Lessons learned on the road to being a Sponsor-Investigator

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Sponsor and PI: COAST, COAST II and PARCS

Introduction

- Pediatric interventional cardiologist
  - No formal research training
  - No epidemiology or statistics training
  - Minimal prior clinical research experience

A candidate to organize and run an IDE trial?

Hutzpah?

At first ignorance was bliss, and then came the rude awakening

Let's get together, it will be alright:

Bob Marley, "One Love" 1977

Working with the FDA

- FDA ≠ FDA
  - FDA/CDRH/ODE/DCD/ICDB
    - Directors, engineers, physician consultants
  - FDA/CDRH/OOC/DBM (BiMo)
    - District offices, inspections, Form 483 observations, warning letters, etc.

Working with the FDA

- FDA rules for clinical trial
  - Device Regulation and Guidance document
    - Title 21 CFR, Parts 1-1499
    - Part 812 – Investigational Device Exemption (IDE)
      - Subparts A-G, Sections 1-150
    - Part 50 – Protection of Human Subjects
      - Subparts A-D,
- OHSR (Office of Human Subject Research) rules
  - Public Welfare
    - Title 45 CFR, Parts 1- 199
    - Part 46 - Protection of Human Subjects
      - Subparts A- D

Start –up Challenges I

- Preclinical/bench testing requirements
  - Extensive and expensive
    - Metallurgy, tissue interactions, corrosion testing, package sterility, device durability, device deliverability, etc.
  - Guidance for Industry and FDA Staff
    - Non Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, 1/13/2005

Start –up Challenges II

- Development of a protocol capable of demonstrating safety and effectiveness in a reasonable time frame
  - Control group?
    - Even though more powerful, is it ethical or practically possible?
  - Performance objectives?
    - Are there adequate comparisons in the literature?

Hell is full of good intentions or desires

Saint Bernard of Clairvaux (1091-1153)

- Physicians are genuinely eager to volunteer for trial participation
  - Enthusiasm vs reality
    - Eager to join, but later are less eager to perform the less glamorous aspects of trial work
  - Desire to be included vs cost of being included
    - MDs may offer to work for little, but institutional budget offices are not so accommodating

Hell is full of good intentions or desires

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- Physicians are genuinely eager to volunteer for enrollment, core lab or DSMB duties, but…
  - Reality: IRB submissions, research nurses, data entry and university overhead are expensive
    - Contract and research administrators are not as generous
  - Investigator fatigue can set in:
    - Novelty wears off, trial drags on, new products emerge
  - Recruitment, data delivery, core lab review and DSMB duties can be time consuming and in reality financial rewards help

Show me the money! *C. Crowe "Jerry MacGuire" 1996*

- Industry estimate: pivotal trials for ~100 subjects costs approximately $3-10,000,000 for recruitment and **five** years of follow up, eg. ~ $600,000/yr

Money makes the world go round

J. Kander, F. Ebb, "Caberet",1972

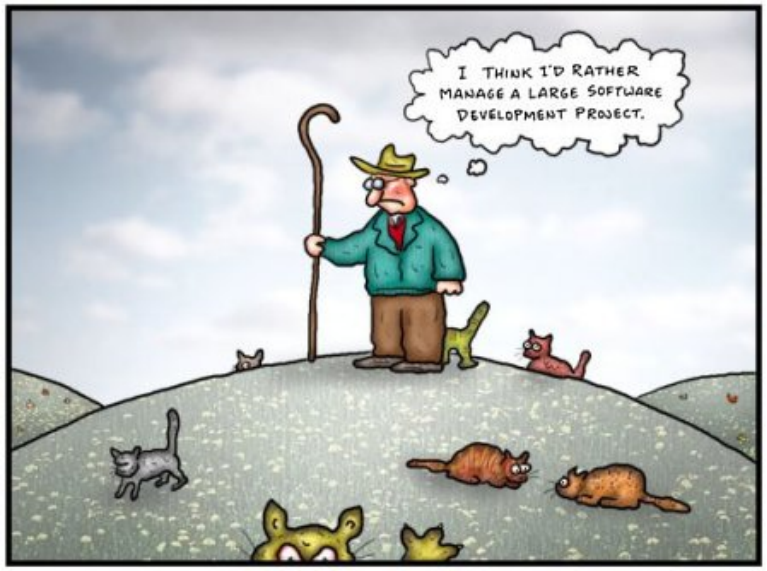
- Clinical trials are expensive, Costs Include:
  - Organizing center: trial PI and research coordinator salaries,
  - Data management: statistician, data coordinator and database management salaries
  - Data collection: Per patient payments
  - Participating centers: Start up expenses, IRB payments, PI and research nurse salary support, and indirect (overhead)
  - Regulatory: DSMB, core labs
  - Miscellaneous: Training and meeting expenses

Money, that's what I want…*Berry Gordy, 1963*

- Clinical Site Expenses
  - Research coordinators or nurses
  - IRB fees
    - new submission, protocol changes, annual continuing reviews
  - Clinic visits, data entry, lab testing
  - Interpreters and translation of consent forms

Learning to herd cats

- Pediatric cardiologists are individualists and very dedicated to their patients
  - Protocol deviations!!!
  - Unauthorized use of devices
- IRBs, ORAs and finance offices are not all alike
  - IRBs, like corporations are people!
  - individualistic, often inflexible
  - Should have uniform mission and guidelines, but interpretations can be quite different



The daydreams of cat herders

Herding Cats

- Complex, detailed protocols are difficult to enforce and lead to many, many protocol deviations
  - looks bad and endangers trial outcome
- Very difficult to keep data flowing
  - Limited response to financial inducement, sense of duty, exposure, begging, etc. need to use all of these
  - Core labs can be slow
    - Discrepancies between Core lab and clinical site challenging to resolve
- Forget academia
  - Protocols should be functional, practical only
- K.I.S.S.!!!

My Conclusions

- Being a Sponsor-Investigator of a multicenter clinical trial is challenging
- Collaboration within the pediatric cardiology world is essential
- There is need for even more collaboration and instruction from our FDA colleagues
- A new mechanism for funding pediatric device trials is needed

My next job…