

Adherence

Concepts, Technologies, Challenges

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Conflicts of Interest

- Inventor and investigator for the Creare Mobile Compliance System for Clinical Trials
- Founder and owner DxRx Inc
- No other conflicts – but always open to more

Adherence – Traditional Definition

- Dictionary:
 - Follow the rules, fidelity
 - Also means 'stick to'
- In medicine:
 - Likelihood subject (or patient) will follow the prescribed treatment.
- Lack of adherence can lead to disease progression and unnecessary expenses
 - Also destroys clinical trials
- Most patients not adherent with treatment
 - We assume research subjects are better but know they are not

Traditional Methods to Assess Adherence

- Ask the patient
- Do a pill count
- Check a blood level

Why don't these methods work

- Patients often reluctant to tell the truth
 - Self report overestimates adherence by up to 300%
 - Treating physicians overestimate adherence by 50%
- Pill counts retrospective
- Some take meds only before testing

Why its crazy to adhere in a clinical trial

- Drug is dangerous. I could even die
 - Consent form says so repeatedly
- If I get hurt you wont pay for my injuries
 - Consent makes this very clear
- I may not even get the real drug
 - And I still don't get paid if I get hurt
- Everyone else is getting paid
 - Not fair.

The Dallas Buyers Club



<https://www.youtube.com/watch?v=WpZ4kY3AJWU>

Why participate if you are not going to take the drug

- It's a job I can do
 - Compensated in status, appreciation
- The people at the trial site are really nice
- It gets the family off my back
 - Taking control, not powerless in the face of disease
- If it does work I already have a supply
- When they have something that really works I'll be first in line

Adherence – Pharmacist's Definition

- Best
 - Drug at effect site
 - Drug or metabolite in a biomatrix (tissue, urine, feces)
- Better
 - Directly Observed Proof of Drug Delivery
- Fair
 - Pill Bottle Monitors
- Poor
 - Pill Counts
 - Proof that the patient or subject was given the drug
 - Writing a Prescription

Measuring Drug at Effect Site

- Direct measurement
 - Biopsy
 - AMS
- Indirect measurement
 - PET Scans
 - Radiolabeled tracers

Measuring Drug Ingestion

- Drug or metabolite levels in blood or urine
 - Only problem is data are retrospective
- Real Time Systems – Three Solutions
 - AiCure
 - Smartphone pill imaging system
 - Proteous
 - RFID Chip ingested with drug
 - Creare MCoSCT
 - Smartphone pill imaging plus biomarker confirmation

AiCure

- Smartphone used to capture real-time images of pills in the mouth
- Uses Artificial Intelligence to confirm ingestion
 - They don't explain how this is actually done
- Claim they can detect cheating
- Only need a smartphone with a front facing camera and an web connectivity to work
- Available now

AiCure Products

- AiView
 - Identifies pills and capsules based on color, shape and markings. The system can be trained to recognize any particular branded medication.
- AiView-SL
 - The technology is trained to confirm sublingual medication under the tongue. Different protocols can be integrated depending on the length of time needed for the medication to dissolve.
- AiBreathe
 - The system can be used to confirm activation of an inhaler using distinct audio and visual signatures.
- AiPen
 - Cure's platform has been extended to include monitoring of injectable pens, and tracking titration levels.

AiCure Data Management

- AiDashboard
 - Real-time adherence data are transmitted to a centralized and cloud-based dashboard to offer a fully HIPAA-compliant audit trail of each dosing activity. Real-time data and longitudinal adherence patterns are used for immediate intervention and predictive algorithms. Secure communications are integrated into the dashboard so that patients may be contacted directly by phone and SMS from the dashboard without release of PHI.
- AiDiary
 - Educational content, patient surveys, patient statistics, feedback, and micro-incentives can be customized and integrated according to patient profile.

AiCure – Pros and Cons

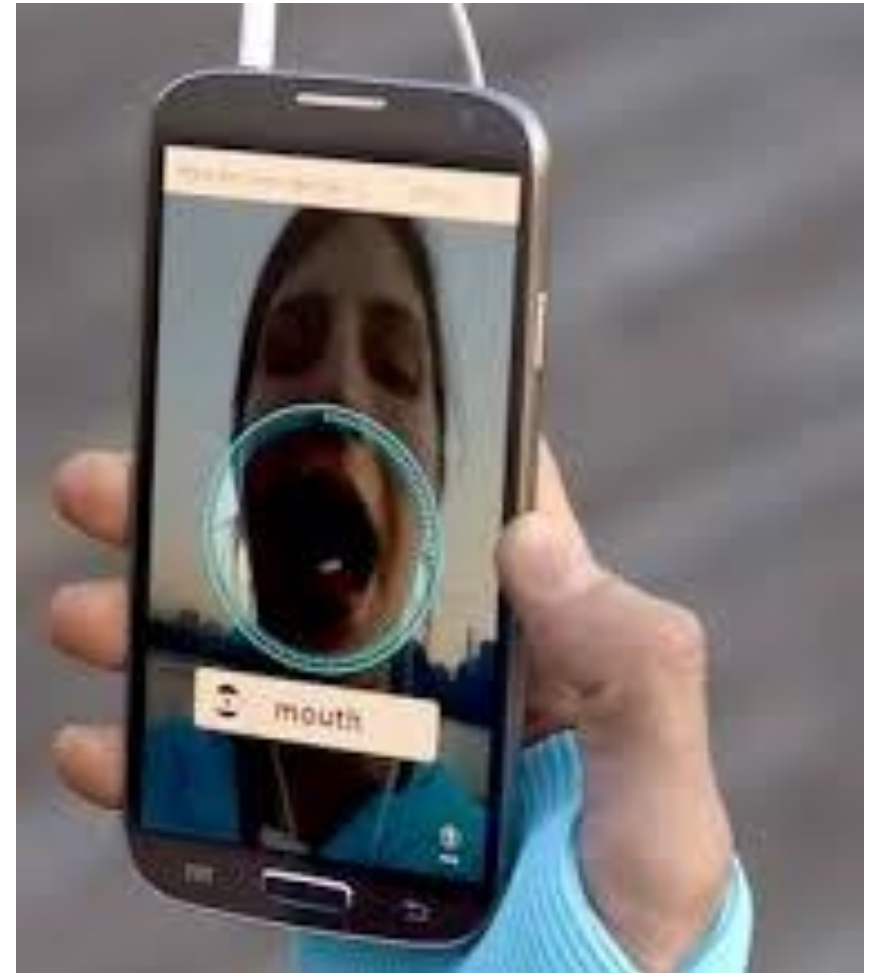
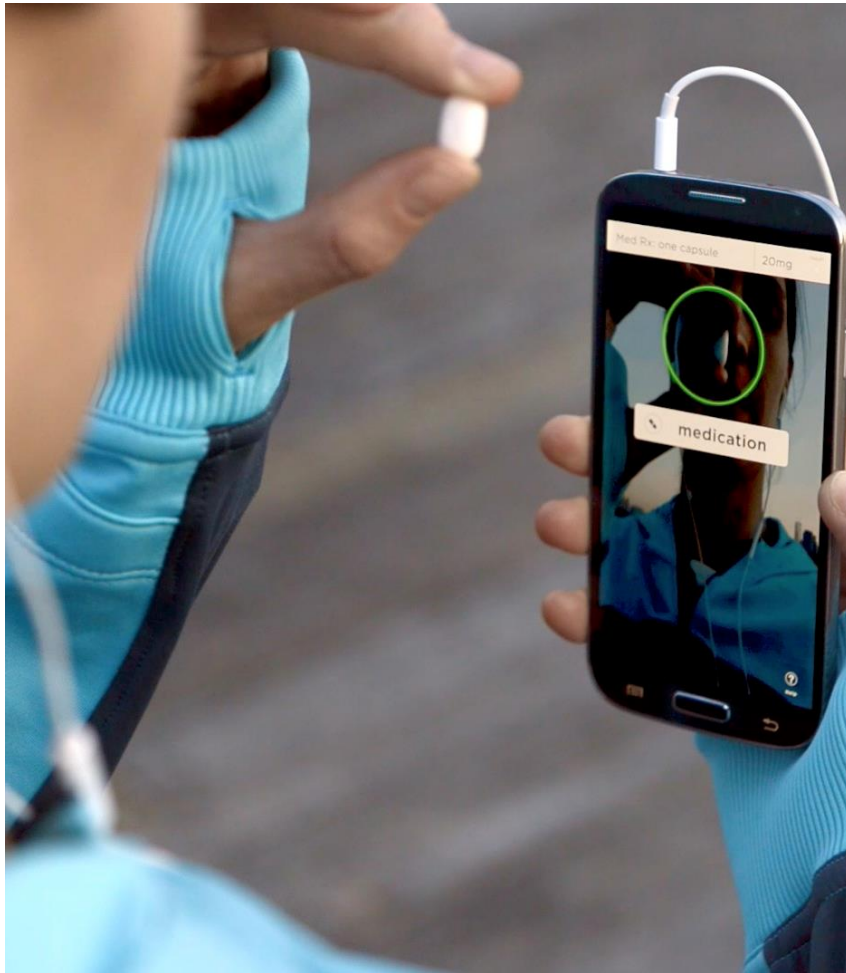
■ Pros

- Elegant and relatively simple system
- Integrates psychosocial management.
- May be able to predict future non-adherence

■ Cons

- Does not confirm actual ingestion or absorption.
- Not clear how robust pill identification is
- Claim to blur out face BUT how good is this tech – IRBs may get nervous.

AiCure



<https://player.vimeo.com/video/150918535>

Examples of Venture-Funded Innovative Health Care Companies

Examples of Venture-Funded Innovative Health Care Companies.*				
Company (Yr Founded, Latest Valuation)	Core Business	Purported Innovation	Disrupted Competitors	Added Value
Theranos (2003, \$9 billion)	Novel laboratory diagnostic test technology using very small amounts of blood	Low-cost laboratory-test processing Patients can order their own laboratory tests and receive results	Traditional laboratories including those in hospitals that provide important revenue stream Physicians who currently control access to tests and results	Patient control of decision making and information
ZocDoc (2013, \$1.8 billion)	Online medical care scheduling	Search engine for finding physicians best suited for patient's perceived problem and schedule Patients can book appointments online without intermediary	Traditional referral mechanisms and networks (e.g., doctors and their assistants)	More efficient booking process Increased patient control
Intarcia Therapeutics (1995, \$1.8 billion)	Novel subcutaneous systems for drug administration that allow continuous slow delivery over long period	Allows once- or twice-yearly administration of medications Improves adherence with prescribed dosing	Pill manufacturers Physicians and other health care professionals who provide adherence education to patients	Improved effectiveness of pharmaceutical products Easy to rule out poor adherence as cause of treatment failure in practice or research
Oscar Health Insurance (2013, \$1.7 billion)	Health insurance	Redesigned health insurance to improve consumer experience Offers free remote advice for health problems through doctor on call Provides transparent medical pricing information before visit	Traditional health insurers	Provides "health insurance that won't make your head explode"
Proteus Digital Health (2001, \$1.1 billion)	Technology to inform patients and physicians about health-related behaviors, especially medication adherence	Ingestible sensor embedded in pills to measure oral administration adherence Combines ingestible, wearable mobile, and cloud computing		Helps determine whether poor compliance contributes to treatment failure
23andMe (2006, \$1.1 billion)	Direct-to-consumer genetic testing using saliva	Informs people of their genetic background and relative risks for numerous diseases	Traditional genetic counseling services and laboratory facilities that may provide a revenue stream for hospitals	Empowers patients to choose which disease-screening strategies best suit them May create more demand for downstream screening

* Data are from a *Wall Street Journal* list of venture-funded health care companies with valuations of \$1 billion or more, excluding biotech companies (<http://graphics.wsj.com/billion-dollar-club>).

Proteus Digital Health

- Tracks pill ingestion and some physiologic parameters – Heart Rate and Activity
- System consists of a:
 - Sensor Enabled Pill
 - Drug over encapsulated with RFID sensor
 - A patch applied to the abdomen
 - Receives sensor signal and sends to web-enabled device
 - An App and a Web Portal
 - For analysis, storage and dissemination of data.

Proteus – Pros and Cons

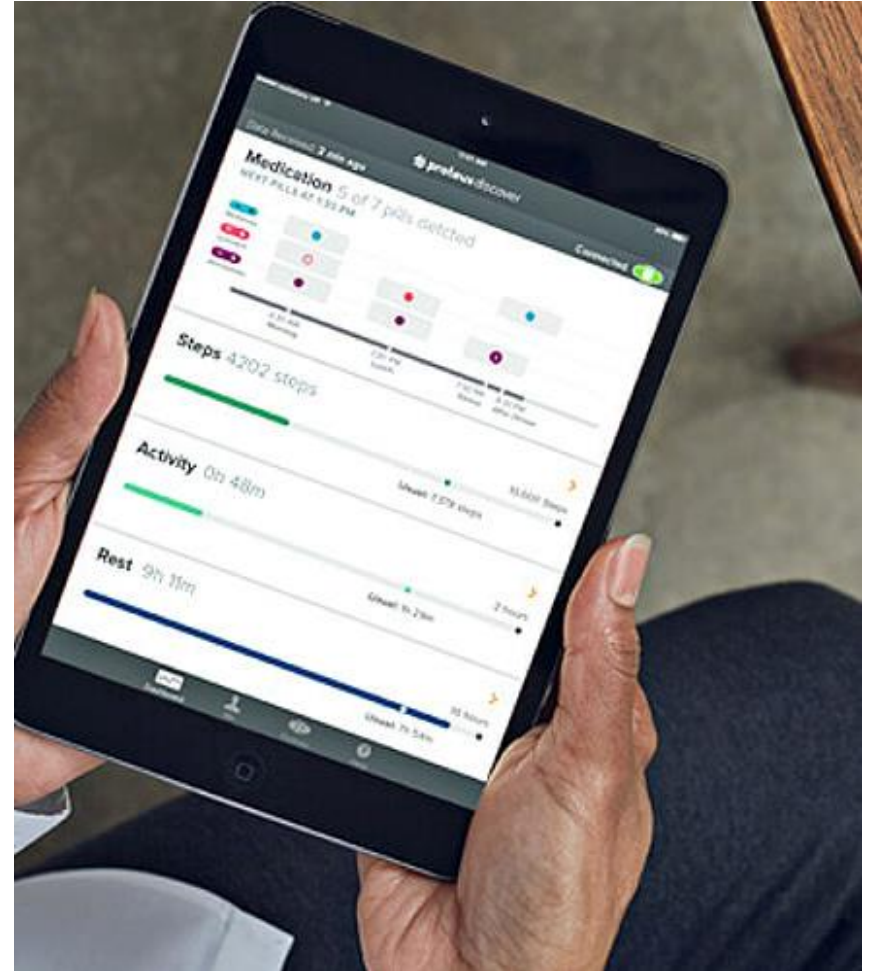
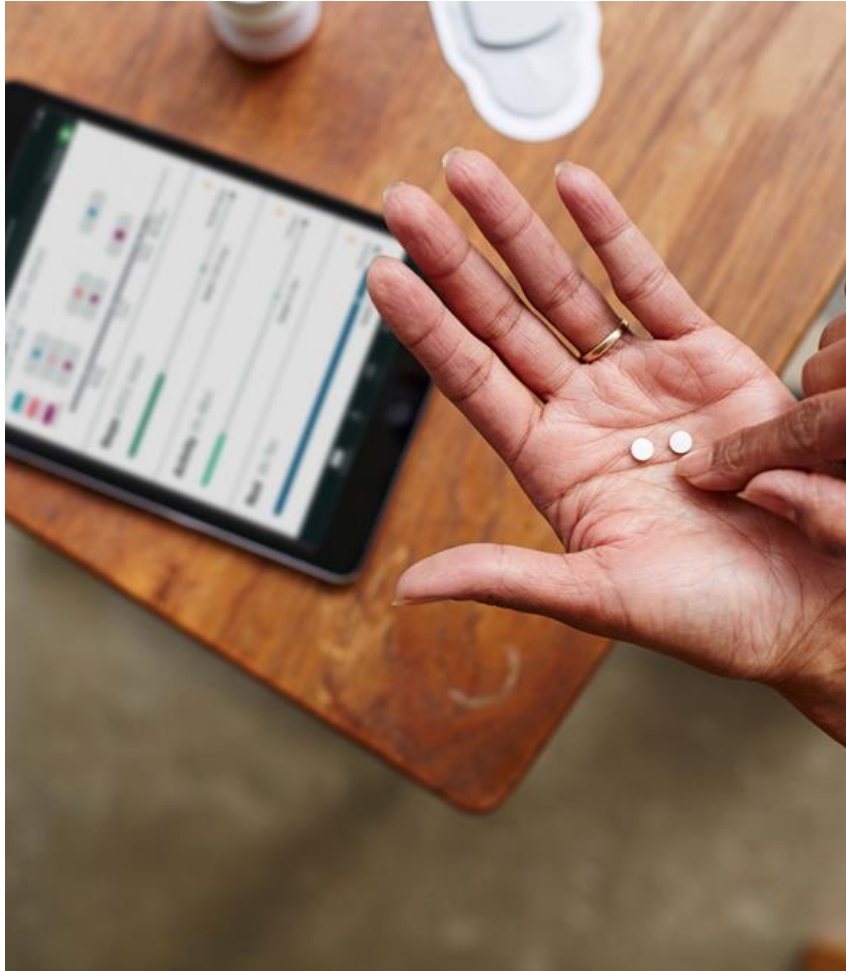
■ Pros

- Confirms ingestion because sensor activates when it reaches the stomach
- Individual pills tagged
- Relatively easy co-formulation
- If you need HR and activity
- FDA approved device

■ Cons

- The patch.
- Theoretically could fool system by placing sensor-enabled pill in warm acidic water.
- Reformulation required
- Claim 66 studies, >800 subjects but no publications

Proteus Pills and App



Proteus Patch

- Essential component of system
- Placed on the abdomen
- Not clear how many days patch lasts.
- And no way to tell who is actually wearing the patch

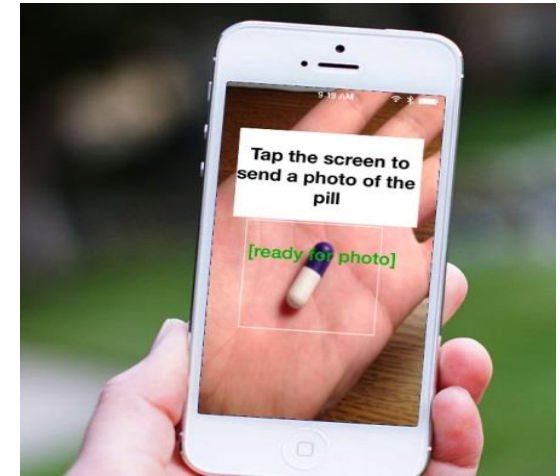


Create Mobile Compliance System for Clinical Trials (MCoSCT)

- Components
 - Smartphone
 - Portable fluorometer paired to phone by Bluetooth
 - Study drug

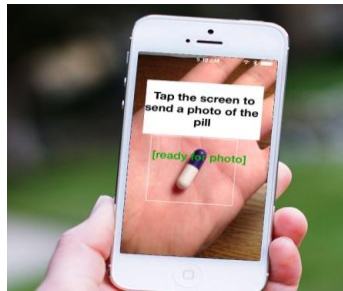
Create Mobile Compliance System For Clinical Trials

- Use mobile technology to monitor dosing *in real time*
 - Know immediately if subject is non-compliant
 - Make subject count by intervening if no pill photo is uploaded
 - Predict impending non-adherence using actual versus prescribed dose time
- Use mobile fluorometer to confirm adherence at home
 - Detect presence or absence of biomarker in the subject urine
 - Increase accuracy of compliance without added cost of subject clinic visit
 - Test as soon as desired after dose time
- Use the cloud to monitor in real time
- Include study-specific self-reports linked to dose time



Create Mobile Compliance System for Clinical Trials (MCoSCT)

Monitor individual dose timing through photos of pill in subject hand, in real time



Confirm actual dosing through at-home detection of biomarker in urine

Monitor all data through the cloud. Detect impending non-adherence and intervene to make subject count

Create Pros and Cons

Pros

- Measures and confirms ingestion
- Works with any smartphone and most camera equipped flip phones
- Can theoretically detect drug or metabolite directly

Cons

- Requires a separate device for confirmatory measure
 - Adds cost (\$200/device)
 - Adds complexity
- Requires over encapsulation with riboflavin or quinine

FDA weighs in...

www.theonion.com/article/fda-recommends-adding-little-tabasco-bad-boy-52328

the ONION

FDA Recommends Adding Little Tabasco To That Bad Boy

SEARCH Q TOP HEADLINES

FDA Recommends Adding Little Tabasco To That Bad Boy

NEWS IN BRIEF
February 9, 2016
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Food · News · Government

f t e

Jack in the box



WASHINGTON—In an effort to ensure all Americans receive a zesty kick, the Food and Drug Administration officially recommended Tuesday adding a little Tabasco to that bad boy.

“Based on years of research and dozens of clinical trials, our agency strongly advocates that

Product GlowCap@.html download.html Show All

An alternative to MEMS caps - Pill Photos taken with Cell Phones.

- Advantages of Cell Phones
 - Widely available
 - In India ~500 million cell phones
 - Only ~300 million toilets
 - Almost everyone has a cell phone with a camera
 - 50% of the all people have a cell phone
 - 75% of new phones have a camera
 - Photos are date and time stamped by the cell network
 - Can be used to prompt dosing

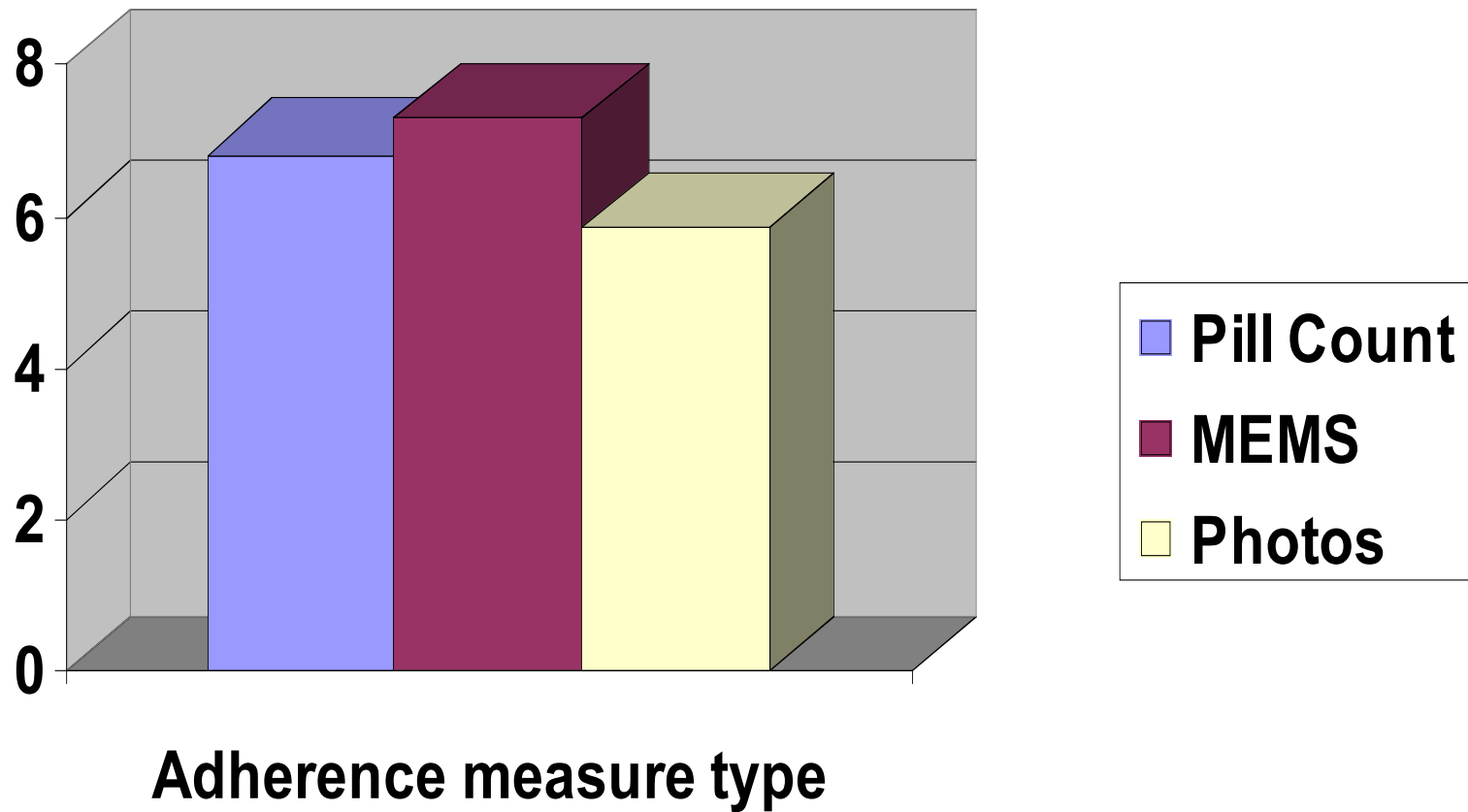
Adherence to Modafinil

- 20 subjects dosed with 200 and 400 mg/day of modafinil
- Medication placed in bottles with MEMS caps
- Instructed to photograph pills just before ingestion
- Paid \$3.00 for each photo sent and \$20 for each bottle returned
- Medication bottles returned weekly, returned pills counted

Actual Photos



Pills taken per week as measured by various adherence methods



Data –

All subjects issued 7 capsules/week

	Mean Cap/week	Mean % Adherence	Impossible Adherence
Photos	5.85±.91	87.2%	13.7%
MEMS	7.27±1.32	106.7%	45.0%
Pill Count	6.79±.98		

- Pill count adherence = 94.9±13.5%
- MEMS adherence = 93.6±15%
- Pill Photo adherence = 76.9±14.6%

How did we do compared to capsule counts?

Estimation (under-, equal, and over) of adherence by MEMS and photographs, compared to capsule counts.

	MEMS	Photos
Under	22% (N=26)	49% (N=59)
Equal	39% (N=47)	37% (N=44)
Over	39% (N=47)	14% (N=17)

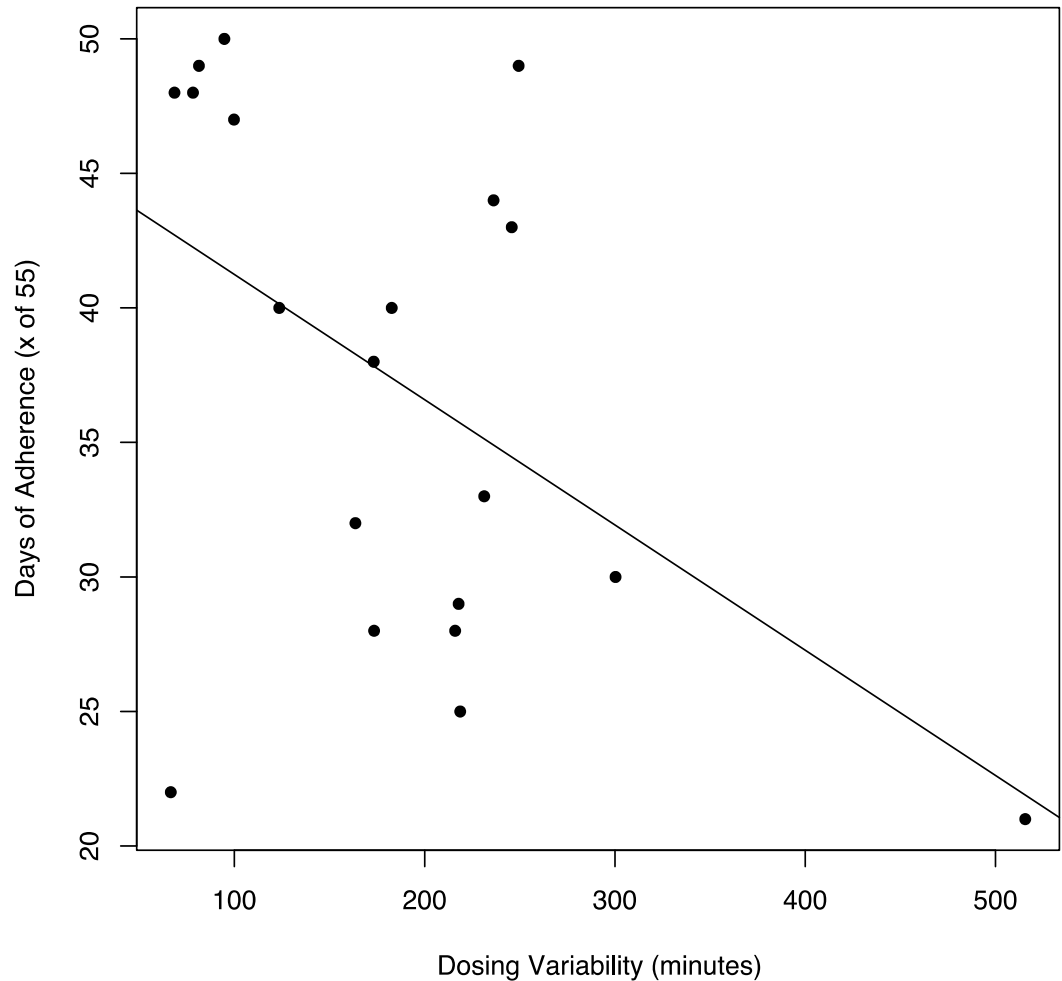
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Emerging Non-Adherence

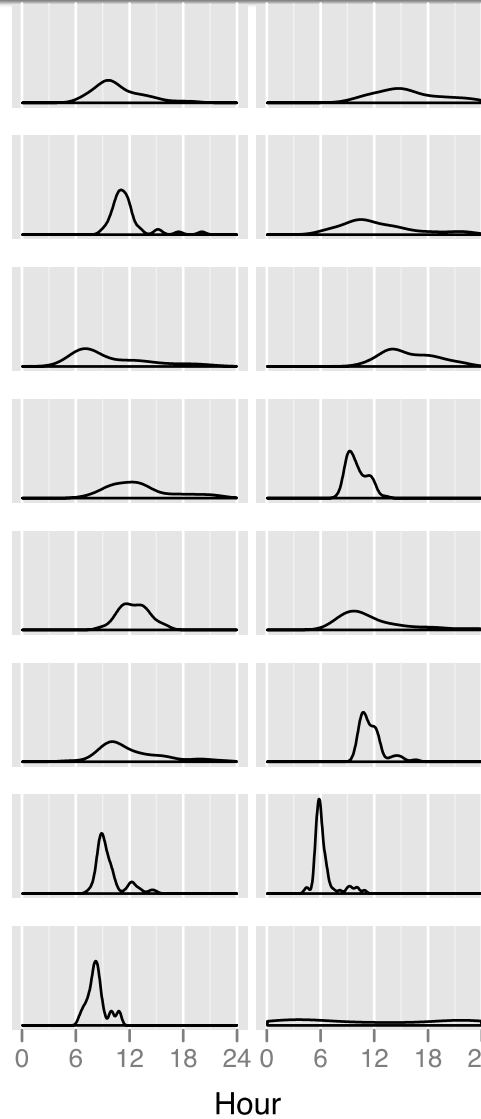
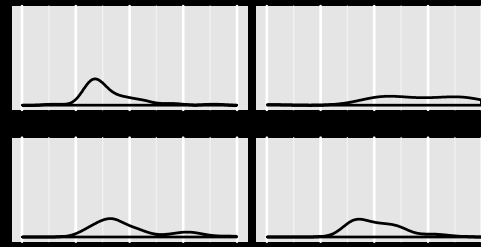
- Noted that adherence varied with dosing time
- The more variability the less likely subjects would remain adherent



Dosing variance and adherence

- Dosing variance predicts adherence:
 - 1 hour of dosing variance predicts 2.79 fewer days of adherence
- Pre-enrollment days of MA use also predicts adherence
 - each additional day of MA use in the 30 days prior to enrollment predicting an increase of 9.4 minutes of DV

Distribution of Dosing Times for Individual Subjects



Problems

- Not all MEMS caps bottles returned
 - Three caps not returned at the end of the study
- MEMS timestamp varied by about 15 min/day
- One phones not returned
- One phone returned broken
- Some subjects exceeded time and text limits
- Valid concern about privacy of photos

Conclusion

- Pill photos sent from cell phones work
- Compared to 'gold standards':
 - Underestimate compliance vs MEMS Caps and pill counts
 - Have far less impossible adherence
- Can be used to prompt dosing, obtain data after dosing and are widely available.

Smart Pill Jars

- MEMs Caps
 - Medication Event Monitoring System
 - Long track record
 - Legacy platform
- GlowCap
 - Temporarily unavailable
- Adhere Tech
 - Emerging leader

MEMS Caps



- MEMS = Medication Event Monitoring Systems
 - A electronic bottle cap that records the time of bottle openings
 - Assumed to correlate with dosing

Glow Cap Screenshot


The screenshot shows a web browser window displaying the product page for GlowCap. The browser's address bar shows the URL www.glowcaps.com/product/. The page features a blue header with the GlowCap logo and navigation links for SERVICE, PRODUCT, and HELP. A 'LOGIN' button is also present for subscribers. The main content area is titled 'Product' and contains three sections, each with an image, a title, a description, and a 'Play Video' link. The first section shows a hand holding a pill bottle cap with a button, titled 'Refills are as easy as the push of a button'. The second section shows a white reminder light plugged into a wall outlet, titled 'Plugin reminder light provides an additional layer of comfort'. The third section shows a hand holding a pill bottle with a GlowCap device attached, titled 'GlowCap® remembers'. On the right side of the page, there is a 'WATCH' button with a play icon and the text 'INSTRUCTIONAL VIDEOS'.

www.glowcaps.com/product/

ALREADY A SUBSCRIBER? SIGN IN HERE : [LOGIN](#)

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Product



Refills are as easy as the push of a button

A button at the base of the GlowCap® lid sends refill requests to your local pharmacy through the AT&T Mobile Broadband Network, which sets up an automatic callback to confirm your refill. Then, simply head to your pharmacy to pick up your medications.


[Play Video](#)



Plugin reminder light provides an additional layer of comfort

GlowCap® features an accompanying reminder light that plugs easily into any outlet around the home. The device works in tandem with the lid by glowing orange at the time of your scheduled medication, and sends immediate updates to you or your caregiver.

[Play Video](#)




GlowCap® remembers

Light and sound notifications from the GlowCap® escalate from subtle to insistent: devices glow, then make noise, then send a text notification or dial your home phone.

[Play Video](#)

INSTRUCTIONAL VIDEOS



[WATCH](#)

Adhere Tech Screenshot

AdhereTech

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Smart Wireless Pill Bottles

Improve and Track Adherence in Real-Time.

Contact Us for Orders or Questions

Learn More

AdhereTech smart wireless pill bottles are currently being used by patients in pharmaceutical and research engagements. These bottles collect and send all adherence data in real-time. The system

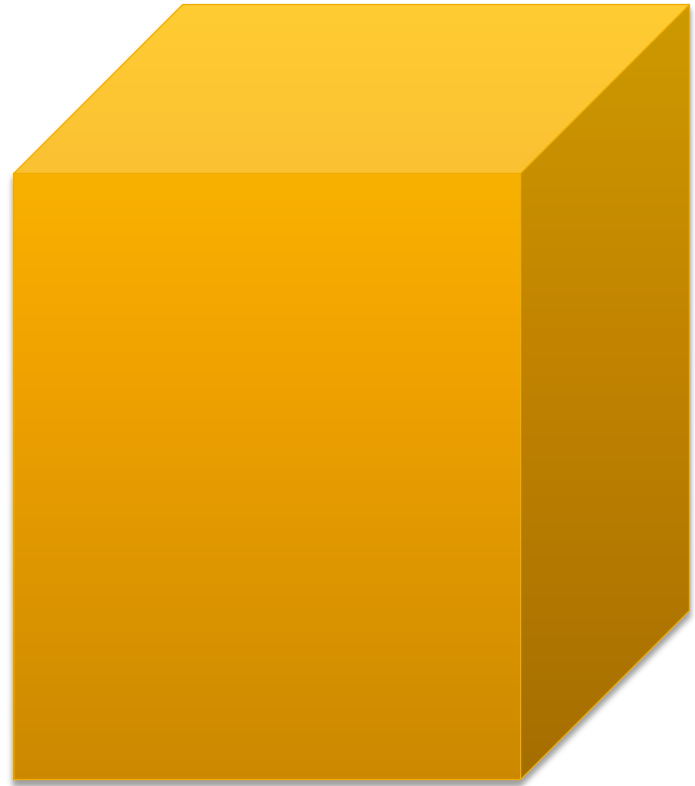
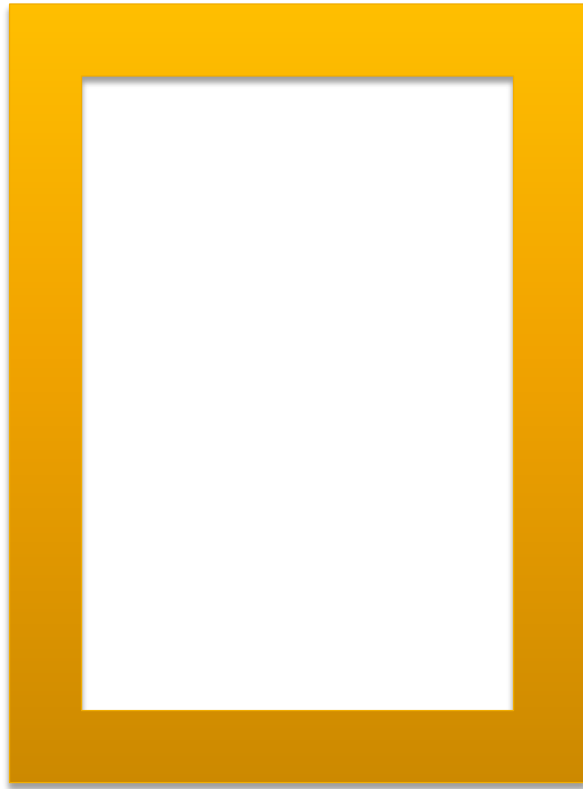
Beyond catching cheaters

- If that's all you care about just do Directly Observed Therapy or long acting parenteral drugs
- Some people are just haters – don't join them

The real potentials of adherence technologies

- Learning
 - What people actually do
 - When they do it
 - Why they wont do what you want
- New ways to characterize and understand drug actions
 - QT prolongation?
 - Abuse liability?
 - Symptom targeted treatments?

Therapeutic Window vs Therapeutic Volume



Perspectives

- Academia
 - Interactions between Behavior and Pharmacology
 - Better understanding of PK/PD interactions
- Regulatory
 - Should we approve drugs people don't take – or take too much of
- Industry
 - Rationale for go/no go decisions and reason to develop new products and delivery systems

Implications: IRB-Industrial Complex

- Adherence not improved by longer consent forms
 - But you can be sure IRBs will now add a page addressing adherence.
- More evidence of failed regulatory system
- The good news –
 - Patients and Subjects actually do behave rationally
- The bad news –
 - IRBs, Investigators and Sponsors don't

