Streamlining HABP/VABP Trials Project

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- Work stream 1: Protocol Elements
- Work stream 2: Data collection
- Work stream 3: Networks
Workstream 1: Protocol Elements

Objectives
Identify barriers and seek solutions for the successful conduct of HABP/VABP studies

Deliverables:
Recommendations on alternate study design elements to overcome barriers in HABP/VABP studies
Protocol Elements: Activities

- **18 APR 2013**
  - Understanding issues in antibacterial drug development
  - Webinar in advance of Workshop

- **22-23 APR 2013**
  - Applying Quality by Design (QbD) principles to HABP/VABP protocols

- **29 AUG 2013**
  - Developing streamlined elements for HABP/VABP studies
  - Webinar

- **Current**
  - Recommendations and Publication
  - Finalized Q2
Issues and Barriers Identified

- Obtaining informed consent
- Inclusion criteria
  - Prior Antibacterial Therapy (PAT)
  - Concern that inclusion criteria may be too restrictive regarding underlying disease and co-morbidities
- Combining HABP and VABP patients
- Need for diagnostics and biomarkers
- Choice of active comparator
- Use of rescue/other non-study antimicrobial drug therapy
- Primary Endpoint Rationale for All-Cause Mortality vs Clinical Response
Public Discussion/Data Review led to Change

See revised FDA HABP/VABP Guidance May 2014:

- Single HABP/VABP trial with supportive evidence
- Allow 24 hrs PAT; sensitivity analysis
- Use of Gram stain as part of enrollment criteria and ITT as primary analysis population; sensitivity analysis in the microbiological ITT
- Approved active comparators not labeled for HABP/VABP
- Risk difference acceptable if control mortality rates are low; use of odds ratio from primary analysis is not required
Direction of Protocol Elements Recommendations

- Informed Consent
  - More training for staff obtaining informed consent
  - Approach patient/legally authorized representative (LAR) earlier, Research Advanced Directives (RAD)

- Use of Centralized IRB

- Expand Inclusion Criteria: include patients who may have been traditionally excluded from HABP/VABP trials

- Enrich: Rapid Diagnostics and Severity of Illness Score

- Primary efficacy endpoint using All Cause Mortality
  - Explore clinical response endpoint
Workstream 2: Data Collection

Objectives
Simplify and reduce the amount of (safety) data collected in HABP/VABP studies

Deliverables
Recommendations on critical data to be collected to simplify data collection
Data Collection

12 NOV 2013
• Optimizing operational efficiencies for data collection in HABP/VABP trials
• Challenges in data collection for HABP/VABP trials
• Regulatory requirements for AE data collection in registration trials
• Strategies to simplify data collection using a QbD approach

5 SEP 2014
• F2F team meeting
• Draft manuscript review

Current
• Recommendations and Publication
• Q2
Direction of Data Collection Recommendations

- Regulatory framework already exists to support streamlining
  - Report SAEs consistent with FDA/EMA regulations
  - Discuss proposed streamlined approach with regulators

- See CTTI Recommendations:
  - [http://www.ctti-clinicaltrials.org/briefing-room/official-recommendations#IND_Safety](http://www.ctti-clinicaltrials.org/briefing-room/official-recommendations#IND_Safety)

- Data collection should be pre-specified in protocol

- Consider less frequent/abbreviated data collection:
  - Vital signs, arterial blood gas, electrolytes
  - Non-serious AEs not associated with drug discontinuation
  - Concomitant medications
    - Sedatives/analgesics e.g. for patients on sedation drips with mechanical ventilation where doses are frequently titrated and changed....consider capturing this info as “days on/off”
Demonstration HABP/VABP Pilot study

- Streamlining data collection recommendations
- Protocol elements recommendations
- Add’l input from stakeholders
- Site Networks
Thank you.