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
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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

15,000 patients with known ASCVD + ≥ 1 “enrichment factor”

Patients identified by research networks in PCORnet through EHR/CDM searches using a computable phenotype that classifies inclusion/exclusion criteria

Patients provided with trial information and link to e-consent on a web portal;† Randomized treatment assignment provided directly to patient

ASA 81 mg QD  ASA 325 mg QD

Electronic patient follow-up for PRO’s: Every 3 or 6 months Supplemented with searches of EHR, CDM, & claims data

Duration: Enrollment over ~ 3 years; maximum follow-up of ~ 4 years

Primary endpoint: Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke

Primary safety endpoint: Hospitalization for major bleeding

† Participants without internet access will be consented and followed via a parallel system.
Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial

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• 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).
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.
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

- Principal investigator and sub-investigators
  - Local provider
  - Electronic platform
    - Patient
    - Patient
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)
• 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