Issues in Operational Efficiency of HAP/VAP Clinical Trials: Current and Future State

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Clinical Trial Evolution: High-Level Drivers of Effort and Cost

1. Investigator Fees

2. Clinical Trial Size and Alternatives

3. Start Up, Monitoring and Data Management

4. Drug Costs (Branded comparators and availability of generics)
Variation on a Theme

Actual vs. Targets: Protocol Level Center/Country Rollup

- Target Screen Protocol
- Target Screen Country Rollup
- Target Screen Center Rollup
- Actual Screen
- Target Rand Protocol
- Target Rand Country Rollup
- Target Rand Center Rollup
- Actual Rand
Objective: streamlined clinical trial MRSA only

1225 Patients enrolled over 5.5 yrs; protocol amendments; DMC changes

448 culture-positive for MRSA (mITT)

348 evaluable at End-of-Study (PP)
- 339 in primary analysis

280 (63%) ventilated at baseline (mITT)

156 Centers
- 90 US (58%)
- 28 EU (18%)
- 16 Latin America (10%)
- 13 Asia (8%)
- 9 Other (6%)
**EMR Data Mining**

Query existing data repositories against patient eligibility criteria captured currently to determine potential population.

**Patient Survey**

Via their physicians, survey patients highlighted during data mining in order to capture data not residing in EMRs (e.g., family history, symptoms).

**Physician Survey**

Survey physicians of the remaining patients to capture any remaining data not able to be provided by patients (e.g., clinically complex questions).

**Patient Education and Consent**

Inform target patients, providing education materials, gauge interest, and obtain consent to be identified and contacted for screening.

**Analysis, Strategy, Reporting**

Synthesize data and report on the number of eligible and interested patients at each site. Analysis may also be integrated with performance data to provide informed recommendations for site selection.

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# Transcelerate Near Term Goals to increase quality, patient safety and accelerate development timelines

**Prioritized Near Term Opportunities**

After an extensive evaluation process, investment has been made to advance five collaboration projects.

1. **Standardized Approach for High-Quality, Risk-Based Monitoring**
   - **Objective:** Develop a standard framework for targeted, risk based clinical trial monitoring
   - **Benefits:** Improvement in data quality and patient safety for clinical trials; reduction in effort expended on low-value activities

2. **Shared Site Qualification and Training**
   - **Objective:** Mutual recognition of GCP training and site qualification between pharmaceutical companies
   - **Benefits:** Improved quality of clinical sites and accelerated study start-up times

3. **Common Investigator Site Portal**
   - **Objective:** Establish a single, intuitive interface for investigators used across the industry
   - **Benefits:** Ease of use and harmonized delivery of content and services for investigators

4. **Clinical Data Standards – Efficacy (in partnership with CDISC)**
   - **Objective:** Accelerate current efforts underway through CDISC to establish efficacy data standards
   - **Benefits:** Increased quality of clinical data and enablement of industry end-to-end data flow

5. **Comparator Drugs for Clinical Trials (marketed drugs only)**
   - **Objective:** Establish a supply model to source comparator drugs between companies for use in trials
   - **Benefits:** Enhanced patient safety due to known product source and acceleration of study timelines
Study monitor workload high & varied with wide disparity by global region

Assessment sets global benchmark for CRA workload and utilization

- Clinical research associates (CRAs) worldwide devote 41% of their time at clinical trial sites, with those based in Europe spending 30% fewer hours on-site than CRAs in North America.

- Sponsor CRAs spend more time than their counterparts at contract research organizations (CROs) conducting on-site monitoring visits, monitoring trials off-site, and handling administrative tasks.

- Half (53%) of CRAs overall rate their work life as good or excellent, those based in Latin America gave the lowest ratings.

- For Phase I studies, CRAs on average conduct 3.8 investigative site visits each month.

- For Phase II-III studies, CRAs on average conduct 7.9 investigative site visits each month.

- CRAs overall have an average of 6.3 years on the job and expect to remain in their position for another 3 years, with both metrics varying widely by region.
Enhanced Monitoring to Improve Data Quality

- **Action**
  - Targeted Oversight
  - Determine & document scope of sites to visit, when
  - Determine approach - findings driven
  - Align resources
  - Action resulting from visits
    - Change protocol – proactive
    - Change in reporting via data exclusion – reactive
    - Change in investigator status - preventative

- **Decisions**
  - Collaborate to develop plan
    - COL & Clinicians
    - Communicate
    - Team, AP, Investigators
  - Risk Triggers
    - Site
    - Volume, first X % of subjects
    - Issue
    - Validated to Support Decisions

- **Analyze Data**
Risk Based Monitoring: Top enrolling sites analyzed for outliers

Site quality risk assessment analysis

Two sets of sites at extremes selected for follow-up
- **High Error Rate**: Sites with high # error types and total errors per randomized patient
- **Low error**: Sites with low # of error types and total errors per randomized patient

- Primary Endpoint
- SAE’s
- Key secondary endpoints
- Drug accountability
- Patient dosing errors
- Other study specific protocol deviations
Growing protocol design complexity stresses investigators, volunteers

Protocol design changes challenge study conduct cycle time and performance

- The annual growth rate of unique procedures per protocol grew 6.5% between 1999 and 2005. During that same period, the total number of times unique procedures were conducted per protocol grew at a faster rate.

- To participate in clinical studies today, volunteers on average must meet a total of 49 eligibility criteria, up 58% since 2002.

- The burden to administer clinical study protocols is rising faster than the rate of growth of unique procedures or their frequency.

- Clinical trials are taking longer: between 1999-02 and 2003-06, total time from protocol design readiness to data lock rose from 460 to 780 days, or 69.6%.

- Protocol design also impacts the ability of sites to recruit and retain volunteers: enrollment rates dropped from 75% in 1999-02 to 59% in 2003-06, while retention rates declined from 69% to 48%.
### Some Factors Driving Operational Costs: Opportunities for Efficiency?

#### Milestones
- First day CRO involvement
- Treatment period for each subject

#### Sites and subjects
- % screen failure rate
- % discontinuation
- Monitoring frequency pre-and post LSFV
- Total # SAEs
- # Sites
- % Sites in each region

#### Data and reporting
- # Total CRF pages per completed patient
- # Unique tables, figures, and listings
Protocol Quality Evaluations and Integrated Quality Management Plans

Integrating scientific integrity and parsimony for the benefit of investigators, patients and clear reporting of data

Complexity Drivers

- AE reporting is one of most burdensome tasks for investigators in Phase 3 clinical trials
- On-site monitoring
- Unnecessary eligibility criteria
- Use of multiple, redundant PRO instruments
- Unnecessary visit scheduling
- Excessive procedures: eg. labs, EKG’s
Additional Mitigating Measures

Reporting needs to drive data collection rather than collect everything in case of “what if questions”

- Streamlined prognostic factor/background data collection
  - Driven by science and relevance to the research hypothesis under study
- Minimal exclusion/inclusion criteria
  - restrict criteria to those absolutely essential for scientific objectives of trial, safety of patients, and to satisfy regulatory requirements.
- Effective use of technology: EDC tools, ePROs
- Use of legacy data to fill evidentiary gap

Use of large, simple trials, when appropriate

- A large sample size, limited collection of data, little or no local site monitoring, and broad eligibility criteria.
- Hard safety endpoints vs current state of “Big Data” retrospective claims data and outcomes

Regulatory guidance and commitment critical

- Agreement on minimum data requirement for review
- Progressive development of safety database
- Balance between confirmatory RCTs and large, simple trials

2012 Guidance on Collection of Safety Data in Late Stage
Red stars indicate origin in India, Pakistan, or Bangladesh; green stars indicate origin in the Balkans or Middle East (adapted from Nordmann, *EID* 2011). Recent reports describe additional cases in Turkey, Croatia, Spain, Czech Republic, Ireland, Belgium, and Algeria.
Staged approval
- Conditional approval with POC data, with limited use and promotion
- Requirement for additional data in a post-approval commitment depending on epidemiology could lead to enhanced label

Advantage
- Brings much needed medicine to patients in a timely manner
- Incentive to Discovery, Early Development
- Benefit-Risk Evolves

Alemayehu et al CID 2012
Post-approval Commitment: Secondary Sources of Data Depending on Resistance Prevalence

Patient Registries
- Collection of uniform data using observational study methods from a broad range of patients

Electronic Healthcare Databases
- Administrative claims data and
- EMR data

Challenges
- Confounding factors, measured and unmeasured
- Significant variation across observational studies with research methods and data quality
- Patient retention in registries over time periods
### Questions to Ask: Secondary Sources of Data

<table>
<thead>
<tr>
<th>Research hypothesis</th>
<th>What are the clinical and/or public health questions of interest?</th>
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<tbody>
<tr>
<td>Exposures and outcomes</td>
<td>How do the clinical questions of interest translate into measurable exposures and outcomes?</td>
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<tr>
<td>Data sources</td>
<td>Where can the necessary data be found?</td>
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<tr>
<td>Study design</td>
<td>What types of design can be used to answer the questions or fulfill the purpose?</td>
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<tr>
<td>Study population</td>
<td>What types of patients are needed for study? Is a comparison group needed? How should patients be selected for study?</td>
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<tr>
<td>Sampling</td>
<td>How should the study population be sampled, taking into account the target populations and study design?</td>
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<tr>
<td>Study size and duration</td>
<td>For how long should data be collected, and for how many patients?</td>
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<td>Internal and external validity</td>
<td>What are the potential biases?</td>
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<td>What are the concerns about generalizability of the results (external validity)?</td>
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Eroom’s Law:
New FDA Approvals / Billion $: halved every 9 years

Anti-bacterial discovery failures

Confirm Development Inefficient
GAIN Legislation Addresses a portion of the Failing Antibacterial Research “Ecosystem”

We are interlinked

Government

Pharma

Biotech

Academia
Simple Substantive Steps Now

- Increased Funding for basic bacterial laboratory work

- Infrastructure and network for clinical trial excellence particularly learn phase development at leading academic medical centers

- Enhance GAIN or other mechanisms (Foundations, NGO’s) for discovery and early development incentives

- Continue and commit to the progressive Regulatory stance we have heard at this meeting and comments in other fora eg PCAST

- Not relaxed standards but efficient development to bring much needed medicines to the clinic faster with robust pharmaco-vigilance and stewardship
  - Use of existing expedited Regulatory Pathways (Sub-part H and PV Guidance)

- Progressive value models eg LSE report from the Swedish Presidency