

A photograph of several red, oval-shaped capsules scattered on a white surface. Some are in sharp focus in the foreground, while others are blurred in the background, suggesting a shallow depth of field.

# CTTI Workshop Quality by Design

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# Quality by Design

Clinical trials have changed and are changing more:

- They are often larger

What you can do in 200 patient phase 3 trials becomes impossible in a 10,000 patient outcome study (CV, DM, pulmonary, adjuvant Ca).

- They are multi-national, dependent ON similar behaviors and practices. Readers and regulators will examine consistency.
- They are often designed and managed by outside contractors, not a new thing, but it raises issues of who does what.

# Different Models

It's not new that trials are managed very differently. At FDA, we have been noting this for years, and CTTI has collected detailed information.

- **Industry model for usual trials:**
  - visit all sites every few weeks, look for all conceivable errors
- **NIH model; VA, government generally, ISIS:**
  - Mostly central monitoring, visits to sites with problems. The “relatively large, relatively simple” model.

Until recently, government-run trials were a source of all the outcome data we valued. ICH E-6 was very conscious of that and built in considerable flexibility for monitoring. Now, many outcome studies are by commercial sponsors. What should they be expected to do?

## Different Models (cont)

- NCI Model
  - Not really monitoring but site validation
- Industry models for large outcome trials
  - More monitoring than NIH but in a 10K person trial, you don't visit all sites q 4 weeks.
- So what is needed?

# Needs

We need more trials, probably more large trials. They are both simpler (solid outcomes, fewer exclusions) and harder (interest in many subsets, enrichment) and, as we know from recent experiences, even what seems like objective endpoints are not always so simple:

- Use of central blinded adjudication (did all cases get referred? review quality, certainty of blinding)
- Definition of endpoints

NB: Some problems cause noise and decreased power, but in an NI study they can create “success”. Also, when you go back and look at safety outcomes. More data (not just study endpoint) become important.

## Needs (cont.)

We need credible trials

Discovery of problems (by FDA or commentators) can lead to monitoring excess, discouragement, loss of ability to learn what we need. Industry, in particular, does not like to risk a major development program because FDA discovers discrepancies, inconsistencies, so they may monitor everything.

## Needs (cont.)

We need credible, large trials that we can afford to carry out.

General view is that current methods focus on the wrong things, i.e., are not designed to detect the most important problems. And we know that industry monitoring and FDA audits missed major fabricators (Borison and Diamond, others).

Where is help? Well, that's what this meeting is about. But we have had these meetings before, so we need to focus on changes that can be made.

# Possibilities

## Build quality in:

Hard to argue, but we need to see what that means.

Some considerations:

- Focus on what matters – identify critical risks at the time of protocol development
  - numerators (endpoints, SAE's) are more critical than denominators/covariates.
- 2. Incorporate electronic approaches
- 3. More comparisons of central vs. onsite methods (perhaps with errors introduced to test approaches).
- 4. Simplify data collection and study design where feasible

# Hopes

- We anticipate a knowledgeable and thoughtful discussion. All parties are necessary and critical. If we say some things matter more than others, everyone has to behave as if that's the case, including FDA, or change will not occur. And, we all retain our interest in valid outcomes or we all lose.

Finally, as I've long believed, we need to appreciate, understand, and come to grips with the very different approaches already in use by government and industry.

- It's all very important, and it is not easy (or it would have been done already)