

Innovative Approaches for Conducting Efficient Lower Cost Pragmatic Clinical Trials

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Overview of Presentation

- Challenges facing clinical trials enterprise in US
- Unique features of pragmatic clinical trials
- Differences between pragmatic trials and traditional explanatory trials
- Example of recently proposed pragmatic trial incorporating several innovative approaches to improve trial efficiency and decrease costs
- Future directions for pragmatic trials

Two Assumptions

1. The increasing cost of conducting clinical poses major challenges to NIH's mission in clinical research and the viability of the clinical research enterprise in the US.
2. Traditional approaches to clinical trials are not providing the evidence base to inform the diagnostic and treatment decisions that clinicians must make in routine practice situations.

High Cost of Clinical Trials

- Costs of conducting trials is now 60% of total drug development costs, compared to 30% in 1980s, while cost of pediatric trials increased 8-fold from 2000 to 2006 (*Pfizer*)
- High costs makes US less competitive worldwide → ***Costs of conducting clinical trials 40-60% lower in India, China, Russia, & Brazil than in US***
- E.g., recently funded NHLBI ISCHEMIA Trial
 - *Randomize 8000 patients with moderate angina on stress testing to cath & possible revasc or medical management with 4 year follow-up*
 - ***Total cost \$84 million → \$10,500 per subject***

High Cost of Clinical Trials

High cost of conducting trials is multi-factorial

- 1) *Increases in regional and national regulations and redundant regulatory review processes*
- 2) *Risk-averse interpretations of regulations*
- 3) *Increasing time and financial pressures on clinical investigators and decreased ability to cross-subsidize trials with clinical revenue*
- 4) ***Inefficiencies in conducting clinical trials***

High Cost of Clinical Trials

A major driver of clinical trial inefficiency is delays in patient recruitment.

- One source estimated that 80% of trials are delayed at least one month because of unfulfilled enrollment.
- The FDA estimated that only 6% of trials are completed on time, while 72% run over schedule by more than one month.
- For each day a drug is delayed from market, sponsors lose up to \$8 million

High Cost of Clinical Trials

Another driver of inefficiency is low enrollment and low retention.

- Overall, clinical trials enrollment rates dropped from 75% in 2000 to 59% in 2006, while retention rates fell from 69% to 48% during same period.
- Less than 1/3 of people who are screened end up completing a clinical trial.
- Clinical research is also being concentrated in a fewer number of sites. Out of all of the clinical research sites in the US, 30% contain 70% of all clinical trials subjects.

High Cost of Clinical Trials

Clinical trials also suffer from low physician participation

- Less than 4% of US physicians participate in clinical trials.
- The number of active investigators in the US has declined 3.5% annually since 2001, compared to 13.5% increase outside the US
- Declining interest may reflect the traditional orientation of clinical trials

Traditional Orientation of Trials

- Most trials are conducted in artificial settings that do not represent routine clinical practice.
- Most trials are **explanatory** (i.e., mechanistic)
 - *Orientation is around biological mechanisms for how and why a treatment works*
 - *Often measure intermediate outcomes that are less relevant to patients (e.g., changes in blood markers or imaging results rather than changes in health or symptoms)*
 - *Often undertaken by ‘expert’ clinicians in specialized settings who carefully select patients*

Explanatory Trials

- Often enroll homogeneous patients with tight characteristics (*e.g., limited number of comorbid conditions*) in effort to reduce response variation
- Often use the ‘wrong’ comparator --> **placebo**
- Often ignore existing treatments and don’t examine if new treatment is better than existing treatments – **key question for clinical practice**
- Above aspects of explanatory trials limit their generalizability to routine clinical practice
- In response, increasing interest in **pragmatic clinical trials**

Pragmatic Clinical Trials

- Term coined by Schwarz and Lellouch in 1967
(*Journal of Chronic Disease* 1967; 20: 637-648)
- Design mimics routine practice, with exception that patients are randomly allocated to treatment
- Because placebos are not used, effectiveness of different treatments are estimated
- Because conditions mimic routine practice, results more applicable to the 'average' patient
- Unfortunately, pragmatic trials often felt to be unscientific because of loss of control of variables

Differences Between Pragmatic and Explanatory Trials

Pragmatic trials

- Determine effectiveness, as opposed to efficacy
- May require longer term follow-up to track outcomes that reflect the “real life” concerns of patients
- Often examine multiple outcomes
- May be better suited to studying chronic conditions that require treatment over many years
- Heterogeneous group of patients --> high external validity but often lower internal validity
- Often require larger sample sizes because of patient heterogeneity

Other Differences Between Pragmatic and Explanatory Trials (cont.)

- Practitioner administering treatment skilled in routine clinical practice
- Patients and practitioners typically not blinded to treatment assignment → *However, allocation to groups should be random & assessor of outcomes should be blinded to group allocation*
- Treatment approach incorporates some flexibility to adapt treatment to individuals needs
- Analysis typically based on “intention-to-treat” approach recognizing that treatment cross-over may be more common than in explanatory trials

Pros and Cons of Pragmatic Trials

- **Con**: May not be generalizable because of wide inclusion criteria and orientation towards finding if a treatment works for 'average' patient --> most patients are not average and the results don't tell us which patients in those recruited does the treatment work. In an explanatory trial we can.
- **Counter Pro Argument**: Few treatments have opposite effects in different subgroups. While the degree of effectiveness may vary, treatments effective in one subgroup are usually effective in other subgroups.

Example of Recently Proposed Efficient Pragmatic Clinical Trial

Goals of Trial

- Examine the impact of nighttime dosing of anti-hypertensive medications among patients with HTN and other comorbid conditions that increase CV risk
- Implement innovative methods for decreasing the costs of patient enrollment and data collection

Example of Recently Proposed Efficient Pragmatic Clinical Trial

Background

- Two recent trials in patients with HTN and DM and HTN and CKD found 3-fold lower risk of CV events in patients randomized to take 1 or more anti-hypertensives at night (adjusted HRs 0.33 & 0.31)
- Patients taking nighttime meds had similar daytime BPs but lower sleep syst BP (115 vs. 122 mm Hg)
- Each 5 mm Hg decrease in sleep time systolic BP associated with a 12% lower risk of CV events

Efficient Pragmatic Clinical Trial: Patients

- 1100 patients with HTN and 1 or more other comorbid conditions that increase CV risk
- 2 or more visits in prior 12 months to General Medicine, Family Medicine, Cardiology, or Nephrology clinics
- 2 sites: University of Iowa and Duke
- Patients followed for 36-42 months

Efficient Pragmatic Clinical Trial: Endpoints

- CV events (CV death, AMI, CVA, admissions for CHF, coronary, cerebral, or peripheral revascularization)
- Blood pressure
- Self-reported medication adherence
- Symptoms, health-related quality of life, adverse drug events
- Resource utilization (admissions for CV disease, ER visits, ambulatory visits)

Strategies for Increasing Efficiency and Lowering Trial Costs

Increase efficiency of patient recruitment

- Identify eligible patients via EMR at both sites from demographics, diagnoses, & lab values from EMR
- Send eligible patients letter informing them of study and referring them to website (preferred) or to toll-free 1-800 telephone number
- Use interactive web-based platform for obtaining informed consent

Strategies for Increasing Efficiency and Lowering Trial Costs

Increase efficiency of data collection

- Use EMR to determine baseline diagnoses, CV risk factors, and medications
- Use EMR to determine CV events, BP, and health care resource utilization
- Use web-based personal health record (PHR) to determine CV events outside UI & Duke systems
- Use PHR to determine other endpoints (self-reported medication adherence, symptoms, HRQL, ADEs, resource utilization)

Preliminary Studies: Identify Patients Using EMR

- NIH funded randomized trial of intervention to increase visual processing speed in older adults.
- EMR-based algorithm used to identify patients in General Med and Family Med clinics who: 1) were ≥ 50 years; 2) had ≥ 2 clinic visits in past 12 months; and 3) didn't have diagnosis of dementia
- Of 5743 eligible patients identified and sent single mailing, 996 expressed interest in participating
- Of these, 681 enrolled over a 6-month period.

Preliminary Studies: Identify Patients Using EMR (cont.)

- Industry trial of new inhalational therapy for asthma
- EMR-based algorithm used to identify outpatients ≥ 18 years with diagnosis of asthma or wheezing and without diagnoses of lung cancer, TB, COPD, bronchiectasis, emphysema, or pregnancy
- Eligible patients sent information letter about study
- 139 expressed interest in participating, allowing investigators to easily reach recruitment goal of 24 patients (*had only enrolled 3 subjects using traditional clinic outreach efforts*)

Preliminary Studies: Interactive Web-Based Platform for Obtaining Informed Consent

- Randomized trial of 95 potential study subjects of a mock study of station treatment with 3 arms:
 - **Control** – *Coordinator provided subject with paper copy of IC document and summarized each sentence of the document*
 - **Web-based** – *IC document presented on webpage with graphics and narration*
 - **Web-based Interactive** – *as above plus questions to subject & feedback on responses*

Interactive Web-Based Platform for Obtaining Informed Consent: Results of Pilot Study

Mean Scores	Control	WB	WBI
Knowledge Scores (0-18)	14.9	15.2	15.9 *
Length of IC Process (1-5; 1 = too short, 5= too long)	4.1	3.7	3.5 *
Difficulty of IC Process (1-5; 1= too easy, 5=too difficult)	3.1	2.8	2.3 *

* $P < .05$ vs. Control

Web-Based Platform for Obtaining Informed Consent: Screen Shot

X-Plain
PATIENT EDUCATION

Statin Treatment and Microvascular Function

Law, Health Policy & Disability Center

Law Health Policy & Disability Center

- Introduction
- Purpose of the Study
- Procedures
- Risks & Benefits
- Alternative Treatments
- Costs & Compensation
- Confidentiality
- Voluntary Study
- Contact Information

If you agree to be in the study, you will have a 1 in 2 (50%) chance (like flipping a coin) of getting one of the following two study pills:

1. Placebo (an inactive pill like a sugar pill)
2. Rosuvastatin (the active drug)



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Web-Based Platform for Obtaining Informed Consent: Screen Shot

The screenshot displays a web-based patient education interface. At the top left is the 'X-Plain PATIENT EDUCATION' logo. The top right features the 'Law, Health Policy & Disability Center' logo and name. Below the header, the page title is 'Statin Treatment and Microvascular Function'. A left-hand navigation menu contains buttons for: Introduction, Purpose of the Study, Procedures, Risks & Benefits, Alternative Treatments, Costs & Compensation, Confidentiality, Voluntary Study, and Contact Information. The main content area shows a quiz question: 'Which of the following is NOT true?' with three options: A (You may quit the study at any time.), B (You will be paid if you complete the study.), and C (The doctor might stop your involvement in the study at any time.). A yellow button labeled 'Press A, B or C' is positioned below the options. At the bottom, a control bar includes a progress indicator for 'Slide 79', a volume icon, a repeat icon, and left/right navigation arrows. The footer contains the text 'powered by X-Plain' and 'Copyright © 1995 - 2011 The Patient Education Institute'.

X-Plain
PATIENT EDUCATION

Law, Health Policy &
Disability Center

Statin Treatment and Microvascular Function

Law Health Policy & Disability Center

Introduction

Purpose of the Study

Procedures

Risks & Benefits

Alternative Treatments

Costs & Compensation

Confidentiality

Voluntary Study

Contact Information

Which of the following is NOT true?

A You may quit the study at any time.

B You will be paid if you complete the study.

C The doctor might stop your involvement in the study at any time.

Press A, B or C

Slide 79

Volume Repeat

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Preliminary Studies: Use of Web-Based PHRs to Obtain Clinical Data and Study Endpoints

- Study will adapt the “IowaPHR,” which is a secure portal developed through AHRQ funding (5R18 HS017034-03) for use with older adults
- Each patient has PW protected webpage that can be customized based on individual preferences for information and communication
- Tested in 6-month RCT assessing impact of IowaPHR on Rx adherence and health behaviors
- Patients sent automated prompts via email or phone to go to PHR and enter study data

Preliminary Studies: Data Obtained from IowaPHR in 516 Older Adults in AHRQ Trial

Self-reported hypertension	58%	Mean SF-12 Mental Health score	55.7
Self-reported arthritis	56%	Mean SF-12 Physical Health score	46.1
Self-reported high cholesterol	53%	Mean # prescription drugs	4.7
Self-reported osteoporosis	20%	Mean # over-the-counter drugs	4.1
Self-reported diabetes	15%	Mean # self-reported chronic conditions	3.8

Iowa PHR Screen Shot: Home Page

The screenshot shows the IowaPHR Home Page in a Windows Internet Explorer browser window. The address bar displays <https://www.iowaphr.org/phr/home.jsp>. The browser's menu bar includes File, Edit, View, Favorites, Tools, and Help. The page features the IowaPHR logo (Personal Health Record) and a navigation menu with links for Home, Medication Lists, Print Reports, Tracking, Allergies, Health Conditions, and About Me. A date indicator shows April 20, 2012. The main content area includes a 'Welcome Back' message, a section for 'Latest safety updates about your medications' with links for Coumadin and advil, a disclaimer, a 'Did you know?' section with advice on medication management, and a video player for a tutorial.

IowaPHR
Personal Health Record

April 20, 2012

Home Medication Lists Print Reports Tracking Allergies Health Conditions About Me

Welcome Back

Latest safety updates about your medications:

- ▶ **Coumadin** - Reduce your risk of serious bleeding side effects
- ▶ **advil** - Do you have risk factors for serious stomach bleeding?

Please note that using IowaPHR should not in any way replace advice given by a doctor, pharmacist, or any other medical professional. Please talk to your doctor or pharmacist before starting, stopping, or changing how you take any medication. Different medications sometimes have very similar names, and a warning could be generated in error. To verify that your medication contains the drug listed in a warning, check the label or ask your pharmacist.

Did you know:

You should keep a record of what each medication is supposed to do.

Over time it seems easier to start medications than to stop them. Older adults take many medications. Making sure each prescribed medication has a reason is one way to possibly reduce the number you take.

What can you do?

- Go to the Medication Lists tab and enter why you take each medication.
- Ask your pharmacist or healthcare team to review your medication list to ensure you have a clearly defined reason for every prescribed medication.
- Ask if there are medications that can be removed.

With the IowaPHR you can:

- Keep an up-to-date list of all your [medications](#).
 - Record what each medication is supposed to do.
 - Get important warnings about the medications you are taking.
- [Print reports](#) to share with your healthcare providers, including:
 - A list of your current medications
 - Warnings for medications you are taking
 - A wallet-sized card
- Track your [health](#), [allergies](#) and [health conditions](#).

Please click play to view the tutorial video below.

Welcome to IowaPHR!
Click here for tutorial

Play

00:00 / 05:22

Iowa PHR Web Screen Shot: Medication Entry Interface

The screenshot shows a web browser window titled "IowaPHR: Medications - Windows Internet Explorer". The address bar shows the URL "https://www.iowaphr.org/phr/medication/medications.jsp". The browser's menu bar includes "File", "Edit", "View", "Favorites", "Tools", and "Help". The "Favorites" bar shows "IowaPHR: Medications".

The main content area features the IowaPHR logo (Personal Health Record) and a date "April 20, 2012". A navigation menu includes "Home", "Medication Lists", "Print Reports", "Tracking", "Allergies", "Health Conditions", and "About Me". Below this, there are tabs for "Current Medication List" and "Previous Medication List", with a link to "view or print your current medication list".

Instructions
 As you begin to type a medication name, our system will recommend product names to help you with spelling. When you see the one you want, click on it to enter it in the field. It is possible that not every product is in our system. In that case, just keep typing, being careful to spell it as accurately as possible. You may see a safety warning about a medicine. Safety warnings are based on expert recommendations, however please note that using IowaPHR should not in any way replace advice given by your doctor, pharmacist, or any other medical professional. Also, different medications sometimes have very similar names, and a warning could be generated in error if a typing mistake is made.
[\[More Information\]](#)

MY CURRENT MEDICATION LIST

Name of Medication or product Example: Tylenol	What Strength do you take? Example: 325mg	How do you take it? Example: 2 Tablets Every 8 Hours As Needed	Why do you take it? Example: Arthritis
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="button" value="Add Medication"/>			

Page	Medication	Strength	Frequency	Reason	Actions
1	zyrtec	10 mg	1 tablet in the morning	Allergies	Edit Delete
	<input type="button" value="Move to Previous Medication List"/>				
	advil	200 mg	One tablet every 4-6 hours	Headaches/Arthritis	Edit Delete
	<input type="button" value="Move to Previous Medication List"/>				
	Coumadin	5 mg	1 tablet in the morning	For my heart	Edit Delete
	<input type="button" value="Move to Previous Medication List"/>				

Additional warnings for Coumadin:
 Do you have risk factors for serious stomach bleeding?
 Reduce your risk of serious bleeding side effects

Iowa PHR Screen Shot: Patient Messaging Interface

Your Personal Health Record

Home Allergies Health Conditions About Me Messages Healthcare Visits Risk Report

Messages

< 1 - 2 of 2 >

04/21/2012 10:14 am	Medication List	Jane, Thanks for entering your medications. I've reviewed your health ... John Smith
04/20/2012 03:35 pm	Hello!	Hi Jane, I noticed that the most recent blood pressure reading you to ... John Smith

New Message

[About IowaPHR](#) | [About this study](#) | [Feedback](#) | [Contact us](#) | [Settings](#) | [Tutorial](#) | [Sign Out](#)

Institute for Clinical and Translational Science | University of Iowa
Supported in part by NIH grants R18 HS017034 and UL1 RR024979

Iowa PHR Screen Shot: Clinician Messaging Interface

The screenshot displays the Iowa PHR Clinician Messaging Interface. At the top left, the logo reads "IOWA PHR Your Personal Health Record". The top right corner shows "Sign Out" and the date "April 20, 2012". A navigation bar contains tabs for "Subjects", "Messages", "Notes", "Communication Forms", "Warnings", "Alerts", and "Actions". Below this, a filter bar shows "Assigned To Me" and "All". A "Show 10" dropdown and a search box are present above a table of patient entries. The table has columns for Id, First, Middle, Last, Last Accessed, and Next Access. Three entries are visible, each with "view" and "add form" links. A footer contains navigation links: "About IowaPHR", "About this study", "Feedback", "Contact us", "Settings", "Tutorial", and "Sign Out".

IowaPHR: Clinician +

Sign Out

April 20, 2012

IOWA
PHR *Your Personal Health Record*

Subjects Messages Notes Communication Forms Warnings Alerts Actions

Assigned To Me All

Show 10 Search:

Id	First	Middle	Last	Last Accessed	Next Access
442	Jane	Anne	Doe	04/20/2012	view add form
444	Mark		Smith	04/20/2012	view add form
445	Audrey		Jones	04/20/2012	view add form

Showing 1 to 3 of 3 entries (filtered from 10 total entries) First Previous 1 Next Last

About IowaPHR | About this study | Feedback | Contact us | Settings | Tutorial | Sign Out

Institute for Clinical and Translational Science | University of Iowa
Supported in part by NIH grants R18 HS017034 and UL1 RR024979

Take Home Points

1. Design of innovative strategies for improving efficiency of patient recruitment, enrollment & data collection are needed to lower costs of clinical trials.
2. Strategies should capitalize on implementation of EMRs and new mobile technologies.
3. Such strategies will be of interest to NIH ICs, which are looking to better leverage funds.

Take Home Points (cont.)

4. Developing evidence base to inform clinical decision making will require greater focus on pragmatic trials in real-world practice settings.
5. Such trials can be a central feature of creating true learning health systems in which

“science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience.” (Institute of Medicine)