U.S. FOOD & DRUG ADMINISTRATION

Decentralized Trials: Policy Considerations

Leonard Sacks, M.D.
Associate Director
Office of Medical Policy
CDER FDA

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DCTs- What's New?

- Decentralized trial practices have been used for years
- Outpatient-trials rely on patient reports and local providers to deal with adverse events
- Interactive Voice Response Systems, telephone follow up, patient diaries are often used to capture off-site data
- What's new is:
  - New technologies for communication, data capture and transmission
  - Recognition of the value of patient-centric approaches using local health providers to perform trial-related functions

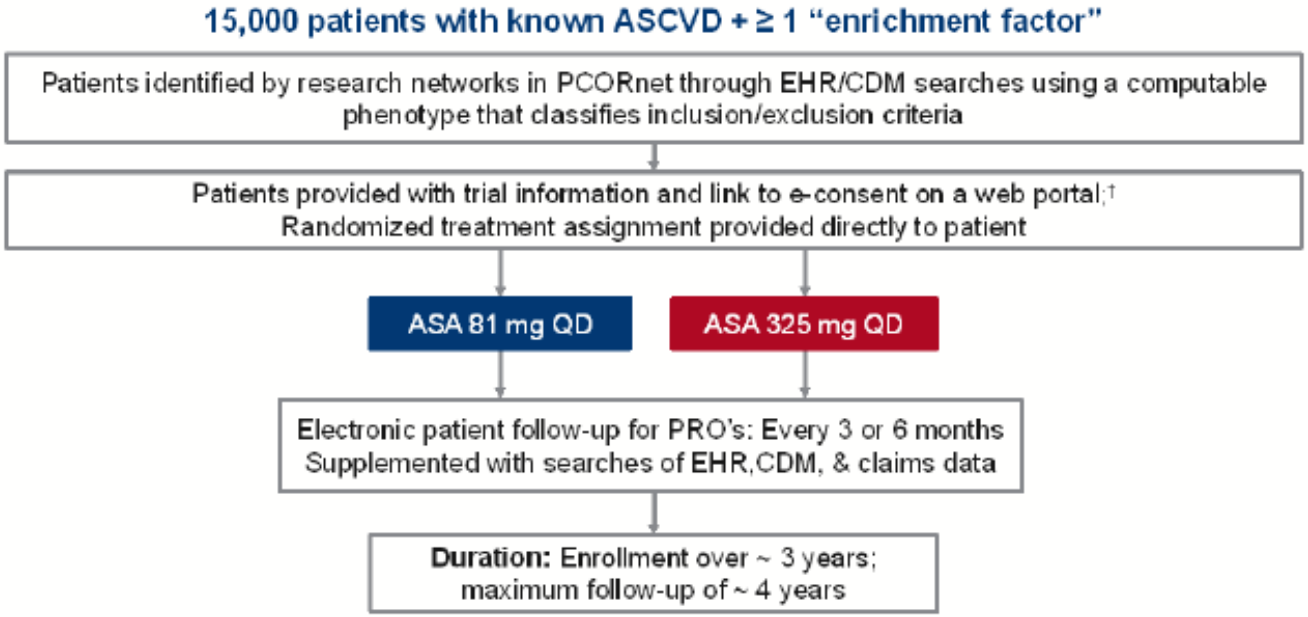
The Lancet · Saturday 22 February 1986

EFFECTIVENESS OF INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION

GRUPPO ITALIANO PER LO STUDIO DELLA STREPTOCHINASI NELL'INFARTO MIOCARDICO (GISSI)*

- **11,806 patients with acute MI**
- **176 Coronary care units**
- **Randomized by telephone call**
- **1.5 mu streptokinase or standard of care**
- **18% decrease in 21 day mortality in streptokinase group**

ADAPTABLE Study Design



† *Participants without internet access will be consented and followed via a parallel system.*

Adaptable

ClinicalTrials.gov: NCT02697916

Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial

Miguel Orri [a,*,1], Craig H. Lipset [b], Bradly P. Jacobs [c,d], Anthony J. Costello [c], Steven R. Cummings [c,d,e]

[a] *Pfizer Ltd, Tadworth, United Kingdom*
[b] *Pfizer Inc, New York, NY, USA*
[c] *University of California-San Francisco, San Francisco, CA, USA*
[d] *Mytrus, San Francisco, CA, USA*
[e] *California Pacific Medical Center Research Institute, San Francisco, CA, USA*

- **First entirely web-based trial under IND**
- **5157 patient registered, 456 signed consent, 188 in placebo run in, 18 randomized to treatment**
- **Electronic informed consent**
- **Randomized to tolterodine 4mg daily x 12 weeks vs placebo**
- **Electronic diaries**
- **Decreased micturition/24 hours: tolterodine - 2.4 placebo - 0.8**
- **Treatment difference (95% CI): − 1.6 (− 3.9, 0.6).**

Contemporary Clinical Trials. Volume 38, Issue 2, July 2014, Pages 190-197

Applying Regulations to a New Paradigm

- Considerations are not unique to decentralized trials- we need to apply our regulations to a new environment
- Considerations seem to vary with
  - Disease area
  - Investigational drug
  - The types of functions that are decentralized

DCT Policy Considerations

- The personnel
- The site
- The tools
- Patient safety

The Personnel

The Clinical Investigator

- ***Investigator*** **means an individual who actually conducts a clinical investigation (*i.e.* , under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.**
- **Sub-investigator includes any other individual member of that team.**

21 CFR 312.3

The Personnel

- Investigator (or CRO if obligations are transferred)
- Sub-investigators
- Local health providers (local clinics, local physicians, nurses, physical therapists, phlebotomists…)
- Ancillary medical services (radiology, laboratories)
- Support services (IT, transport, administrative)

The Different Personnel Roles

- **Investigator/Sub-investigator traditional role:**
  - **Direct and substantial involvement**
  - **Need to understand the protocol, investigator's brochure, investigational product, and the informed consent to perform trial related duties**
  - **Listed on Form FDA-1572 and assumes investigator responsibilities**
- **Local providers' role:**
  - **No difference between tasks they perform in clinical care or clinical research**
  - **Knowledge of protocol and drug unnecessary (e.g. phlebotomy, reading a radiological or pathology report, performing ECG)**

Investigator Responsibilities (Form FDA-1572)

- Follow the protocol
- Personally conduct or supervise the study (delegation is permitted)
- Informed consent and institutional review board (IRB)
- Report adverse experiences
- Understand potential risks and side effects of the drug
- Ensure that all associates assisting in the conduct of the study are informed about their obligations
- Adequate and accurate record keeping and retention
- Reports to the IRB

The Site

- Traditionally a physical site, but this is not defined in regulation
- Site is usually where the intervention is provided and assessments for the trial are carried out
- Are there limits to decentralization of these activities under a single investigator's supervision?
- How will decentralized sites be supervised, monitored and inspected?

The Tools

- Communication systems, video or audio
- Remote data capture
- Biosensors
  - Which part 11 requirements apply?

The Tools

- Attribution – ensuring data comes from the right patient
- Accuracy and precision of biosensor measurements
- Data security - secure transmission
- Data integrity, audit trails - date, time and source of data

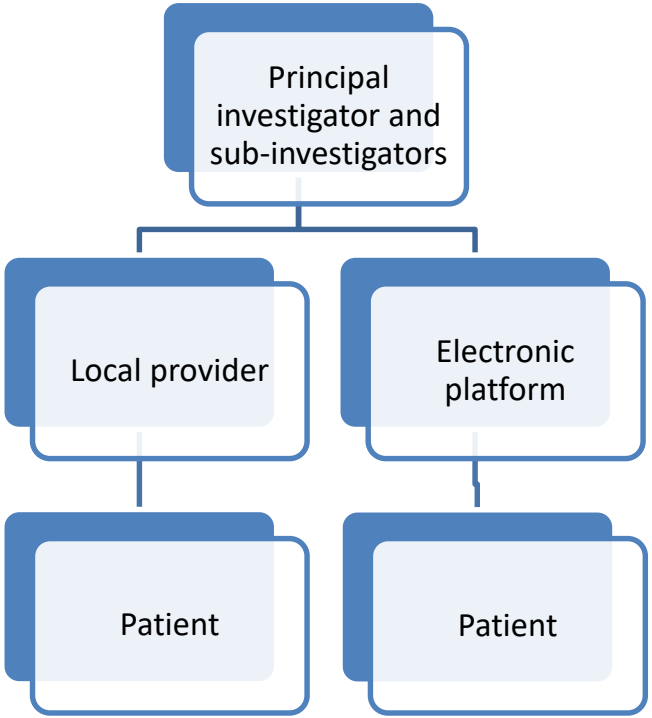
Patient Safety

- **Not that different from traditional outpatient trials**
  - **Ensuring access to qualified professionals to address adverse events**
  - **Ensuring prompt capture of safety data from patients and healthcare providers**

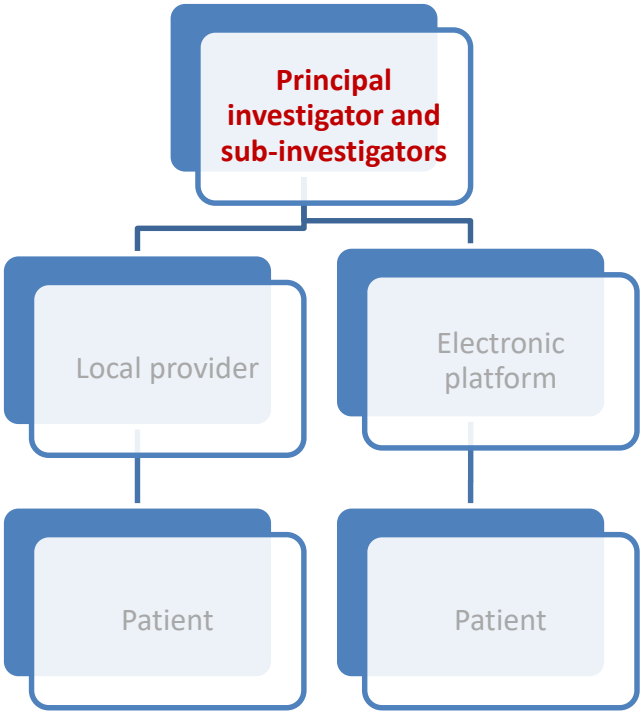
Patient Safety

- Opportunities for greater oversight of safety by using technology to replace episodic monitoring with continuous monitoring (e.g. glucose, heart rate/rhythm)
- Concerns to be addressed
  - Technology failure
  - Need for specialized care due to nature of intervention/disease
  - Inability to contact study staff for AE if distances are large
  - Physical risks of biosensors (e.g., occluding blood supply)
  - Risks of erroneous data (e.g., low glucose reading)

Decentralized Clinical Trial

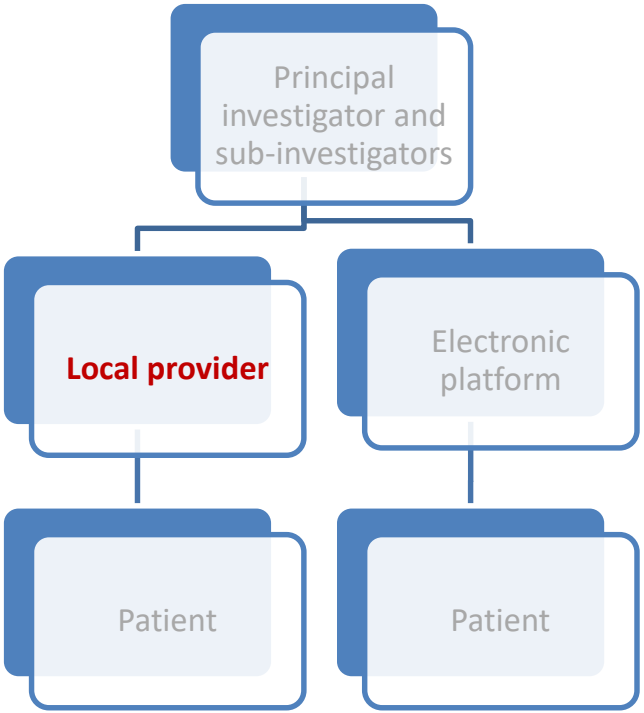


Investigators and Sub-investigators



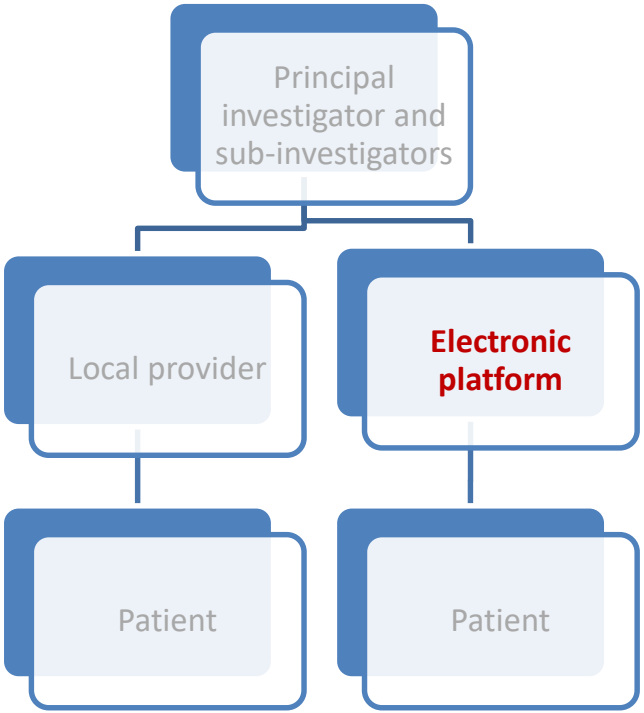
- Substantial role
- Qualified by experience and training
- Requires knowledge of study to perform his functions
  - Protocol
  - Investigational drug
  - Investigator's brochure
  - Rules for withdrawal
  - Safety concerns
  - Informed consent

Local Provider



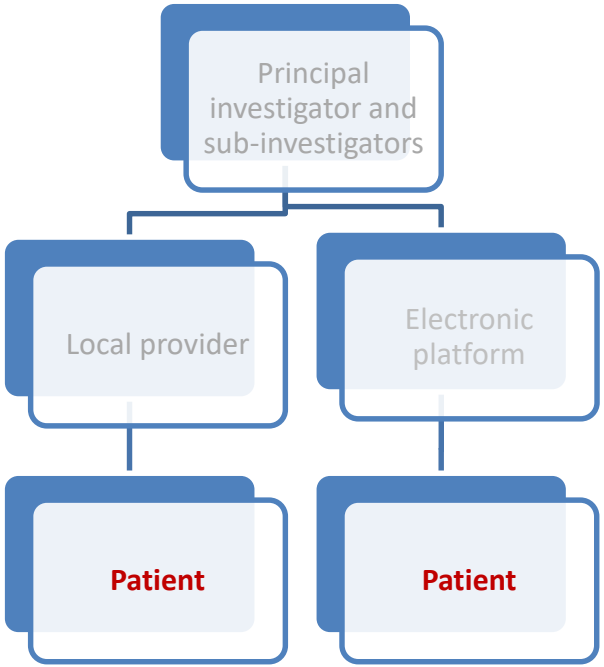
- **Experience and training to perform clinical function**
- **May not require knowledge of study – examples:**
  - **Phlebotomist**
  - **Pathologist**
  - **Endoscopist**
  - **Radiologist**

Electronic Platform



- **Communication – examples:**
  - **Phone**
  - **Videoconference**
  - **Chat**
- **Data capture – examples:**
  - **Biosensor**
  - **PRO tool**
  - **Diary**
- **Security and data integrity (CFR, Part 11)**

Patient



- Informed consent
- Usable technology
- Tech support
- Adequate communication tools with investigator

Conclusions

- New opportunities exist to use mobile technologies and local providers to bring the trial to the patient
- Promises inclusivity, convenience and real-world experience
- Need to address patient safety, privacy, data integrity and responsibilities of the investigator