to 9 (*next slide*)
• 14 studies (13%) used a measure of adherence that was valid, reliable, objective, unobtrusive and longitudinal
• 52 studies (48%) used only subjective adherence measures

Major issues
• Validation
• Assessing reliability
• Optimizing objectivity
• Blinding
• Longitudinal measures vs ‘snapshots’
Table 1. Categorization of features of adherence measures (reliability, validity, objectivity, unobtrusiveness, and longitudinality) into scale scores based on whether the feature is absent (no), uncertainly absent or present (uncertain), or present (yes).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score 0 (no)</th>
<th>Score 1 (uncertain)</th>
<th>Score 2 (yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reliability</td>
<td>Documented not to be reliable</td>
<td>Reliability not assessed</td>
<td>Measure documented to be reliable</td>
</tr>
<tr>
<td>Validity</td>
<td>Documented not to be valid</td>
<td>Validity not assessed</td>
<td>Measure documented to be valid in comparison with a criterion standard</td>
</tr>
<tr>
<td>Objectivity</td>
<td>Subjective measure without appropriate blinding to patients’ treatment group (appropriate blinding = method of blinding stated and blinding of patient and assessor or blinding of assessor when impossible to blind patients)</td>
<td>Subjective measure with uncertain blinding (method or blinded group not explicitly stated)</td>
<td>Objective measure (medication event monitoring system, pharmacy refill data, biologic measure of drug) or subjective measure with method of blinding explained and includes appropriate blinding</td>
</tr>
<tr>
<td>Unobtrusiveness</td>
<td>Obtrusive to patient leading to potential Hawthorne effect (eg, electronic monitoring)</td>
<td>Unclear whether the patient is aware adherence is being measured or the extent to which the measure would interfere with their usual medication consumption</td>
<td>Patient is unaware the measure is being taken and the measure does not interrupt the normal pattern of medication consumption (pharmacy refill record)</td>
</tr>
<tr>
<td>Longitudinality</td>
<td>Data provided by measure covers the past 1—7 days of adherence for a chronic (long-term) regimen</td>
<td>Data by measure covers a longer period (&gt;7 days) for a chronic medication regimen</td>
<td>Data by measure covers a longer period (&gt;7 days) for a chronic medication regimen</td>
</tr>
</tbody>
</table>
### Table 3. Measurement qualities of all generic types of adherence measures from a sample of randomized trials of interventions to increase patient adherence

<table>
<thead>
<tr>
<th>Measure</th>
<th>Frequency of use in sample of RCTs (n)</th>
<th>Median validity score (max 2) and range&lt;sup&gt;&lt;sup&gt;b&lt;/sup&gt;&lt;/sup&gt;</th>
<th>Median reliability score (max 2) and range&lt;sup&gt;&lt;sup&gt;b&lt;/sup&gt;&lt;/sup&gt;</th>
<th>Median objectivity score (max 2) and range&lt;sup&gt;&lt;sup&gt;b&lt;/sup&gt;&lt;/sup&gt;</th>
<th>Median unobtrusive score (max 2) and range&lt;sup&gt;&lt;sup&gt;b&lt;/sup&gt;&lt;/sup&gt;</th>
<th>Median longitudinality score (max 1) and range&lt;sup&gt;&lt;sup&gt;b&lt;/sup&gt;&lt;/sup&gt;</th>
<th>Median total score (max 9) and IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attendance</td>
<td>2</td>
<td>0.5 (0–1)</td>
<td>0.5 (0–1)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Clinician judgment</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Direct observation</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0.5 (0–1)</td>
<td>4.5 (0.5)</td>
</tr>
<tr>
<td>Drug concentration in body</td>
<td>6</td>
<td>1</td>
<td>1 (1–2)</td>
<td>2</td>
<td>1.5 (1–2)</td>
<td>1</td>
<td>7 (0.75)</td>
</tr>
<tr>
<td>MEMS</td>
<td>16</td>
<td>2 (1–2)</td>
<td>2 (1–2)</td>
<td>2 (0–2)</td>
<td>0 (0–2)</td>
<td>1</td>
<td>6.5 (2.25)</td>
</tr>
<tr>
<td>Pharmacy refill record</td>
<td>14</td>
<td>1.5 (1–2)</td>
<td>1.5 (1–2)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Pill count</td>
<td>20</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>2 (0–2)</td>
<td>0 (0–2)</td>
<td>1</td>
<td>5 (1.25)</td>
</tr>
<tr>
<td>Self-report questionnaire</td>
<td>17</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>0 (0–1)</td>
<td>0</td>
<td>0 (0–1)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Self-report diary</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Self-report interview</td>
<td>8</td>
<td>1.5 (0–2)</td>
<td>1.5 (0–2)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>4.5 (3.25)</td>
</tr>
<tr>
<td>Therapeutic response</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1 (1–2)</td>
<td>1</td>
<td>6 (0.5)</td>
</tr>
</tbody>
</table>

*Abbreviations: IQR, interquartile range; MEMS, medication event monitoring system; RCT, randomized controlled trials.*

<sup>a</sup> Measures are not meant to be compared against each other as the nature of each quality category (i.e., validity, and so forth) is not comparable between measure types as criterion standards can differ. Some measures are from the same study as some studies used multiple measures of adherence.

<sup>b</sup> Range is only included in brackets if a range is possible to include based on the data.
Why Require Clinical Outcomes?

• Adherence measurement typically has a high risk of bias (clinical events; important to patients and objectively verifiable)

• Potential adverse effects despite improved adherence:
  ✓ Loss of privacy / autonomy
  ✓ Increased adverse effects of medication
  ✓ Attention drawn away from other health issues

• Short-term improvements in adherence are not important for chronic care if they cannot be sustained

Of 109 new RCTs
• Reporting patient-important clinical events - 34 (31%)
• Reporting biological outcomes - 73 (67%)
• Reporting patient reported outcomes - 71 (65%)
Among 109 new RCTs

- Concealment of allocation prior to the exact time of randomization was unclear in 71 trials (65%) and not done in 3 (3%)

- ‘Active’ control group (balance the increased attention) – 27 (25%)

- Blinding
  - Of patients - 9 (8%)
  - Of personnel - 7 (6%)

  ✓ *Neither are fatal flaws, IF adherence measures are objective and outcome assessors can be blinded*

- Using a cluster design - 11 (10%)
Minimum sample size requirement
As a general guide, studies with a single intervention group and control group would need to include at least 60 participants per group if they are to have at least 80% power to detect an absolute difference of 25% in the proportion of patients judged to have adequate adherence

Actual power of RCTs
• According to this rule, the new RCTs were as likely to be underpowered (44/109; 40%) as RCTs in the previous update (36/78; 46%)
• Among the 17 lowest risk of bias RCTs in the present update, 4 had insufficient power
Intervention Design

- Intervention design explicitly based on theoretical framework – 39%
- Key stakeholders involved in intervention design – 33%
- ‘Kitchen sink’ approaches could work. If effective:
  - Test individual components
  - Assess cost-effectiveness
  - Assess practicality
Intervention Types

• Allied health professionals, lay health workers
  – Specific roles & standardized training

• Technology: mobile devices, web-based, new developments

• Enhanced social support – peers, family, friends

• Combination therapy, simplified dosing

• Interventions obviating the need for adherence (implantable)

• Novel ideas!!
Incomplete Reporting


Table 1: Items Included in the Template for Intervention Description and Replication (TIDieR) checklist: Information to include when describing an intervention. Full version of checklist provides space for authors and reviewers to give location of the information (see appendix 3)

<table>
<thead>
<tr>
<th>Item No</th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief name</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Provide the name or a phrase that describes the intervention</td>
</tr>
<tr>
<td>Why</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Describe any rationale, theory, or goal of the elements essential to the intervention</td>
</tr>
<tr>
<td>What</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (such as online appendix, URL)</td>
</tr>
<tr>
<td>4</td>
<td>Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities</td>
</tr>
<tr>
<td>Who provided</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>For each category of intervention provider (such as psychologist, nursing assistant), describe their expertise, background, and any specific training given</td>
</tr>
<tr>
<td>How</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group</td>
</tr>
<tr>
<td>Where</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features</td>
</tr>
<tr>
<td>When and How Much</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose</td>
</tr>
<tr>
<td>Tailoring</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how</td>
</tr>
<tr>
<td>Modifications</td>
<td></td>
</tr>
<tr>
<td>10*</td>
<td>If the intervention was modified during the course of the study, describe the changes (what, why, when, and how)</td>
</tr>
<tr>
<td>How well</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them</td>
</tr>
<tr>
<td>12*</td>
<td>Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned</td>
</tr>
</tbody>
</table>

*If checklist is completed for a protocol, these items are not relevant to protocol and cannot be described until study is complete.
"Sorry, pal, right metaphor, wrong motivation."
Limitations
• Missed studies
• Eligibility criteria
• Risk of bias assessment

Remedies
• Report missed studies
• Provide suggestions for classification of RCTs
• Also assess systematic reviews on specific conditions
• Share data
Implications for Practice

New studies and high quality studies frequently used interventions that are complex, and delivered (partly) by allied health care professionals with regular patient interaction

HOWEVER

1. Even these complex, intensive long-term strategies were not very effective, despite the effort and resources they can consume
2. There is insufficient evidence at present to conclude that newer interventions (SMS, web-based) can assist in improving adherence
3. There is no evidence that low adherence can be ’cured’

Recommendation (for now)
Adherence approaches should be maintained for as long as the treatment is needed, aiming for cost-effective* integration into the care system

1. **Barriers causing low medication adherence** need to be better understood.

2. **Theoretical frameworks** to aid in the design of complex interventions:
   - Provide rationale of design and hypothesized mechanisms of effect
   - If effective, evaluate components in factorial design

3. **Adherence research methodology** needs improvement in several areas:
   - Recruitment of patients with low adherence
   - Employ best-in-class adherence measurements (blinding)
   - Power studies to find potentially meaningful effects
   - Provide sufficient details on research methods in publications

4. **Intervention types** to consider:
   - Treatments that obviate the need for adherence (e.g. implantable)
   - Simplified regimen
   - Newer information-communication technologies
Data Sharing

• Low adherence is a **ubiquitous problem** for all self-administered medications
• Joined efforts are needed to advance the field

**HIRU makes its database available for collaborations on sub-analyses**

Current sub-analyses
• Risk of bias
• Technology-mediated interventions
• HIV/AIDS
• Pediatric interventions
• Use if theory to design interventions
Cochrane Publication


**Publication date:** November 20\(^{th}\), 2014