Informed Consent & Information Technology
Effectiveness of Discontinuing Bisphosphonate (EDGE)
Pragmatic Clinical Trial Use Case

Kenneth G. Saag, MD, MSc
Jane Knight Lowe Professor
Division of Clinical Immunology and Rheumatology
Director, Center for Education and Research on Therapeutics (CERTs), Center for Outcomes, Effectiveness Research, and Education (COERE), and Center for Research Translation (CORT) on Gout and Hyperuricemia
Disclosures

• Mytrus has provided contracted work to UAB under federal supported research grants

• No proprietary or investment interest in Mytrus
Overview

- Pragmatic Controlled Trials (PCTs) and Tribulations
- Challenges with informed consent in PCTs
- Electronic informed consent
  - Process
  - Benefits and Challenges for Patients and Providers
  - Comparisons with paper consent
- EDGE as a use case for electronic consent
- Policy implications
Challenges in Obtaining Consent
What are Pragmatic Clinical Trials (PCT)s?

- Measure “real world” effectiveness (NOT efficacy)
- Large sample size = generalizable results
- Minimal patient eligibility criteria (broad inclusion / exclusion)
- Broad patient population (variably cooperative, less motivated)
- Simpler treatment arms (less complicated design)
- Objective natural endpoints (outcomes)
- Most investigators NOT experienced researchers
National Challenges With PCTs

- Cost, Cost, Cost

- Efficiently collecting data and conducting study procedures
  - Recruitment
  - Measuring outcomes
  - Informed consent

- Complex regulatory requirements of multiple IRBs and Institutions/Partners for large multi-site studies

- Engaging busy practicing clinicians and/or clinical staff NOT dedicated to research

Eapen Z, Temple, R.J. et al. JAMA 2014;311:1397
Informed Consent Challenges in PCTs

- Few validated methods for soliciting effective, efficient, and ethical informed consent in community settings among sites with limited research expertise.

- Few community practices have dedicated research staff or on-site coordinators.

- Maintaining IRB know how/certification challenging for groups whose primary business not research.

- Need to optimize
  - Patient comprehension and satisfaction
  - Investigator/Staff time requirements/complexity.
Maybe add is to business is not research
Gary Cutter, 7/20/2014
Electronic Informed Consent

“This is precedent setting”
“we support this novel approach”
“Continue to use”

• Reviewed by >30 additional local and academic IRBs/RECs, KFEB (Hungary) CONEP (Brazil)
• DHHS-SACHRP Review – “Continue to use”
This slide could go if you need to reduce slides
Gary Cutter, 7/20/2014
E-Consent

Potential Benefits for Researchers

• Paperless- but can still print copy to for subjects
• Multiple study sites with the same consent or slightly modified consent based on local IRBs
• Real time monitoring of recruitment/informed consent process
  • Interactions recorded immediately into tracking system
  • Audit trail of timed and dated information on process
  • Manage process from any location
• Multiple languages/translations
GC4 multiple languages/translations

One question raised with this slide - what if there are questions about the process?
Gary Cutter, 7/20/2014
Data Collection and Storage

128 Bit AES Encryption
- In Transit
- At Rest

HIPAA Compliant Data Storage

- NO PHI stored on devices
- ALL data stored on off-site databases to comply with HIPAA
This slide could be eliminated and the essence said with the prior slide if you need time - and I suspect you will.

Gary Cutter, 7/20/2014
E-Consent
Potential Benefits for Participants

• Patient –centered: can review consent form and consult with family (particularly if study can be enrolled at home/online)

• Audiovisual aides assist comprehension
  • Animated consent with narrative of study procedures
  • Difficult words highlighted and linked to dictionary to assist subject understanding

• Knowledge assessed in real time to determine whether consent material understood
## E-Consent Challenges

**For Researchers**

- **Expense** - initial infrastructure and technology to manage online documents and validate electronic consent
- **Verification** - Confirming identity of participant
- **Compliance** - FDA: Part 11 Compliance
  - 21 CFR 11 (1997) imposes certain requirements on an entity when it chooses to maintain FDA-required records and signatures in electronic form
  - Requirements under Part 11 i to ensure integrity, validity, and trustworthiness of e-records and e-signatures

**For Participants**

- Challenges in use of new electronic technologies
- Potentially more difficulty or fragmented consent discussion with investigators
- Confidentiality – Who has access to and can view consent documentation and answers to screening questions?
Interventions to Improve Informed Consent Comprehension

- Systematic review of 12 trials using multimedia
- 3 showed significant improvement in understanding
- Authors conclusions:

  “Having a study team member or a neutral educator spend more time talking one-on-one to study participants appears to be the most effective available way of improving research participants’ understanding; however, further research is needed.”

Flory JA and Emanuel E. JAMA 2004;292:1593
Electronic Informed Consent & PCTs
Use Case – Effectiveness of Discontinuing BisphophonatEs (EDGE)

NIH: 1R21AR062300; 1U34AR062891
What is EDGE?
Current Study Design
(n = 9500 subjects; 300 study sites)

• Open-label, non inferiority randomized trial of alendronate continuation vs. discontinuation (in chronic alendronate users 3+ years)

• Participants screened, consented, and randomized using iPad (or paper form) application in the US and abroad

• Adheres to principles of Pragmatic Clinical Trials (PCTs)
  • Minimal inclusion/exclusion criteria
  • Limited patient responsibilities and minimal provider time commitment
  • Same day single enrollment (40 minute) visit
  • Dynamic randomization performed centrally on visit day

• 24-36 month follow up of outcomes ascertained through Medicare and/or other insurance linkage and/or EHR; periodic mail and CATI surveys
A lot for 1 slide - you could say some of the bullets - such as the 4 under adheres to principles...

Gary Cutter, 7/20/2014
Patients like Using iPads in Primary Care Clinics
Findings from UAB Pilot Study

- iPad compared to Interactive Voice Response system (IVRS) in EDGE pilot
- 160 women (80% of those approached) agreed to complete the osteoporosis screening questions in 10 family physicians offices

Patient satisfaction and feasibility survey comparing an iPad with IVRS

<table>
<thead>
<tr>
<th></th>
<th>iPad (n=93 pts.)</th>
<th>IVRS (n=67 pts.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strongly agree or agree</td>
<td>Neither agree nor disagree</td>
</tr>
<tr>
<td>The iPAD/phone was easy to use</td>
<td>78 (85.7%)</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>The questions were easy to see/hear</td>
<td>88 (96.7%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>The questions were easy to answer</td>
<td>90 (97.8%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>The process did not take too long</td>
<td>84 (91.3%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>If eligible, I would be interested in participating osteoporosis drug trial</td>
<td>32 (35.2%)</td>
<td>22 (24.2%)</td>
</tr>
<tr>
<td>I would not mind spending extra time at my doctor visit to enroll in the study</td>
<td>37 (41.1%)</td>
<td>17 (18.9%)</td>
</tr>
</tbody>
</table>

P = 0.045 by Pearson’s chi-square test comparing tablet computer to IVRS for those who answered “strongly agree or agree”, all other comparisons were not significant.

Dr. Saag i add it this data table
Michael B Saddekni, 7/21/2014
Patients Like Using iPads in Primary Care Clinics

Findings from First UAB Pilot Study for EDGE

• 160 women (80% of those approached) age 65+ agreed to complete the osteoporosis screening questions in 10 family physicians offices

• iPad compared to Interactive Voice Response system (IVRS) in EDGE pilot focused on screening criteria
  • Easier to use and understand
  • Less time consuming
  • Users more likely to express interest in future trial
  • Users would not mind spending extra time in their physicians office to enroll in a study

• Office staff reported that using these technologies not burdensome and did not interrupt clinic flow

Results

iPad compared to Interactive Voice Response system (IVRS)

- Easier to use and understand
- Less time consuming
- Users more likely to express interest in future trial
- Users would not mind spending extra time in their physicians office to enroll in a study

Office staff reported that using these technologies not burdensome and did not interrupt clinic flow
EDGE Electronic Informed Consent
Second Pilot Study

• “Mock Trial” as further step towards EDGE

• To determine feasibility and acceptability of iPad informed consent compared to traditional paper informed consent

• Hypothesis: iPad preferred by clinics and patients over traditional paper consent and leads to improved efficiencies and effectiveness of process

• 9 primary care sites enrolled from PBRNs
  • 5AL sites
  • 2 CO sites
  • 2 TX sites

• 41 participants screened- 31 enrolled
EDGE Consent Video/Screen Shots
"This is precedent setting"
"we support this novel approach"
"Continue to use"

- Reviewed by >30 additional local and academic IRBs/RECs, KFEB (Hungary) CONEP (Brazil)
- DHHS-SACHRP Review – “Continue to use”
Hi. This iPad is a new type of learning device for patients like you who may be interested in participating in clinical research studies.

Doctor comes in, speech bubble appears immediately. As iPad comes down into doctor’s hand, the speech bubble goes away. The "new" burst comes in after the the iPad and then goes away.
It is unknown how long people with osteoporosis should be treated. This study compares what happens to people who discontinue alendronate after three or more years, to those who continue taking it.
Informed Consent

TITLE OF RESEARCH: Effectiveness of Discontinuing bisphosphonateS Study (EDGE):
(Pilot Studies for the Active Comparator Osteoporosis Large Sample Trial (ATLAST)

IRB PROTOCOL: F120404006

INVESTIGATOR: Dr. Kenneth Saag, MD

SPONSOR: National Institutes of Health (NIH)

Version Date: 10/31/13

Continue
Please read the informed consent document before continuing on to answer some questions about what participating in this study involves. Swipe the screen from bottom to top with your finger to scroll through the informed consent document. When you reach the end of the document, you will be able to click the Continue button.

Introductory Statement

You have previously participated in the Fracture Intervention Trial, a study involving the investigational drug, alendronate. To obtain additional information about the safety and effect of alendronate in the treatment of osteoporosis, you are being invited to participate in a five-year extension of that study. The following will describe new information about the effects of alendronate on osteoporosis and our current understanding of its safety and tolerability. The requirements of this extension study and your role as a participant are also discussed below. The investigator or other qualified study personnel will answer any questions you may have about this form and about the study. Please read this consent form carefully and do not hesitate to ask questions about the information presented below.

2. Purpose of this Study

Osteoporosis is a systemic skeletal disease in which low bone mass results in reduced bone strength and a consequent increased risk of fracture. When you began your participation in the Fracture Intervention Trial, alendronate was not commercially available in the United States. Your participation in that study has helped provide information about the safety and effect of alendronate treatment for up to several years. The drug is now commercially available under the trade name FOSAMAX for the treatment (10 mg tablet) and prevention (5 mg tablet) of osteoporosis (thinning of bone) in women after menopause. Since FOSAMAX could potentially be used by patients for many years, it would be beneficial to obtain more information on the effects of alendronate treatment. The inclusion of a five-year extension study will bring this information closer to the marketplace.
Question 1 of 7

The main reason for carrying out the osteoporosis research study described in the consent form is to...

- study the difference between continuing alendronate (Fosamax or Binosto) to stopping alendronate (Fosamax or Binosto)
- find treatments with no side effects
- help pay for osteoporosis treatments
- study high blood pressure medications
Please tell us about yourself ...

What is your name?
First Name: Tinker
Last Name: Bell

When were you born?
Month: January
Day: 01
Year: 1903

What is your social security number?
Social Security Number: Tap to enter...
Confirm your social security number: Tap to enter...

We need this so we can access your Medicare information. We will not share it with anyone not related to this study.
Your Signature

I have read the information in this consent form (or it has been read to me). All my questions about the study and my participation in it have been answered. I freely consent to participate in this research study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form I have not waived any of the legal rights that I otherwise would have as a subject in a research study.

Please sign below, inside the box with your finger or stylus.
Inclusion/Exclusion

Patient Name: S S
Birth: March 15, 1945 (Age: 68)

Have all of the following inclusion/exclusion requirements been met?

- The patient does NOT have a history of any other metabolic bone condition.

- The patient is NOT currently receiving treatment for ongoing cancer, excluding non-melanoma skin cancer.

- The patient does NOT have significant underlying illness that would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival to less than 3 years).

- The patient is NOT involved in a conflicting (investigational drug) clinical trial.

If the patient does not meet all of the above criteria, then she is not eligible for the study.

Eligible

Dr. Howard Williamson
This patient is ready to be randomized into the study.

Touch the Randomize button to randomize the patient and see the group assignment.
This patient is assigned to the following study group:

**DISCONTINUE THE USE OF ALENDRONATE**
### UAB eConsent EDGE Pilot

iPad vs. Paper – Patient Perceptions (n = 31)

<table>
<thead>
<tr>
<th>Patient Comprehension</th>
<th>iPad (n=14)</th>
<th>Paper (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of PHI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risks/Benefits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data access</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Satisfaction</th>
<th>iPad (n=14)</th>
<th>Paper (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of assistance required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall satisfaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time required for completion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
This is mixing a row-- purpose
Kenneth G Saag (Campus), 7/27/2014
## Informed Consent Pilot
### iPad vs. Paper - Patients

Survey Responses: 1-7 Scale; 7=“Extremely Satisfied”

<table>
<thead>
<tr>
<th></th>
<th>iPad (n=14)</th>
<th>Paper (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Comprehension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purpose</td>
<td>6.79 (0.6)</td>
<td>6.24 (1.1)</td>
</tr>
<tr>
<td>Use of PHI</td>
<td>6.36 (1.3)</td>
<td>6.24 (1.1)</td>
</tr>
<tr>
<td>Medication changes</td>
<td>6.64 (0.7)</td>
<td>6.35 (1.1)</td>
</tr>
<tr>
<td>Risks/Benefits</td>
<td>6.86 (0.4)</td>
<td>6.13 (1.5)</td>
</tr>
<tr>
<td>Randomization</td>
<td>6.21 (1.3)</td>
<td>5.76 (1.6)</td>
</tr>
<tr>
<td>Data access</td>
<td>6.43 (1.1)</td>
<td>6.06 (1.3)</td>
</tr>
<tr>
<td>Other treatment</td>
<td>6.79 (0.6)</td>
<td>6.24 (1.5)</td>
</tr>
<tr>
<td><strong>Patient Satisfaction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount of assistance required</td>
<td>6.57 (0.8)</td>
<td>6.41 (1.1)</td>
</tr>
<tr>
<td>Overall Satisfaction</td>
<td>6.62 (0.8)</td>
<td>5.82 (1.7)</td>
</tr>
<tr>
<td>Time required for completion</td>
<td>6.15 (1.5)</td>
<td>6.18 (1.4)</td>
</tr>
<tr>
<td>Perceived time to complete (min)</td>
<td>22.5 (7.5)</td>
<td>22.9 (14.2)</td>
</tr>
</tbody>
</table>
GC15  Want to include p-values or forest plots for these?  
Gary Cutter, 7/20/2014

MBS27  Dr. Saag i combined 38 with 37 or you prefer 37 alone and 38 alone  
Michael B Saddekni, 7/22/2014
UAB eConsent EDGE Pilot
iPad vs. Paper Results
Patients Knowledge (n = 31)

• On 10/13 Comprehension questions
  • iPad users had as good or better comprehension vs. Paper

• Mean (sd) Correct Response
  iPad = 12.4 (0.8)
  Paper = 11.5 (1.6), p= 0.08
Informed Consent Pilot

Survey Responses: 1-7 Scale; 7=“Extremely Satisfied”

<table>
<thead>
<tr>
<th></th>
<th>iPad (n=14)</th>
<th>Paper (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Comprehension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purpose</td>
<td>6.79 (0.6)</td>
<td>6.24 (1.1)</td>
</tr>
<tr>
<td>Use of PHI</td>
<td>6.36 (1.3)</td>
<td>6.24 (1.1)</td>
</tr>
<tr>
<td>Medication changes</td>
<td>6.64 (0.7)</td>
<td>6.35 (1.1)</td>
</tr>
<tr>
<td>Risks/Benefits</td>
<td>6.86 (0.4)</td>
<td>6.13 (1.5)</td>
</tr>
<tr>
<td>Randomization</td>
<td>6.21 (1.3)</td>
<td>5.76 (1.6)</td>
</tr>
<tr>
<td>Data access</td>
<td>6.43 (1.1)</td>
<td>6.06 (1.3)</td>
</tr>
<tr>
<td>Other treatment</td>
<td>6.79 (0.6)</td>
<td>6.24 (1.5)</td>
</tr>
<tr>
<td><strong>Patient Satisfaction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount of assistance required</td>
<td>6.57 (0.8)</td>
<td>6.41 (1.1)</td>
</tr>
<tr>
<td>Overall Satisfaction</td>
<td>6.62 (0.8)</td>
<td>5.82 (1.7)</td>
</tr>
<tr>
<td>Time required for completion</td>
<td>6.15 (1.5)</td>
<td>6.18 (1.4)</td>
</tr>
<tr>
<td>Perceived time to complete (min)</td>
<td>22.5 (7.5)</td>
<td>22.9 (14.2)</td>
</tr>
</tbody>
</table>
Want to include p-values or forest plots for these?
Gary Cutter, 7/20/2014
UAB eConsent Project
Provider Preference and Time Required \( (n = 8) \)

<table>
<thead>
<tr>
<th>Favors</th>
<th>iPad</th>
<th>Paper</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.67</td>
<td>4.89</td>
</tr>
<tr>
<td></td>
<td>5.22</td>
<td>5.22</td>
</tr>
<tr>
<td></td>
<td>5.22</td>
<td>5.33</td>
</tr>
<tr>
<td></td>
<td>4.00</td>
<td></td>
</tr>
</tbody>
</table>

Easiest to use: 5.67
Consent process was Efficient: 4.89
Most helpful: 5.22
Required least amount of time: 5.22
Appealed more to patients: 5.33
The entire IC process: 4.00

Perceived time to complete iPad: 29.44 (20.4)
If this is a preference slide the perceived time row doesn't make sense

while the first 5 favor iPad, why is there indifference on the entire informed consent process????

Gary Cutter, 7/20/2014
Informed Consent Project

Providers (n = 8)

Overall Preference: 1-7 Scale (1=paper; 7=iPad)

<table>
<thead>
<tr>
<th>Feature</th>
<th>M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easiest to use</td>
<td>5.67 (1.9)</td>
</tr>
<tr>
<td>Consent process efficient</td>
<td>4.89 (2.3)</td>
</tr>
<tr>
<td>Most helpful</td>
<td>5.22 (2.0)</td>
</tr>
<tr>
<td>Required least amount of time</td>
<td>5.22 (2.0)</td>
</tr>
<tr>
<td>Appealed more to patients</td>
<td>5.33 (2.1)</td>
</tr>
<tr>
<td>Entire informed consent process</td>
<td>4.00 (1.0)</td>
</tr>
<tr>
<td>Perceived time to complete (min)</td>
<td>29.44 (20.4)</td>
</tr>
</tbody>
</table>
If this is a preference slide the perceived time row doesn't make sense

while the first 5 favor iPad, why is there indifference on the entire informed consent process????

Gary Cutter, 7/20/2014
Informed Consent Project

Providers (n = 8)

Overall Preference: 1-7 Scale (1=paper; 7=iPad)

Provider Overall Preference of iPad vs. Paper, iPad = 7, Paper = 1, Mean (SD)
If this is a preference slide the perceived time row doesn't make sense

while the first 5 favor iPad, why is there indifference on the entire informed consent process????

Gary Cutter, 7/20/2014
Interactive Informed Consent
Randomized Comparison with Paper Consents

Rowbotham MC, Astin J, Greene K, Cummings SR
PLOS ONE. 2013;3:e58603
Spelling is correct
Michael B. Saddekni, 7/10/2014
Specific Aims and Methods

• Prospective randomized study comparing
  • IRB-approved paper with an interactive presentation using an iPad
• 2 populations- Clinical Research Professionals and Patients

Methods

• Part 1
  1. Clinical research professionals randomized to review clinical study consent either via standard paper or iPad interactive system
  2. Each participant completed an online survey next day

• Part 2
  1. Patients randomized to review clinical study consent either via standard paper or iPad interactive system
  2. Each participant completed an online survey the next day
# Results

<table>
<thead>
<tr>
<th>Question</th>
<th>group1</th>
<th>group1</th>
<th>group2</th>
<th>group2</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPad Paper</td>
<td>88</td>
<td>67</td>
<td>69</td>
<td>72</td>
</tr>
<tr>
<td>Q1 (Reason for study) *</td>
<td>100</td>
<td>83</td>
<td>89</td>
<td>72</td>
</tr>
<tr>
<td>Q2 (Who to call if injured)</td>
<td>38</td>
<td>33</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Q3 (Who to call if questions)</td>
<td>75</td>
<td>33</td>
<td>89</td>
<td>62</td>
</tr>
<tr>
<td>Q4 (Continue with normal treatments) *</td>
<td>50</td>
<td>67</td>
<td>77</td>
<td>55</td>
</tr>
<tr>
<td>Q5 (What involved in QST)</td>
<td>100</td>
<td>50</td>
<td>77</td>
<td>48</td>
</tr>
<tr>
<td>Q6 (Risks of QST) *</td>
<td>88</td>
<td>67</td>
<td>96</td>
<td>59</td>
</tr>
<tr>
<td>Q7 (If you require treatment)</td>
<td>100</td>
<td>83</td>
<td>96</td>
<td>76</td>
</tr>
<tr>
<td>Q8 (Amount of compensation)</td>
<td>88</td>
<td>33</td>
<td>69</td>
<td>72</td>
</tr>
<tr>
<td>Q9 (Duration of Study)</td>
<td>75</td>
<td>83</td>
<td>69</td>
<td>72</td>
</tr>
<tr>
<td>Q10 (What involved in study)</td>
<td>38</td>
<td>0</td>
<td>42</td>
<td>21</td>
</tr>
<tr>
<td>Q11 (What involved in QST)</td>
<td>88</td>
<td>83</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td>OVERALL PERCENT CORRECT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*denotes questions also appearing on the iPad quiz at the time of review. Group 1 (n = 14) overall % correct p,0.07 in favor of iPad. Group 2 (n = 55) overall p,0.001 in favor of iPad. Combined overall difference P,0.001 in favor of iPad. doi:10.1371/journal.pone.0058603.t001

Rowbotham MC, Astin J, Greene K, Cummings SR
PLOS ONE. 2013;3:e58603
Dr. Saag do you want me to delete this table
Michael B Saddekni, 7/22/2014
Interactive Informed Consent
Randomized Simulated Comparison with Paper Consents

- Information recall (% correct)

- Time to complete consent

P < 0.001
P < 0.07

Patients (n = 55)
Clinical Research Professional (n = 14)

Paper
iPad

22.7 min
13.2 min

Rowbotham MC, Astin J, Greene K, Cummings SR
PLOS ONE. 2013;3:e58603
Results Cont.

(On the duplicated questions)

Patients N=55

- iPad Correct: 41
- Paper correct: 14

Patients N=55

- iPad Correct: 35
- Paper correct: 20

Rowbotham MC, Astin J, Greene K, Cummings SR
PLOS ONE. 2013;3:e58603
Summary

Combining an introductory video, standard consent language, and an interactive quiz on a tablet-based system improved comprehension of consent procedures and risks.
Informed Consent & Information Technology

Summary

• Informed consent barriers of particular concern for growing national interest in pragmatic clinical trials
• Platforms exist that utilize multi-media IT to facilitate informed consent process
• Preliminary data suggest similar to better effectiveness and satisfaction and adequate efficiency compared to traditional pen and paper consent
• Regulatory and economic barriers may delay the widespread implementation of e-consent technology
Informed Consent Policy Implications
Video Delivered ICF May Benefit Specific Groups and Study Designs

- **Best study types for e-consent?**
  - Pragmatic
  - Direct to patient
  - More complex designs
  - Higher risk

- **Best patient populations?**
  - Low literacy
  - Children
  - Non-English speaking
  - Mentally ill

- **Best Investigators?**
  - Community based
  - Less staff (pragmatic designs)
  - With ability to link to electronic health records
Acknowledgements

- Bridget Alday, BD
- Walter Calmbach, MD, MPH
- Jeffrey Curtis, MD, MPH, MS
- Gary Cutter, PhD
- Mary Elkins, BS
- Jeffrey Foster, MPH
- T. Michael Harrington, MD
- Meredith Kilgore, PhD
- Beth Lewis, MD, MSPH
- Jonathan Miller, MPPA, CIP
- Sarah Morgan, RD, MD
- Amy Mudano, MPH
- Ruth McConnell, BS
- Ryan Outman, MS
- Wilson Pace, MD
- David Redden, PhD
- Douglas Roblin, PhD
- Michael Saddekni, MD
- Jasvinder Singh, MD
- Wilson Smith, BS
- Amy Warriner, MD
- Nicole Wright, PhD
- Steve Cummings, M.D
- Susan Booth, BS
- Michael Tucker, M.D
- Rob French, BS
- Anthony Costello, BS
- Sasha Zucker, BA

NIH: 1R21AR062300; 1U34AR062891

K24AR05261; R01AR060240

U18HS10389
Informed Consent and Information Technology
The Effectiveness of Discontinuing Bisphosphonate (EDGE) Pragmatic Clinical Trial Use Case

Kenneth G. Saag, MD, MSc
Jane Knight Lowe Professor
Division of Clinical Immunology and Rheumatology
Director, Center for Education and Research on Therapeutics (CERTs) and Center for Outcomes, Effectiveness Research, and Education (COERE)
Consent has become...
...but it doesn’t have to be
Overview

• Pragmatic Controlled Trials (PCTs) and Tribulations
• Challenges with informed consent in PCT
• Electronic informed consent
  • Process
  • Benefits and Risk for Patients and Providers
  • Comparisons with paper consent
• EDGE as a use case for electronic consent
• Policy implications
Case law on e-sig (precedent)
Security/Encryption of data electronically

Is there data we can add on this?
Kenneth Saag, 7/20/2014
Overview

- Challenges with PCTs
  - In practice challenges
- Challenges with consent (general overview)
  - 3-4 slides from JM on challenges
  - Quote slides
- Electronic consent overview
  - Case law on e-sig (precedent)
  - Security/Encryption of data electronically
  - Compliance
  - Benefits to research
  - Slides from S. Cummings paper
- Science and policy implications
- EDGE as a use case
- Pilot study results
- Mytrus slides
Consent Versions & Amendments Management

- Multiple study sites with the same consent or slightly modified consent based on the local IRB
This can show how you can have multiple study sites with the same consent or consents that have been modified based local IRB and that the e-consent can be managed and pushed out from a central location.

Jeffrey Foster, 7/16/2014

I don't think the figure is that helpful. We can probably incorporate text to be a bullet in slide 10.

Kenneth Saag, 7/21/2014
What are Pragmatic Clinical Trials (PCT)s?

- Measure “real world” effectiveness (NOT efficacy)
- Large sample size = generalizable results
- Minimal patient eligibility criteria (broad inclusion / exclusion)
- Broad patient population (variably cooperative, less motivated)
- Simpler treatment arms (less complicated design and follow-up)
- Objective natural endpoints (outcomes)
- Investigators NOT experienced researchers
NOT: Explanatory versus Pragmatic

- It’s a *continuum*, not a dichotomy
- Consider patient-compliance:

Explanatory

Exclude non-compliant before the RCT starts.....

...apply compliance-improving strategies to all...

...monitor compliance and intervene if low...

Pragmatic

...monitor only...

...ignore
Pragmatic Clinical Trials (PCT) National Challenges

- Cost, Cost, Cost
- Engaging representative participants
- Efficiently collecting data
  - Recruitment
  - Measuring outcomes
  - Informed consent
- Complex regulatory requirements of multiple IRBs and Institutions/Partners
- Engaging busy practicing clinicians and/or clinical staff not dedicated to research

Eapen Z, Temple, R.J. et al. JAMA 2014;311:1397
Novel Informed Consent Tool for Pragmatic Clinical Trials

Overview

• “Mock Trial” as first step towards EDGE

• Pilot project to determine feasibility and acceptability of patient administered iPad informed consent compared to traditional paper informed consent

• Hypothesis: iPad preferred by clinics and patients over traditional paper consent and leads to improved efficiencies and effectiveness of process
GC21  This is confusing in that you have already presented 23 slides - why give an overview slide now??
Gary Cutter, 7/20/2014
Informed Consent Features

• Must be legally effective
• Must provide sufficient opportunity to consider whether or not to Participate
• Must minimize the possibility of coercion or undue influence
• Must be understandable
• Must not appear to waive any of the subject’s rights or release the investigator, the sponsor or the institution or its agents from liability or negligence
• See 45 CFR 46.116(a)
Consent Concepts

• Consenting to research isn’t consenting to treatment
• Usually risks to individuals & benefits to society
• Generally, physicians shouldn’t consent patients; may fear their care will change if they decline or withdraw

“… with subject populations that are mostly medically naïve and for whom the whole concept of clinical research (is) alien, the true essence of an ‘informed’ and ‘autonomous’ decision is largely lost.”

Informed Consent Challenges in the “Real World” Medical Community

- **Resources**: few practices have dedicated research staff or on-site coordinators

- **Time/Workflow**: informed consent can be a very time-consuming process

- **Subject Comprehension**: often very limited
Challenges

“Ethical errors are increasing not only in numbers but in variety – for example, in the recently added problems arising in transplantation of organs.” – Henry K. Beecher

• Success and a challenge
• Consider today’s challenges – genomics, Internet research, etc.
Consent and ethics and triathlons

“An experiment is ethical or not at its inception; it does not become ethical post hoc – ends do not justify means.” - Henry K. Beecher¹
# Results

**Table 1. Post-review online survey test question results.**

<table>
<thead>
<tr>
<th>Question</th>
<th>group1 iPad</th>
<th>group 1 Paper</th>
<th>group 2 iPad</th>
<th>group 2 Paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (Reason for study) *</td>
<td>88</td>
<td>67</td>
<td>69</td>
<td>72</td>
</tr>
<tr>
<td>Q2 (Who to call if injured)</td>
<td>100</td>
<td>83</td>
<td>89</td>
<td>72</td>
</tr>
<tr>
<td>Q3 (Who to call if questions)</td>
<td>38</td>
<td>33</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Q4 (Continue with normal treatments) *</td>
<td>75</td>
<td>33</td>
<td>89</td>
<td>62</td>
</tr>
<tr>
<td>Q5 (What involved in QST)</td>
<td>50</td>
<td>67</td>
<td>77</td>
<td>55</td>
</tr>
<tr>
<td>Q6 (Risks of QST) *</td>
<td>100</td>
<td>50</td>
<td>77</td>
<td>48</td>
</tr>
<tr>
<td>Q7 (If you require treatment)</td>
<td>88</td>
<td>67</td>
<td>96</td>
<td>59</td>
</tr>
<tr>
<td>Q8 (Amount of compensation) *</td>
<td>100</td>
<td>83</td>
<td>96</td>
<td>76</td>
</tr>
<tr>
<td>Q9 (Duration of Study) *</td>
<td>88</td>
<td>33</td>
<td>96</td>
<td>59</td>
</tr>
<tr>
<td>Q10 (What involved in study)</td>
<td>75</td>
<td>83</td>
<td>69</td>
<td>72</td>
</tr>
<tr>
<td>Q11 (What involved in QST)</td>
<td>38</td>
<td>0</td>
<td>42</td>
<td>21</td>
</tr>
<tr>
<td>Q12 (Free to stop participating any time)</td>
<td>88</td>
<td>83</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td><strong>OVERALL PERCENT CORRECT</strong></td>
<td><strong>77</strong></td>
<td><strong>57</strong></td>
<td><strong>75</strong></td>
<td><strong>58</strong></td>
</tr>
</tbody>
</table>

*denotes questions also appearing on the iPad quiz at the time of review. Group 1 (n = 14) overall % correct p<0.07 in favor of iPad. Group 2 (n = 55) overall p <0.001 in favor of iPad. Combined overall difference P<0.001 in favor of iPad.

doi:10.1371/journal.pone.0058603.t001

Rowbotham MC, Astin J, Greene K, Cummings SR
PLOS ONE. 2013;3:e58603
PCTs in Community Practices
What we know

• Every practice is different
• Blinding is difficult—if not impossible
• Consistent communication—practices want feedback
• Providing technical assistance is crucial
• Not interested in statistical significance but “real meaning”
• Relationship building is key

Helms PJ. Pediatric Allergy Immunology. 2003;13:4-9
Informed Consent Key Concepts

• An ethical mandate to protect human subjects
• An ongoing process between research staff & subjects
  • Informed - fully understood / comprehended; based on facts
  • Consent - voluntary agreement, but not acquiescence
  • Autonomous - individual; of one’s own choosing
• Must always be documented
Internet communities’ members do not expect to be research subjects²

“When I joined this, I thought it would be a support group, not a fishbowl for a bunch of guinea pigs. I certainly don’t feel at this point that it is a safe environment, as a support group is supposed to be, and I will not open myself up to be dissected by students or scientists.”

Participants upset about socio-economic questions and relevance to their disease risk
Importance of consent

“It is absolutely essential to strive for [consent] for moral, sociologic and legal reasons. The statement that consent has been obtained has little meaning unless the subject or his guardian is capable of understanding what is to be undertaken and unless all hazards are made clear.” – Henry K. Beecher¹
E-consent benefits and challenges
Benefits continued

• Aid deployment of centralized monitoring and reduce visits
• Provide input Risk-Based monitoring calculation
• Drive site selection and site management decisions
E-Consent Challenges For Researchers

• **Expense** - High initial expense for infrastructure and technology to manage online documents and establish systems to validate electronic consent

• **Verification** - Confirming legitimacy of signature and identity of participant

• **Compliance** - FDA: Part 11 Compliance
  • 21 CFR 11 (1997) imposes certain requirements on an entity when it chooses to maintain FDA-required records and signatures in electronic form
  • Requirements under Part 11 intended to ensure the integrity, validity, and trustworthiness of e-records and e-signatures
E-Consent Challenges For Participants

• Use of new electronic technologies

• Consent discussion
  • Maybe more difficult than with paper consent
  • Possibly limited consent discussion with staff

• Confidentiality – Who has access to and can view consent documentation or answers to screening questions?
Direct to Patient Trials

Electronic Informed Consent
Reinvent Consent
Study Teams
Analyze Results...
...Real-Time
Progress
Internationalization

- Translations
- Traction
- Most of Top 10 Pharma is using
- Institutional adoption is growing
Regulatory

“This is precedent setting”
“we support this novel approach”
“Continue to use”

- Reviewed by >30 additional local and academic IRBs/RECs, KFEB (Hungary) CONEP (Brazil)
- DHHS-SACHRP Review – “Continue to use”
## Comparing Benefits of Paper vs. Electronic iPad

<table>
<thead>
<tr>
<th>Paper</th>
<th>iPad</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consent discussion with real person</td>
<td>• Multi-media videos w/reinforced messaging and “quiz questions”</td>
</tr>
<tr>
<td>• Access to “hard copy” documentation</td>
<td>• Ability to email signed consent</td>
</tr>
<tr>
<td>• Less expensive</td>
<td>• Patient friendly and administered with reduced staff input</td>
</tr>
<tr>
<td>• Established IRB Compliance</td>
<td>• Secure data storage at a central location</td>
</tr>
</tbody>
</table>
Part 2 Methods and Counts

• Inclusion Criteria
  • Age 18-80
  • Literate in written and spoken English
  • Internet access
  • Able to stay after medical visit

• Exclusion Criteria
  • Cancer or chemotherapy treatment
Industry Validation

- Randomized trial @ Sutter Hospital in California
- Measured recall of study details 24 hours after consent
- 58% correct answers in Paper Group vs. 75% in iPad Group

\[ p = < .01 \]
E-consent Benefits for Researchers

- Time savings for the site
- Consent language learnings
- Amendment management
- Site management/selection
- CRA oversight/remote monitoring
- Risk calculations
- Better patient retention
Compliance

- IRBs consider eICF signature a ‘wet’ handwritten signature per 21 CFR Part 11
- Mytrus can support video, photo and fingerprint capture of consent where required by emerging regulations
- No PHI stored on devices
- All data stored on off-site databases to comply with HIPAA
- Security maintained through mobile device management to control all settings and physically locate device at all times
Methods

Part 1
1. Clinical research professionals randomized to review clinical study consent either via standard paper or IPad interactive system
2. Each participant completed an online survey next day

Part 2
1. Patients randomized to review clinical study consent either via standard paper or IPad interactive system
2. Each participant completed an online survey the next day
Science and Policy Implications
I still think this is addressed above in the benefits and challenges slides.
Novel Informed Consent Tool for Pragmatic Clinical Trials
EDGE Study Outcomes

- **Primary outcome**
  - All clinical fracture incidence rates after 3 years (NO fingers, toes, face, or skull)

- **Secondary outcome**
  - Hip fracture incidence rates
  - Incidence of adverse events (likely contingent on long term extensions)
    - Atypical femoral fracture
    - Osteonecrosis of the jaw
Electronically Delivered Informed Consent

- Full iPad delivered Informed Consent process
- Deliver entire content of Informed Consent on web vs. providing full paper copy (ability to download pdf)
- Multi-media videos to describe details of trial
- “Quiz method” to assess patient understanding of Informed Consent (ranked and scored)
- Electronic signature by study participant and PI
- Secure data storage at a central location (not on local device)
KGS11  still current  
Kenneth G Saag (Campus), 7/7/2014

MBS22  They get approved in 2011  
Michael B Saddekni, 7/10/2014

JF19  Are they currently recruiting or have them finished and published all findings?  
Jeffrey Foster, 7/10/2014
What’s on the iPad

• Full Informed Consent
  • Delivered largely via Multi-media videos
  • Quizzes to assess patient understanding
  • Electronic signatures
  • Ability to download and/or print signed document

• Secure data storage at a central location (not on local device)
• Patient friendly and administered
• Delivers multi-media videos w/reinforced study messaging
• Delivers full text informed consent (paginated w/ “quiz questions”)
• Ability to print/email signed consent
• Delivers randomization assignment
• Pushes data to secure server at a central location
  • 21 CFR Part 11 compliant
Question 1 of 7

The main reason for carrying out the osteoporosis research study described in the consent form is to...

- study the difference between continuing alendronate (Fosamax or Binosto) to stopping alendronate (Fosamax or Binosto)
- find treatments with no side effects
- help pay for osteoporosis treatments
- study high blood pressure medications
Your Signature

I have read the information in this consent form (or it has been read to me). All my questions about the study and my participation in it have been answered. I freely consent to participate in this research study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form I have not waived any of the legal rights that I otherwise would have as a subject in a research study.

Please sign below, inside the box with your finger or stylus.
This iPad will allow you to read the entire informed consent document and to sign it.
Please select your name and enter your PIN

Enter your PIN

1  ABC  2  DEF
4  GHI  5  JKL
7  PQRS  8  TUV
0

Cancel
UAB
iPad vs Paper Informed Consent Project

• Developed study materials including:
  • Introductory site webinar
  • Abbreviated study site personnel IRB training (through CITI)
  • Intro screening form
  • End of study form
  • Patient questionnaires
    • Comprehension
    • Satisfaction
    • Demographic
• Conducted qualitative research on facilitators and barriers

• 9 sites enrolled (convenience sample of sites)
  • 5AL sites
  • 2 CO sites
  • 2 TX sites

• 41 participants screened-31 enrolled
UAB Informed Consent Pilot Study

Methods

• Paper vs iPad, randomized to start with one mode then crossed over (at the level of the clinic)

• Data collected:
  - Patient demographics
  - Patient informed consent comprehension and satisfaction by process
  - Physician/staff satisfaction with administering each process (most important)
  - Perceived time for each process
Questions - 1

• What experiences have you had with informed consent?
• What methods are you currently using?
• What novel methods have you tried?
• Who in your practice is responsible for informed consent?
• Who in your practice makes decisions about research?
Questions - 2

• How do you ensure that subjects are informed and decisions autonomous?
• How do you manage the dual role of personal physician and researcher?
• How do you separate routine care / treatment and research participation when dealing with patients?
• How accepting are patients & staff of newer methods?
Questions - 3

• How accepting are IRBs of newer methods?
• If consent processes were more efficient, do you think more physicians would engage in clinical trials?
• Technology has replaced face-to-face interaction in many aspects of our culture. Should it also in research?
• Can technology effectively protect human subjects?
• What are your top 3 concerns about engaging in clinical trials in your practice?
EDGE Application ICF
Electronic tool Needs

- Patient friendly with paginated ICF with questions for understanding / comprehension
- Video/animated delivery of ICF
- Ability to pause or hold enrollment progress per individual participant
- Real time/dynamic randomization on tablet
- Site agnostic study ID generation
- Ability for physician to review archived participant enrollment and verify status (continue/discontinue) for yearly follow-up
- Cross platform capability---IOS/Android/Windows
EDGE Application ICF Electronic tool needs (continued)

• Integrate study inclusion and exclusion

• HIPAA/21 CFR part 11 compliant

• Deliver encrypted patient/production data from tablet to UAB controlled servers

• Web interface/dashboard to review site status and recruitment progress
UAB
iPad vs Paper Informed Consent Project

- Paper vs iPad, randomized to start with one mode then crossed over (at the level of the clinic)
- 9 sites enrolled (convenience sample of sites)
  - 5AL sites
  - 2 CO sites
  - 2 TX sites
- 41 participants screened-31 enrolled
<table>
<thead>
<tr>
<th>Code</th>
<th>Comment</th>
</tr>
</thead>
</table>
| KS13  | what can we say about those who did not enroll Reasons?  
Kenneth Saag, 7/20/2014 |
| GC22  | This should be earlier or maybe even eliminated  
Gary Cutter, 7/20/2014 |
| MBS26 | We can say they do not want to participate  
Michael B Saddeki, 7/21/2014 |