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A Global Perspective from Ethics, Accreditation Bodies and Industry on Conduct of Clinical Trials

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Objective: Developing Quality Systems to Ensure Compliance

- Discuss the global requirements for conducting clinical trials from regulatory, industry and ethics perspectives
- Identify challenges in conducting global clinical trials
- Summarize the essential steps required to develop an effective quality program
- Describe best practice concepts used by industry and ethics committees
- Provide tools for implementing effective quality systems

Regulatory Considerations - Global requirements for accepting clinical data outside of U.S.Clinical trials

TOPIC	REQUIREMENT	REGs
FDA Perspective	**-**U.S. IND not required -Recognizes study if conducted per GCP requirements -FDA will conduct on-site inspections to validate data if needed -Applicable to the US population and US medical practice -Non-U.S. data can be relied upon as basis for approval	**21 CFR 314.106; 21 CFR 312.120**

Reference: FDA Perspective on International Clinical Trials: Murray M. Lumpkin, M.D., FDA Clinical Trials Workshop; Silver Spring, Maryland' 08 November 2011

Regulatory Considerations: Global requirements for accepting clinical data in Third Countries

TOPIC	REQUIREMENT	REFERENCE
EMA Perspective	■Data from trials run in 3rd countries can be included as part of the MAA, only if it meets the required ethical principles and acceptable levels of data quality. ■EMA must consider suitability of the trials being run in 3rd countries were to the European population and to their medical needs	'Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in Marketing Authorisation Applications to the EMA', May 2010.

Ethics and Industry – Global factors to consider for conducting clinical trials

Reference: Acceptability of Data by the U.S.; Russell Katz, M.D.,CDER: 27 May 2007

Ethics Committees Considerations	Industry Considerations
Evaluation of compensation payment: differences per region/country	Level of reimbursement for Sites and Researchers/staff
Compare affect of Individual ethics versus population ethics	Possible differences in blinding of data?
How is “standard of care” evaluated when there are no treatment therapies offered?	Regional consideration for data collection - is it large enough to show effectiveness and compare ethic differences?
Defining legitimate “consent” versus social contexts?	Effect on study data: Are all researchers in different regions following the same medical care standards re: hospitalization, surgeries, stopping treatment, retention/outcomes?
How does the Ethics Committee evaluate whether they have sufficient resources to review studies?	How source data is captured and reported? Special considerations for e-source data.

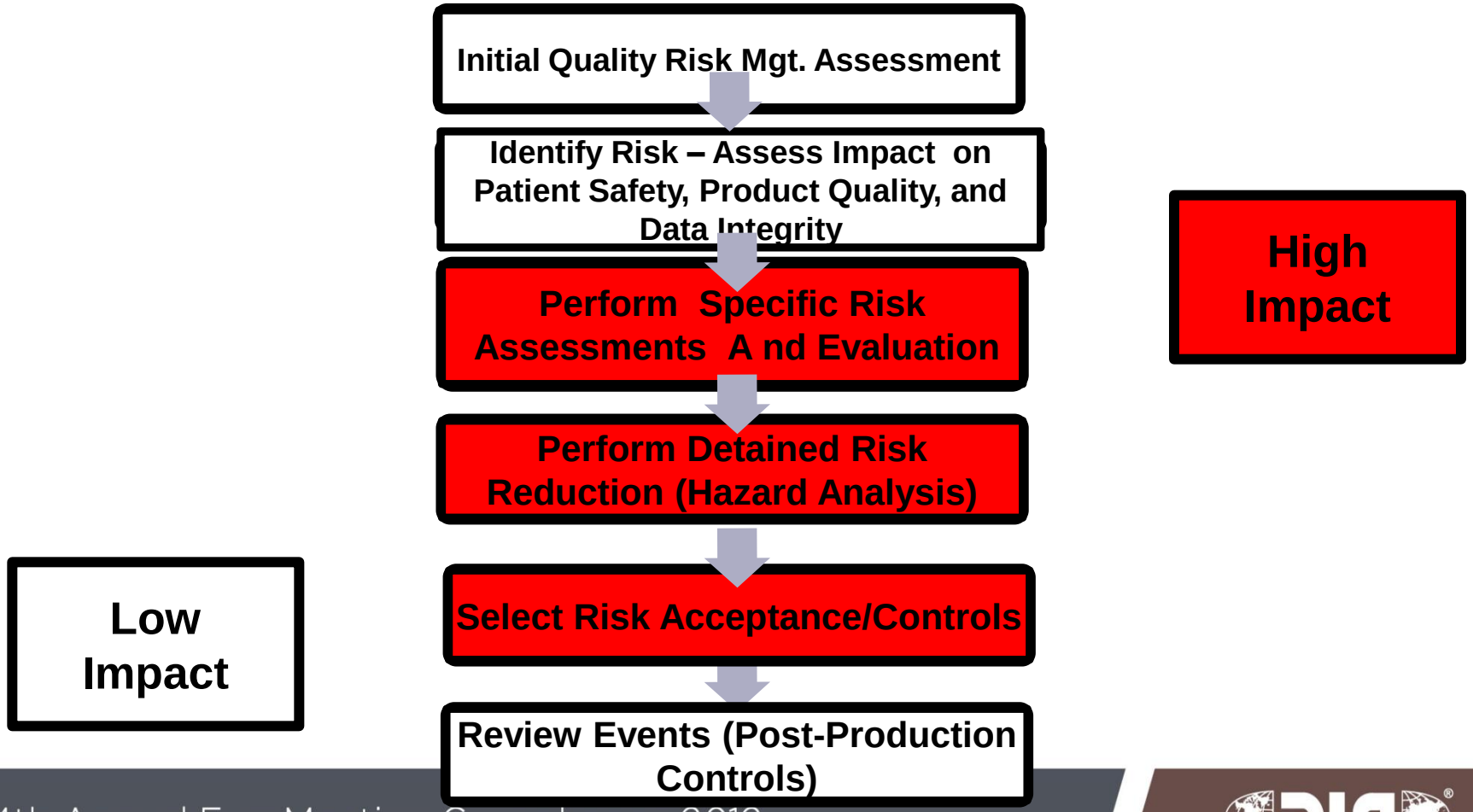
Challenges Sponsor face on Conducting Global Clinical Trials

1. CONSENTING ISSUES	• DIFFERENCES WITH MEDICAL INSTITUTIONS / PATIENT POPULATIONS
2. POOR HOSPITAL INFRASTRUCTURE	• COMMUNITY INFRASTRUCTURE MAY NOT BE SET UP TO SUPPORT CLINICAL TRIALS
3. LACK OF CLINICAL TRIAL EXPERIENCE	• RESEARCH NAIVE/UNTRAINED SITES; DOCTOR/PATIENT RELATIONSHIPS/CONFLICTS
4. Translational Differences	• ECRF CHALLENGES IN CONVERSIONS TO ALPHABET, DIFFERENT LITERAL TRANSLATIONS
5. NON-EXISTANT DATA PRIVACY	• NO AWARENESS OF DP LAWS IN COUNTRIES WHERE TRIALS ARE CONDUCTED
6. ELECTRONIC CHALLENGES	• COMPUTER CONNECTIVITY ISSUES/ECRF DATA ENTRY CHALLENGES
7. COUNTRY/CULTURAL DIFFERENCES	• LITERACY ISSUES, COMMUNITY PRESSURES, COMPENSATION ISSUES

Challenges Ethic Committee face on Conducting Global Clinical Trials

1. COMPOSITION	• MEMBERSHIP MAY NOT MEET INTERNATIONAL REQUIREMENTS
2. FUNCTION AND OPERATIONS	• OVERWHELMING LOCAL AND REGULATORY REQUIREMENTS
3. SELECTION OF SUBJECTS	• CONDUCTING APPROPRIATE REVIEWS WITH COMMUNITY LEADERS TO PROTECT VULNERABLE POPULATIONS
4. APPROPRIATE MEMBERSHIP	• MEMBERSHIP MAY NOT INCLUDE TECHNICAL EXPERTISE TO UNDERSTANDING COMPLEX PROTOCOLS
5. SCIENTIFIC BACKGROUND	• CHOOSING APPROPRIATE RESEARCH QUESTIONS AND DESIGN
6. COMPLIANCE CHALLENGES	• NO TIME/RESOURCES TO MONITOR PROGRESS OF STUDY
7. INABILITY TO INTERPRET SAFETY DATA/RESULTS	• INADEQUATE SYSTEM TO RECEIVE/UNDERSTAND INFORMATION FROM DSMB BOARDS

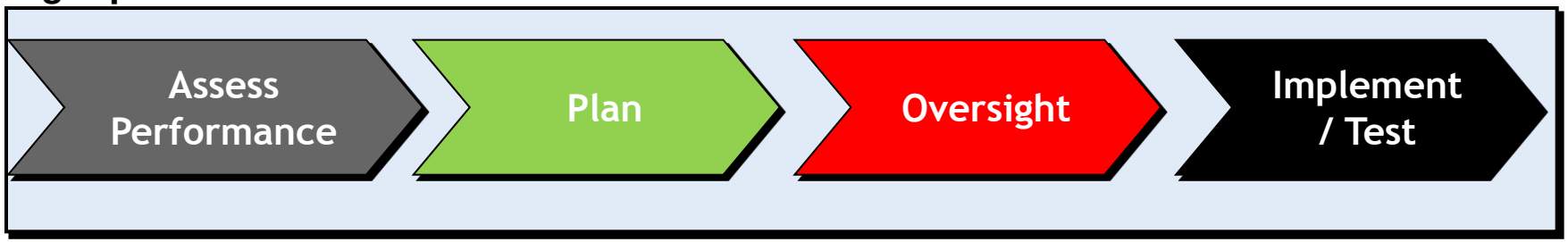
Implementing a Quality Risk Mgt. Process



Essential Steps for an Effective Quality Program

Quick Reference Guide

Auditing Tips:



Differences	Examples
Medical Community	•Research naïve sites •Inadequate facilities to conduct research •Populations may metabolize medications differently •Different Standards of Care
Local Communication	•Influences from doctor/patient relationships •Community involvement from local leaders may be required •Misinterpretation of medical care offered and perceived outcome/affect of trial
Language Barriers	•Cultural/Regional differences in dialect •Illiteracy Issues

Remember to Review
• Local Hospital Contract
• Review Delegation and Duties
• Tour facility/evaluate equipment used
• CTM or IMP cold chain distribution challenges in tracking/shipment temperature, delivery and chain of custody under controlled environment

Best Practices for Ethics Committees and Industry

- **Standardize international and national ethical framework and communities** to discuss differences in assessments of safety , risks and practices
- **Increased sharing of information between countries for multi-country trials** :
  - Use of a voluntary exchange system with scientific communities
  - Encourage discussions of data privacy issues, i.e., use of WHO and regulatory agencies interworking committees.
  - including Data Safety Monitoring Boards (DSMB) with ethics committees, health system officials and local community.
  - To develop a central ethics committee for multi-center trials. Currently system is very country-specific.
- **Strengthening Ethics committees** to ensure they have expertise to analyze scientific issues
- **Improve knowledge of EC** through WHO and other international agency training
- **Encourage dialog of Local or national governments with sponsors** to overcome clinical trial barriers, i.e., access to IMP after trial.

Checklists for Assessing Adequacy of Global Studies: Example: Trials using EMR/e-Source Data

Computer System Requirements	Key Evidence to Consider
□ Validated Systems to main audit trail and prevent overwriting of existing information	√Audit trail time/date stamp/author of changes or deletion √Limited system access to authorized individuals √Ability to generate accurate and complete copies of records in both human readable and electronic form
System Controls for ID/Passwords □Password or other access keys to be changed at established intervals □Automatic logoff or password protected screen saver after a set period of time of inactivity? □ Limits the number of log-in attempts and record unauthorized attempts	**Processes governing:** √ Assures no two individuals have the same combination of identification code and password √Prevents unauthorized use of passwords and/or identification codes √Detects and reports attempts at their unauthorized use
□Controlled system for creating, maintaining and applying roles, access permissions and capabilities of each user. □ Controlled Access to system features and functions per granted admin References: **Practical Considerations for Clinical Trial Sites using Electronic Health Records (EHRs) Certified for Clinical Research: Addressing Regulatory considerations** eClinical Forum 2011; Release 1.0; June 2011	**Procedure for Logical Security of Controlled System:** √Unique ID Password Creation, Distribution, and √Management linked to user's system assigned √users groups, roles and privileges. √System for Granting and Revoking Access

Checklist for Assessing Adequacy of Global Studies: Example: Trials using EMR/e-Source Data

Computer System Requirements	Key Evidence to Consider
□**System/ process controls to prevent viruses, worms, or other harmful software code**	√Protection against External Threats √Firewalls/Virus Protection
□ **Education/training/experience for individuals who develop, maintain or use computer systems to perform assigned task**	√Training Records, CV, Job Description
□ **Proper control of computer system to prevent loss of data?**	√Business Continuity Plan √Disaster Recovery Plan/Testing Report and Results √Backup and Recovery Schedule/Media √Storage/protection/Catalog of Tapes √Backup/Restore Logs, Media Rotation Schedule √Data System Archival √System Decommission
□**Evidence of good software development lifecycle practices**	√System Validation and Change Control procedures , i.e., software upgrades and patches, security, and equipment √Evaluation of System for Business/Regulatory Risk
□ **Ability to store/retrieve records attributable to a patient?** □	√Printout testing showing storage/record retrieval √ Global Privacy and Data Protection Policy √Confidentiality Statement/Informed Consent from Subjects

Key Summary:

Understand the Regulatory Requirements for Conducting Global Trials!

- **Key Concepts and areas of focus:**
  - **Establish a Quality Management System**
    --Assess, Plan, Monitor and Implement
    --Establish Checklists to audit, e.g., EMR/e-Source
  - **Evaluate Data Integrity/Assess Systems**
    - validated systems
    - clear processes with audit trail, defined by SOPs
    - appropriate approvals and clear traceability
  - **Consider the Regulatory, Ethics and Industry Challenges**
  - **Implement Best Practices**
- **Remember: 'if it isn't documented, it didn't happen'**