Clinical Research Seminar

Using the Internet to Conduct Research and Recruit Subjects
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Types of Studies that Work Best
- Cohort Studies
  - Loss to follow up may be a problem
- Health Education
- Surveys
  - Difficulty determining denominator and low response rate issues raise issues about generalizability
- Traditional Clinical Trials
  - Randomization
  - Data entry
  - Study management/communications
- Online Clinical Trials
  - “Nutriceuticals” or non-invasive interventions

Benefits of Internet in Research
- Capture data in real time
- Data collection for clinical research
  - Paperless
- Communications and management for multi-site trials
- Subject recruitment
  - Reach greater target population

Risks
- No direct contact with subjects
  - Unable to intervene if subjects become distressed or experience other adverse events
- Breach of confidentiality
  - Most common risk
  - Via insecure transfer of data
  - Via environment in which subject is accessing Internet (e.g., Internet café, public library)

Validity
- Non-representative populations (i.e., tend to be of higher SE and educational status)
- Falsification of data
- Multiple submissions by same subject
  - “Subject naught”
- Invalid results places subjects unnecessarily at risk

Consent
- Waiver of consent
  - [45 CFR 56.116(d)]: (1) The research involves no more than minimal risk to the subjects;
  - (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
  - (3) The research could not practicably be carried out without the waiver or alteration;
    - AND-
  - (4) Subjects will be provided with additional information/results after participation
### Consent
- Waiver of documentation of consent
  - [45 CFR 56.117(c)]: (1) Only record linking subject to research would be the consent document and this is the primary risk of harm (i.e., in the event of breach of confidentiality) -OR-
  - (2) Research presents no more than minimal risk to subjects and involves no procedures for which written consent is normally required outside of the research context
  - Can still create a consent page that subjects must read and electronically accept before proceeding
- Subjects may also print/sign consent form from Internet and fax/mail to investigator to receive password for website

### Privacy
- Identifiable vs. Anonymous
  - Screen names/handles/e-mail addresses commonly used online
  - Though subject names may not appear with these, often can be “readily ascertained” via search engines
  - Online identity may be as important to a subject as real identity

### Privacy
- Public vs. Private
  - Most online activity is publicly accessible
  - Federal regulations base definition of private information on the “reasonable expectation” of privacy
    - e.g., chat rooms, chatters expect privacy and not to have their chat studied

### Minors as Subjects
- If research qualifies for waiver of parental permissions, no additional safeguards required
- Otherwise parental consent must be obtained unless criteria for Waiver of Informed Consent or Waiver of Documentation of Informed Consent are met
- Online services can help but none are 100% foolproof
  - AdultCheck
  - NetNanny

### Confidentiality
- Breaches
  - Inadvertent disclosure (e.g., stolen laptops/computers with subject data)
  - Deliberate attempts to gain access (i.e., hackers, no documented evidence of this occurring in a research setting)
  - E-mail is considered “individually identifiable information” by IRB
  - Information or data transmitted by e-mail is not secure unless additional steps are taken (e.g., encryption)

### Web Systems Security
- Website on secure server behind firewall
- Server housed in locked room with restricted access
- Data are encrypted (Secure Socket Layering (SSL) technology)
- Login restricted by username and password
- Automatic timeout
- Daily backup of web-server and database
Subject Compensation

- Several Different Approaches May Be Used
  - Mailed check/cash
  - E-money (e.g., PayPal)
  - Electronic gift cards (e.g., giftcertificates.com)
  - Charitable donation
- Be careful with raffles!
  - Closely scrutinized by IRB
  - Must be conducted in a way that is equitable to all subjects

Study Advertisement/Recruitment Sites

- Online search engines
  - Google
  - Yahoo
- Links on other sites
  - Gout.com
- Trial listing services
  - Centerwatch
  - Study response project
- Banner Ads
  - Gay.com
- NIH
  - ClinicalTrials.gov

Example of a Recruitment/Study Registration Site

Centerwatch Clinical Trial Site

Institutional Research Subject Recruitment

Disease Specific
Craig’s List

For local research studies. However, note there are many restrictions on posts:

- Cannot post continuously
- Cannot post same ad repeatedly
- Cannot post same ad in more than one city at a time
- Restrictions vary by city
  - Designated cities restrict posts to 3 days (Boston, San Francisco, New York)
  - Other cities allow posts for up to 45 days

Craig’s List “Volunteers”

Website for NIH Funded Research

Case Study: The Non-Gay Identifying Men Who Have Sex with Men Studies (US and India)

- Compensation
  - US: giftcertificates.com
  - Eligible AND ineligible subjects randomly selected for online gift code
  - Code was displayed in a separate window with text warning respondent to print or carefully write down code (i.e., NOT e-mailed)
  - India: Used similar method with an online vendor in India
Case Study: The Non-Gay Identifying Men Who Have Sex with Men Studies (US and India)

Recruitment
- US: Google AdWords, gay.com, manhunt.com, African-American and gay community newspapers (Boston, NYC, Washington DC)
- India: Banner advertising in gay chat room on indiatimes.com website

Accrual of Eligibles and Ineligibles: March 29, 2005-January 3, 2006

Internet in Clinical Trials
- Study management and communications
- Randomization
- Data collection
- Real-time SAE reporting
- Data querying
- Real-time reporting
- Form dissemination
- FAQ
- Etc.

Great for International Trials

Welcome to the DIFUNISAL TRIAL

Data Entry, Screening, Randomization, Tracking

If you forget your password, if you are a new user, then please click here.
Stratified Randomization

Confirm Eligibility and Randomize

Real-time Reporting

Electronic Data Capture “Cleaner”

Secure, Web-based Data Querying (no faxes)

Web-based Problem Resolution
Click-through to Correct Data

Online Clinical Trials: Nutraceuticals

Example: Paperless Trial System
- MGH / Roche Diagnostics collaboration
- Web-based electronic data capture
- Double entry of paper forms
- Data cleaning (queries)
- Monitoring
- Reporting
- Data exporting
- Electronic Signature (21 CFR, part 11)

Possibilities

“We now have the potential to conduct a cohort study of users of the World Wide Web” …
“…[the Internet] can have people recruit themselves, enter their own data into our computers, and provide for fast, convenient electronic follow-up.”


Example of Cohort Study
- Elizabeth Hatch, Kenneth Rothman Laura Wise, BUSPH co-investigators
- Study taking place in Denmark where centralized medical records are available
- Subjects consent online and provide Central Population Registration # and consent to view record
Internet-based Study of Time to Pregnancy

- Over 7,000 women screened to date
- 3,700 eligible and have consented to take part
- Subjects followed bi-monthly or until pregnant
- 85% of subjects had 4 month follow up
- Self reported medical history validated against medical record

Online Gout Study, Yuqing Zhang, PI Study

- Subjects recruited online
- Each subject serves as own control
  - control period = no symptoms
  - hazard period = acute attack
- Online consent with waiver of documentation
- All study questionnaires completed online
- Disease status and symptoms confirmed with medical records

Case-crossover Study of Triggers for Gout

- 48-Hour Control period
- 48-Hour Hazard Period
- Triggers?
- 25-48 hrs
- 1-24 hrs
- Without Acute Gout Attack
- Acute Gout Attack

Recruitment Plan

1. Referral through former rheumatology fellows
2. Banners/ads and links to other sites
3. Search engines (link to search terms)
4. Prevention magazine
5. e-Zines
6. Set up a chat room
7. Traditional print media

Online Search Engine

Google Ad Linked to Search Term
Incentives

- 5 Points accumulated for each questionnaire with $1/point cash pay-out at end of study
- ‘Gout Study’ pens mailed with Medical Record Release forms as incentive to sign and return forms

GOUT SUBJECTS BY STATE

Study Continues: Gout II

- Original Gout Study: 02/03 - 05/05
- New Gout Study: 11/05 –
  - Recruitment strategy to use Google based on results of Gout I

But Things Change…

In the meantime, Google went public and prices went up -- dramatically
- Ad placement went from first or second ad to third or fourth
- Cost/click rose from $0.16 to > $0.40
- Click-through rate dropped from 6.9% to 2.4%

RECRUITMENT: G1 VS G2

*Search Engine Ad Cost: $9,339 ($34 per subject)
Typical Chat Room Postings

Why you do have a few questions or concerns about this study?

1. Do we use list-based email service, but not necessarily a secure service? To
2. Is the information used for observations?
3. Is the website the author of the study remaining anonymous? "Online
4. What level of statistical analysis did you possibly expect by doing a

Avoid that gout study. They insist on sending emails to you as attachments instead of as text
and they will send annoying 'thank you' messages and 'birthday greeting' messages.

> another user trying to milk the gout group of hard earned income
doubts. "I"
> some of the gout police arsehole and watch they would have missed out
> character

Current Strategies

- Google advertisements
- Link on Gout.com
- Postings under volunteer section of Craig's list (selected cities)
- Link on Centerwatch

Hits to Online Gout Study Website in Last Year

- Google Ads: 36,488
- Craigslist: 596
- TAP website, gout.com: 182
- CenterWatch: 1

Conclusions

- Several types of study designs lend themselves to Internet implementation
- The Internet poses unique challenges in risk to human subjects, validity of study data, obtaining informed consent, privacy, confidentiality, and recruitment
- Important to begin with a well-defined target population to determine the feasibility of Internet recruitment and retention
- Things change quickly so be prepared to revise your strategies