



Adherence Strategies and Measurement in Clinical Trials

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Areas To Be Addressed

- ◆ Definitions
- ◆ Significance
- ◆ Challenges
- ◆ Measurements
- ◆ Strategies
- ◆ Recommendations

Definitions of Adherence

- ◆ **Participant:** Level of correspondence between protocol required behaviors and participant behavior. May include treatment, visit attendance, assessment schedule, reporting, others
- ◆ **Staff:** Level of correspondence between protocol required behaviors and staff behavior. May include intervention integrity, scheduling, assessment procedures, forms completion, others

Significance



Impact on Clinical Research of Participant Adherence

1. Lack of Study Power
2. Dropouts
3. Missing Data
4. Inadequate Treatment Effect
5. Increased Sample Size Needs
6. Increased Cost
7. Underestimate of Effectiveness
8. Overestimate of Safety
9. Underestimate of Risks, Adverse Effects

Impact on Staff Adherence on Clinical Research

1. Bias or Error in Findings
2. Poor Data Quality
3. Inadequate Test of Intervention Effectiveness
4. Loss of Subjects
5. Reduction in Study Power

Can Poor Adherence Change Study Results?

YES!



Adherence and Interpretation of Clinical Trials ¹

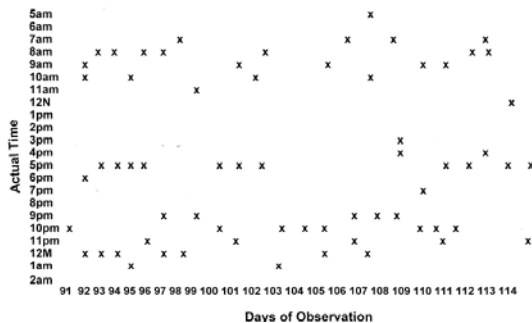
Significance of Differences Between Means - Adjusted and Unadjusted For Compliance-

Treatment Variable	Adjusted	p	Unadjusted	p
Active Joints				
Phenylbutazone	2.79	.01	3.49	.20
Placebo	4.02		4.03	
C20410	2.65	.01	1.47	.001

¹ Joyce et al, 1962

DAILY VARIABILITY VS. STABLE LOW/NO ADHERENCE

Three Times a Day Dosing Prescription



The Impact of Adherence to One Drug May be Related to the Clinical Outcome Indicator of Another Condition

Relationship of Adherence to Other Conditions

Percent of Days Adherent [DM2] SBP $r = .127, p = .042$
 TChol $r = .125, p = .046$

Percent of Prescribed Doses [Chol] SBP $r = -.158, p = .021$

Percent of Prescribed Doses [HBP] FGI $r = .128, p = .045$

J. Dunbar-Jacob, 2005
 NIH NIDDK R01 DK59048

Complexity

	M	sd	range
Co-morbidities	6.86 ± 3.1		1-20
No. Medications Prescribed	7.30 ± 3.5		2-20
OTC	2.20 ± 2.1		0-10
All meds	9.50 ± 4.0		3-20

CMS 2008

Relationship of Co-Morbidities to Days Adherent

Diabetes: $r_s = -.132, p \cong .034$

No. of Co-Morbidities	Days Adherent		Total
	<80%	≥80%	
<4	12 (23%)	40 (77%)	52
5-7	37 (31.6%)	80 (68%)	117
>8	34 (38.6%)	54 (61%)	88
			257

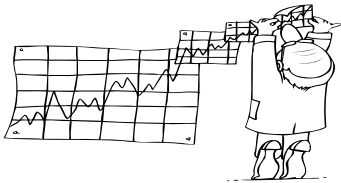
Hypertension: $r_s = -.148, p \cong .017$

No. of Co-Morbidities	Days Adherent		Total
	<80%	≥80%	
<4	4 (7.7%)	48 (92.3%)	52
5-7	19 (16.4%)	97 (83.6%)	116
>8	19 (21.8%)	69 (79%)	87
			255

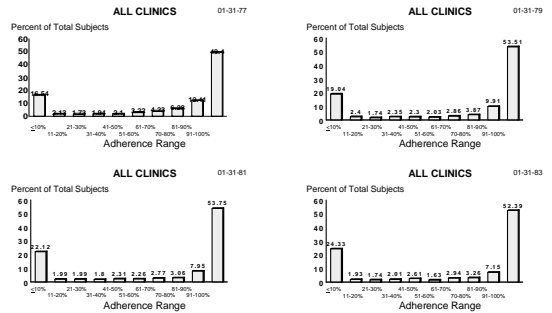
Self-report: $r = .091, p = .15$

CMS 2008

PATTERNS OF ADHERENCE SEEN OVER TIME IN CLINICAL TRIALS

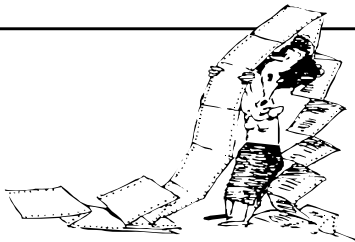


Distribution Of Levels Of Adherence Over Time: LRC-CPPT All Clinics



Dunbar-Jacob, et al., 1994

HOW SHOULD WE MEASURE ADHERENCE?



Typical Methods of Assessing Adherence

	Biological Assay	Pharmacy Refill	Self-Report	Pill Count	Electronic Monitors
Doses Adherent		X	X	X	X
Days Adherent			X		X
Intervals Adherent			X		X
Doses Available		X		X	
Recent Doses Taken	X		X		X

Comparability of Measures

	Self-Report		Pill Count		Total
	<80%	>80%	<80%	>80%	
<80%	2.5%	21.5%	8.0%	16.0%	23.9%
>80%	2.5%	73.6%	0.6%	75.5%	76.1%
Total	4.9%	95.1%	8.6%	91.4%	100%
	X ² = 3.14, df=1, p=.038		X ² = 39.98, df=1, p=.000		

Electronic Monitor

J. Dunbar-Jacob, 2002, ACT

Correspondence Between Diary and EEM Monitored Adherence by Method of Defining Adherence

Definition	Kappa
♦ \geq or $<$ 80% of Doses Taken	.241
♦ \geq or $<$ 80% of Days Compliant	.280
♦ \geq or $<$ 80% of Doses in Correct Interval	.198

RAC-1

Relationship of Adherence to Cholesterol Change

Adherence	% Δ Total	
	Cholesterol	p-value
EEM ₁	.26	.043
EEM ₂	.18	NS
7-Day EEM ₁	.34	.009
7-Day EEM ₂	.26	.050
Pill Count	.12	NS
7-Day Recall ₁	.20	NS
7-Day Recall ₂	.00	NS

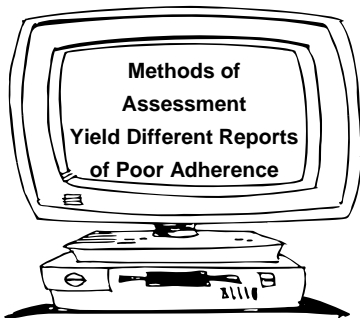
1 # pills
2 # pills in correct dosing interval

J. Dunbar-Jacob, 2002, ACT

Predictors of Adherence by Measurement Method

	Monitored	Interview
Gender	X	
Employment	X	
Income	X	
Tangible Support	X	
Symptom Support	X	
Symptom Severity	X	
Age		X
Cost of Medication		X

Dunbar-Jacob J, Sereika S, Rohay JM, Burke LE, & Kwok CK. Predictors of Adherence: Event monitoring vs. self-report.



Measuring Staff Adherence

- ♦ Observation of Intervention Integrity
- ♦ Quality Control Procedures



STRATEGIES TO IMPROVE ADHERENCE

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Impact of The Clinical Protocol

- ◆ Frequency of Contact
- ◆ Frequency of Visits
- ◆ Complexity of the Treatment Program
- ◆ Blind (Treatment Regimen/Lab Results)
- ◆ Long Term Comprehension of the Protocol
- ◆ Duration of the Study

Recognize Alerts

- ◆ Neglected Cohort
- ◆ Missed Visits
- ◆ Declines in Adherence
- ◆ Change in Critical Staff
- ◆ Change in Life Circumstances
- ◆ Study Complaints

Prevention Strategies

- ◆ Plan Study Contact to Reinforce Continuation
 - Feedback on Status Where Possible
 - Emphasize Value of Participation
 - Provide Positive Communication
 - Education Opportunities Throughout
 - Time with Key Staff
 - Regular Contact
 - Strategies to Address Alerts
 - Reminders

Recommendations

- ◆ Anticipate Adherence Problems Participants and Staff
- ◆ Recognize Burden of Protocol
- ◆ Measure Routinely, Obtaining Best Data
- ◆ Respond to Measures
- ◆ Consider Adherence in Analysis and Interpretation

Thank You!
Questions?

