



Electronic Technology in Clinical Trials

Leonard Sacks, M.D.

Office of Medical Policy

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

FDA Clinical Trial Investigator Training Course

November 13, 2018

The Clinical Trial



Clinical trials have lagged behind in the use of information technology

The purpose of this short lecture is to tell you what progress has been made to move us into the modern age

- Electronic case report forms and EDC
- Electronic informed consent
- Electronic health records
- Mobile technologies
- Decentralized clinical trials

I will not be covering electronic data submissions to FDA- that should be discussed at each of the center breakouts

Regulatory Framework

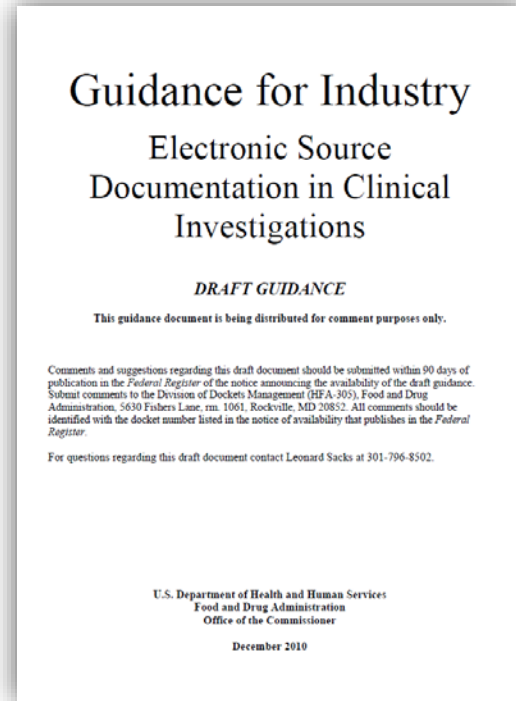
- We have a set of “predicate rules” which tell us at FDA what we need to ask of sponsors and investigators about patient records.
- For drugs, the relevant predicate rule appears in 21.CFR.312.62(b)
 - (b) *Case histories*. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
- These were the rules that traditionally supported using paper records



Part 11

- In 1997 a small set of regulations was published, called “part 11” explaining how to use electronic records and signatures instead of paper
 - Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with 11.2, unless paper records are specifically required.
- They described an outdated model of open and closed electronic systems, and they described the necessary attributes of electronic records and signatures which would be required in order for companies to use electronic platforms.
- They included things like validation of electronic systems, the ability to generate complete accurate copies of records, the need for audit trails, access controls, training of users.
- Within these regulations, we had enough regulatory support for us to move trials to electronic platforms.

- Our first effort was to write the eSource guidance
- The guidance says that no paper records may be necessary if you have an acceptable electronic system



<https://www.fda.gov/downloads/drugs/guidances/ucm328691.pdf>

Electronic source documentation in clinical investigations



- In the guidance we suggest that the electronic case report form acts as the ‘trial machine’ used to assemble all trial data
- Data can enter the eCRF from many different sources: investigators, study staff, clinical labs, patient reports, imaging facilities, bar code readers, electronic health record systems and devices etc.
- Each data element entering the system needs to be tagged
 - a data originator (the person or machine entering the data)
 - the date and time
 - a patient identifier



Original and transcribed data

- We distinguish between original data and transcribed data e.g.,
 - If a data originator measures a blood pressure, or reports abdominal tenderness or the presence of a rash, the electronic data entry into the electronic case report form is all that is needed
 - If a data originator transcribes a finding from a radiology report or a lab report, the original record must be kept



Ensuring data integrity

- The systems needs an audit trail so that any changes to the data can be tracked
- Clinical investigators should review and sign off on the data electronically before it is submitted to FDA
- The data should be saved in a way that the investigator has control of the record and outside parties can't meddle with it

Electronic source data- what next?



- Once the electronic platform for clinical trial data is in operation it becomes possible integrate all sorts of electronic information in creative ways....



Use of electronic informed consent

- The first opportunity was electronic informed consent
- Regulations on informed consent appear in 21CFR 50. They describe the required content of the informed consent and the necessary documentation:
 - (a) Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.
- Traditional informed consent involves long documents that are sometimes meaningless to patients. Why can't we show videos and interact electronically with patients?

<https://www.fda.gov/downloads/drugs/guidances/ucm436811.pdf>

Use of Electronic Informed Consent – questions and answers

December 2016

- Better patient comprehension
- Prompt documentation
- The opportunity for patients to review informed consent programs and sign consent at home with no duress



but there are challenges...

- We have to keep to the regulations which describe the required content of the informed consent form (21CFR 50.25)
- Opportunities for patients to ask questions
- We have to provide patients with an adequate electronic equivalent of a copy of the informed consent
- The materials have to satisfy IRBs and FDA inspectors
- It may be possible for patients to sign these at home but we have to make sure that we know the study subject is the one who signs the document

Use of Electronic Health Record Data in Clinical Investigations



July 2018

- Another area of increasing interest is the use of electronic health records in clinical research.
- Today, clinical investigators and clinical caregivers generally use different systems to record their findings
- Integrating research and care is an important public health goal: both care givers and investigators should know what happens to their patients
- Integrated systems can avoid duplication of data entry (e.g. demographics, concomitant meds, comorbidities)
- EHRs are an important resource for identifying and recruiting patients for studies

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM501068.pdf>





Ensuring reliability of EHR data

- In the US, EHRs are meant to comply with “meaningful use” standards laid out by the office of the national coordinator.
- These standards mirror our part 11 requirements
- Effectively certified EHRs can be used in the US for clinical research and we have stated that part 11 requirements will not be enforced in this environment



- The challenge is how to deal with EHR systems that we know nothing about, for example at many overseas sites
- Sponsors need to satisfy themselves that those uncertified EHR systems are reliable, that they ensure confidentiality, integrity and security of data.
- Access controls and audit trails are needed to prevent unauthorized data entry.
- Electronic health records used in clinical trials need to be accessible for FDA inspections

Mobile Technology Tools

- An exciting prospect for clinical trials is the use of mobile technology tools
- Potentially revolutionize the way trials are conducted
- They may include wearables, biosensors, cell phones, tablets, environmental sensors (invisibles)

Think of the opportunities





Advantages and Challenges

Advantages

- Patients can be monitored from the comfort of their homes
- Objective measurements can be made
- Measurements can be made continuously- not just during an office visit
- Video communications may be used in research just as they are for telemedicine- access to rare diseases, patient with mobility problems
- From a regulatory perspective, medical devices that are not used to affect patient care do not require FDA approval

Challenges

- When such devices are used for research it will obviously be critical to standardize the reliability, attributibility, sensitivity and specificity of measurements



Reliability

- Performance specifications
 - accuracy and precision to measure velocity, temperature, pressure, battery life, memory size
- Validation of measurement (e.g., steps, breaths, heartbeats, sleep)
 - When appropriate, compare with observation or video, compare in patients with disease and without, mild and severe, treated and not treated, avoid confounding by similar activities, physical or chemical interference

Endpoints

- Components
 - The **thing** you are measuring: steps, breaths, seizures, falls, blood glucose
 - **Formulation** of the endpoint: e.g., change from baseline, mean value, AUC, responder/non-responder, time-to-event
 - **Window of observation** e.g., 24 hours after completion of therapy, response 3 months after start of therapy
- Should reflect how patients feel, function or survive

Relevance of Novel Endpoints

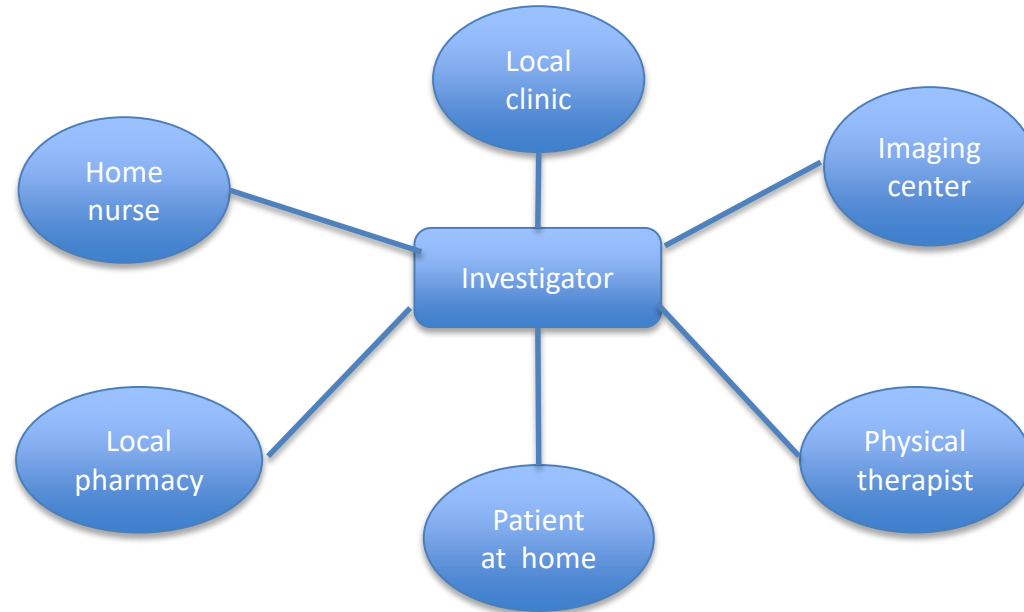
- If possible correlate electronic endpoint with:
 - Similar accepted traditional endpoint
 - Clinical outcome e.g., hospitalization, death
 - Patient reported outcome
- Novel endpoints: develop in consultation with regulators, patients, caregivers, disease experts payers



Usability and safety

- Usability by intended population e.g., children, elderly
- Comfortable and convenient
- Safe and secure
- Technological support-malfunction, loss

Decentralized Clinical Trials



This is just the beginning

- My prediction is that clinical trials in 10 years' time will be hard for us to recognize
- Increasingly they will occur at patient homes or at their private doctors. Patients may potentially wear their sensor devices, flash pictures of their lesions from their cellphones, submit patient reported outcomes on their tablet computers, perhaps even receive their study drugs by drone

Summary

- Discuss existing regulatory framework for using electronic systems
- Discuss the opportunities and challenges using electronic technologies to modernize clinical trials