Streamlining Regulatory Issues – Achievements and Challenges
USA Regulatory Perspective

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Sensible Guidelines for the Conduct of Clinical Trials
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Major Issues with Regulatory Implications

As talks up to now and to follow make clear, it is fairly straightforward to identify factors that make trials more difficult. The problem is that some of those factors, at least on face, seem related to study quality/integrity/adequacy

1. Study monitoring
2. Data collection – extent, completeness, accuracy
3. IRB review and approval; consent
4. ADR reporting
5. Recruitment

Study Monitoring

Study monitoring, especially on-site monitoring, is a huge cost component of clinical trials. ICH E-6 describes considerable flexibility, all the way to no on-site monitoring at all, but the reality is that this is very rare for industry-sponsored trials.

In August 2011 we made available a draft guidance – Oversight of Clinical Investigators – A Risk-Based Approach to Monitoring. The guidance does not explicitly call for uniformly less onsite monitoring but it

- Urges focus on the important data ("critical study parameters") and use of a variety of monitoring activities to assure patient protection and data integrity.

Study Monitoring

- Describes the wide variety of practices in use, long known and confirmed by CTTI survey, ranging from
  - Industry practice – every 4-8 weeks, all sites
  - academic coordinating centers, government organizations in US and abroad – far less, sometimes none, until central monitoring suggests a problem
  - NCI Cooperative groups use site qualification, not really on-site trial monitoring

FDA accepts all of these approaches

Study Monitoring (cont)

- Notes WD of 1988 monitoring guidance that strongly endorsed uniform frequent on-site monitoring

  ICH E-6 is "flexible" but suggests that reduced monitoring is very much the exception.

  1998 Clinical Evidence Guidance is explicit in noting that many credible, valuable studies had little on-site monitoring but assured quality by training, control review of submissions, etc.

- Notes new ways to conduct source data verification centrally.

  "Risk-based monitoring, including the appropriate use of centralized monitoring and technological advances (e.g., e-mail, web casts, and online training modules), can meet statutory and regulatory requirements under appropriate circumstances."

Study Monitoring (cont)

A few critical points

1. Need for inhouse training on all this (If inspectors and reviewers consider all errors equal, nothing will change)
2. Will consider process for reviewing monitoring plans prospectively
3. We expect that, for the foreseeable future, industry will continue at least some on-site monitoring, but we encourage greater use of central
4. Recognize what is most critical to a study
   - Primary and secondary endpoints
   - Serious AE's and events leading to DC
   - Blinding, referring events for adjudication

   and what is less

   - Baseline characteristics (age, concomitant treatments, concomitant illness)

   Numerator vs denominator/covariates (real, but small error rate not critical). Note that even unbiased error rates on important endpoints will not lead to a false positive effectiveness finding.

Study Monitoring (cont)

The guidance is a step, not yet revolution but we hope it will set thoughts in motion and create comfort with new approaches.

Data Collection

Not as critical as risk-based monitoring, but reducing collection of unhelpful safety data makes everything easier.

In February 2012, FDA published a guidance: "Determining the Extent of Safety Data Collection Needed in Late Stage Pre-market and Post-approval Clinical Investigations."

The general premise is that late in pre-market development and in post-marketing studies, when the safety profile is well-established, certain types of safety data become superfluous, waste resources, and may even discourage investigator participation and interfere with the "large simple trials" we need to gain outcome data, assess long-term effects of drugs and compare drugs.

Data Collection (cont)

Simplification is not new – Cardiovascular outcome trials have, with our agreements not collected data on

- Non-serious AEs that did not lead to DC, change in dose
- Concomitant Rx not related to drug or disease being studied
- Lab measurements known not to be affected; could also use less frequent collection

Late in phase 3 similar reductions may be appropriate and more complete data could be collected, if necessary, in a sample of products or sites.

Data Collection (cont)

Less data collection would be considered when

- Safety profile is well-characterized
- AE's generally similar across studies
- Population to be studied would be expected to be similar and similar doses used

This would be likely for

- Studies of new indications in same dose range
- Post-marketing studies focused on a particular safety concern (e.g., the diabetes CV studies)
- Large outcome trials (if pre-market, could collect more data in a sample)
- Late phase 3 studies

<u>Would</u> collect data on SAE's, AE's leading to DC or dose modification, other potentially serious AEs (suicidal ideation or suicide attempts)

Actually want <u>more</u> attention to reasons for study withdrawal

IRB Approval and Informed Consent

Not FDA's problem, but we hear that IRB approval can take many months. Remedies to consider include

- Central IRB's – we explicitly allow, but not widely used. Growing use in Europe
- Standard protocols for commonly studied conditions. Any changes could be easily identified
- A longer subject, but all agree that I.C. should be shorter. There are explorations of on-line I.C. (with questions to be answered)

ADR Reporting

Patrick told you, FDA's proposal simultaneously will reduce the number of useless submissions to FDA, investigators and IRBs, BUT will require an internal process for reviewing unexpected SAE's and determining when they reach the threshold for "suspected."

Recruitment

Plainly, the dream is that patients in HMOs and HMOs themselves, and other health systems will recognize the need for outcome data and comparative data that can only be reliably obtained from randomized trials and encourage patients to participate in them. The VA is, of course, a long-standing model for this. [All the people in this room who attend CER meetings really must remind people that differences between treatment cannot be reliably assessed through epidemiologic methods.]

It seems likely that available databases would allow potential subjects for trials to be invited to consider participation.

Bottom Line

A more efficient, more focused, more rapid clinical trial enterprise will enhance all aspects of health. Drugs, after all, are only one intervention. We also pay fortunes for physical therapy, behavior modifications, dietary maneuvers, dietary supplements, and a wide range of other interventions that have been poorly, if at all, evaluated. All of these could be better studied.