Electronic Technology in Clinical Trials

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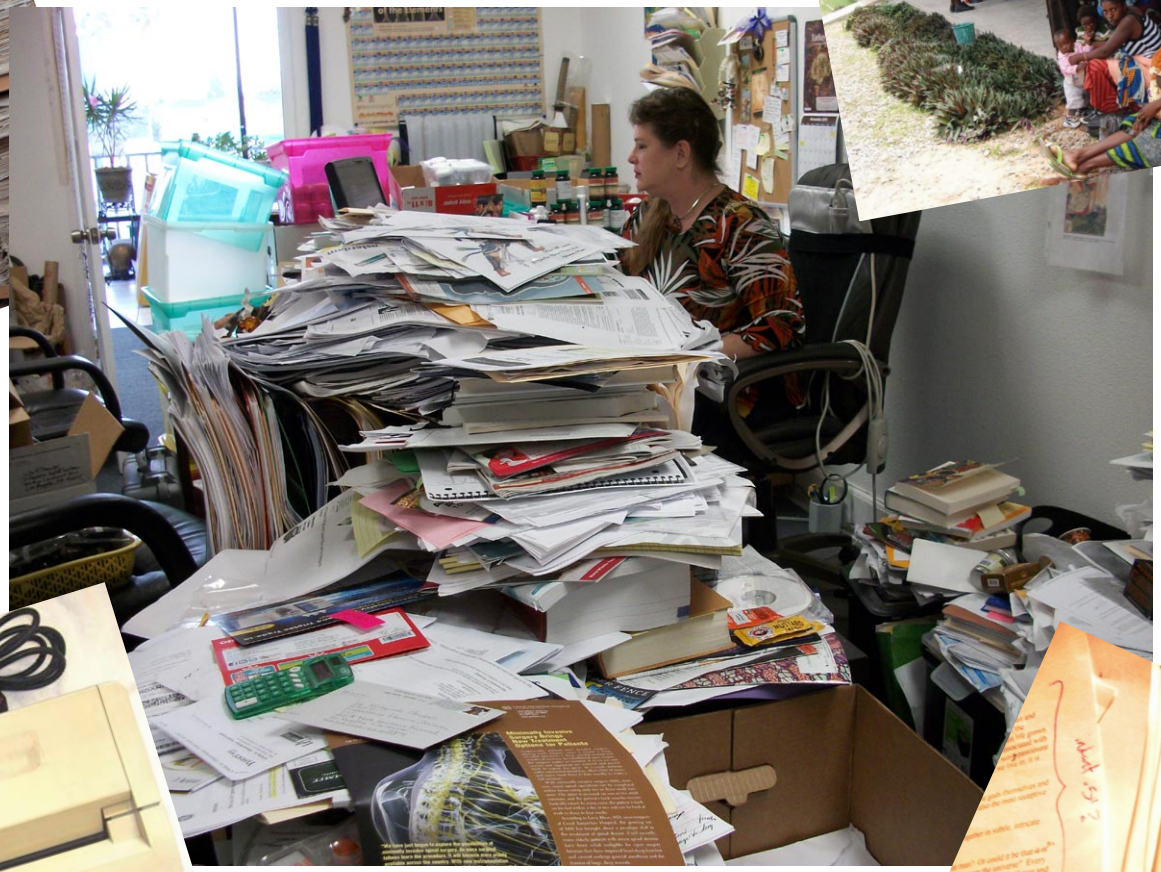
The Clinical Trial



How did clinical trials escape from the computer age?

- Was the problem FDA's regulations on record keeping
- Was it industry's nervousness to try anything new?
- Was it informed consent regulations?
- Was it FDA inspection requirements?

It was clear that FDA had to do something

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

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

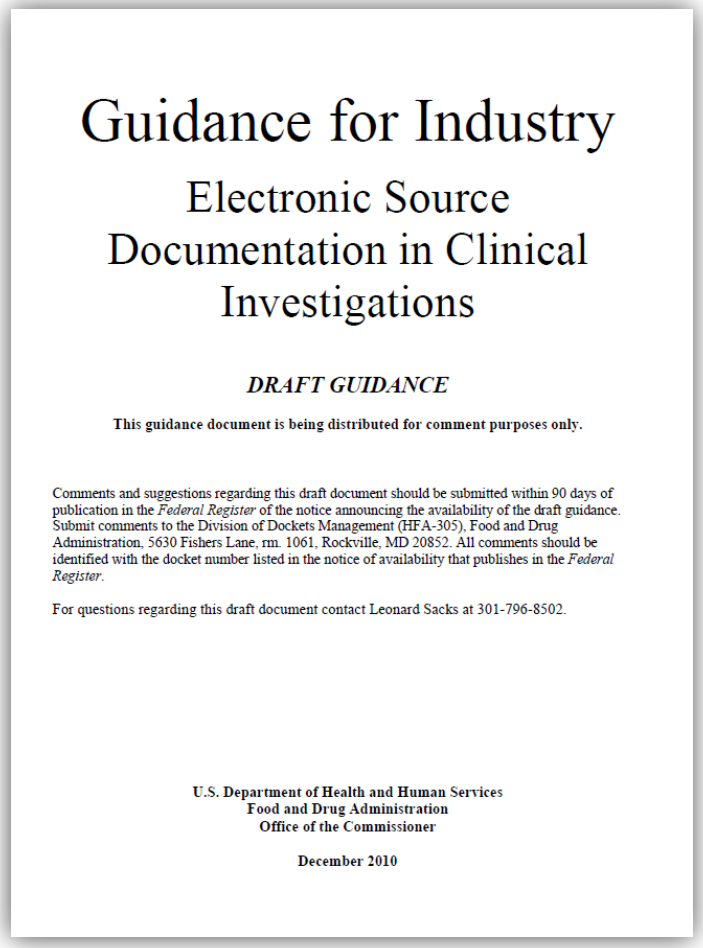
Part 11

- 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 a guidance we affectionately call the eSource guidance

- The guidance says that no paper records may be necessary if you have an acceptable electronic system



Guidance for Industry

Electronic Source Documentation in Clinical Investigations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Leonard Sacks at 301-796-8502.

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Office of the Commissioner

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- 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 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

- 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

- 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

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

Electronic informed consent

- The first opportunity that interests us is 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?

The opportunities for electronic informed consent are obvious

- 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 would have to make sure that we know the study subject is the one who signs the document

Electronic health records

- 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
- So why are EHRs not part of the clinical research infrastructure?

Progress in 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 in many overseas sites
- Quality criteria will need to be developed by sponsors using those systems to ensure data integrity, attributability and reliability
- EHRs records used in clinical trials need to accessible for FDA inspections
- We anticipate a lot of active discussion to pave the way for use of EHRs all over the world.

Mobile devices

- An exciting prospect for clinical trials is the use of mobile devices
- Potentially revolutionize the way trials are conducted
- It surprised me to discover how little they are used in drug development
- A meeting on Duchene's revolved around the 6 minute walk test. We could potentially get a much more reliable idea of patients' performance from mobile sensors

Think of the opportunities

Comes with Black / Blue band & clip

Mobile devices offer many potential advantages

- Patients can be monitored from the comfort of their homes
- Reliable objective measurements can be made
- Measurements can be made at any time of the day- not just during an office visit
- Video communications may be used in research just as they are for telemedicine
- 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

The big picture: more work to be done

- Part 11 regs are old. They were written before we had google.
- Things have changed
- Many electronic systems are used by sponsors that belong to other parties
- Some electronic services are contracted out.
- Sponsors typically use electronic service vendors to process, store and analyze data e.g. toolkits, cloud services
- Some electronic systems are so broadly adopted, e.g. word processing, electronic imaging, making copies that we've almost forgotten how to use paper

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