Overview of Global Harmonization Task Force Study Group 5

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GHTF SG5

Slide Development with assistance of Herb Lerner

Background

- SG5 was established at the June 2004 meeting of the GHTF Steering Committee
- First meeting was January 2005
- Mandate: to work towards convergence of clinical evidence requirements which should yield common data for the purpose of mutual acceptance by global regulators

“Assignments”

- First phase:
  - harmonise clinical definitions;
  - review existing GHTF documents and applicable ISO/ICH documents, to assure terminology is consistent and interfaces are clear;
  - Develop guidance on how to conduct and document the clinical evaluation; and
  - harmonise the content and format for clinical evaluation reports.
- Second phase:
  - harmonise principles to determine when clinical investigation, as opposed to other forms of clinical evidence, is necessary

“Assignments”

- Current work
  - harmonise principles to determine when post-market clinical follow-up studies are required, and the content of such a study
  - evaluate the need for harmonization of adverse event reporting (future proposal)

Current Status

- So far, we have held 12 meetings
- Meetings occur approximately once every 4 months
  - Most recent: Brussels, Belgium, January, 2008
  - Next: Tokyo, Japan, May 2008

Current Status

- So far, we have produced:
  - Two “final” documents:
    - *Clinical Evidence – Key Definitions and Concepts* (GHTF SG5/N1:2007)
    - *Clinical Evaluation (GHTF SG5/N2:2007)*
  - *Two “In Progress” documents*
    - *Clinical Investigation- GHTF SG5/N3 (est:2008)*
    - *Post-market Clinical Follow-up SG5/N4 (est:2008/Q1 2009)*
    - *Plus adaptation of N2 document for IVDs*
  - Memorandum of Understanding with ISO TC 194 (responsible for ISO 14155) – close liaison necessary to avoid overlap

Definitions and Concepts Document

- Focuses on key definitions related to clinical investigations and the clinical evaluation process only
- Defines:
  - Clinical Investigation
  - Clinical Evaluation
  - Clinical Data
  - Clinical Evidence

Definitions

- Clinical Investigation
  - "Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device"

Definitions

- Clinical Data
  - "Safety and/or performance information that are generated from the clinical use of a medical device"

Definitions

- Clinical Evaluation
  - "The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer."

Definitions

- Clinical Evidence
  - "The clinical data and the clinical evaluation report pertaining to a medical device."

Clinical Evaluation – What Is It?

- Process for assessing the clinical information known about a device to determine whether the relevant Essential Principles for safety and performance have been satisfied
  - Relevant Clinical Information Includes:
    - Scientific Literature
    - Clinical Experience
      - e.g. market experience, adverse event reports
    - Clinical Investigations

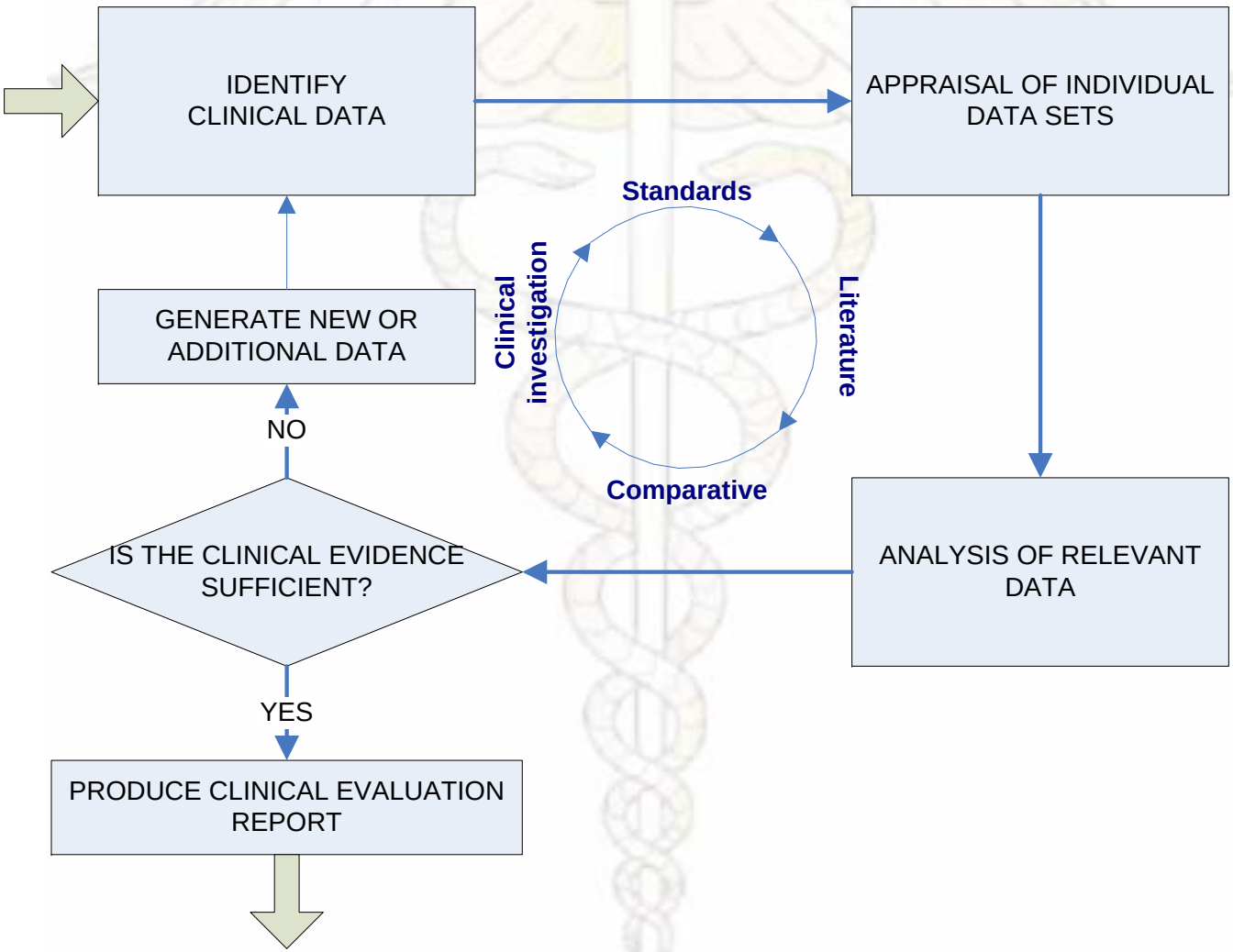
Clinical Evaluation – What Is It?

- a critical appraisal of available clinical information
- to determine if a favorable benefit-to-risk ratio exists for the device
- nature and amount of information needed will vary with the type of device, conditions of use, and experience with similar devices, along with other available data (e.g. preclinical/bench-top)

Clinical Evaluation – What Is It?

- Each device assessed individually, but builds off of knowledge obtained from similar devices
- Context of Risk Assessment and Analysis is critical
- Ongoing process as new information emerges (e.g. post-market)

STED & clinical evidence



Asia-Pacific Economic Cooperation

Then What?

- Contents of Clinical Evaluation Report and Clinical Data constitute Clinical Evidence
- Used as part of technical documentation (may be submitted for review as part of STED) to support market authorization

Contents of Clinical Evaluation Guidance

- Sources of information
- How to conduct and document literature reviews
- How to incorporate various information sources
- How to report the clinical evaluation

Clinical Evaluation – General Principles

- What is the scope of a Clinical Evaluation?
  - Comprehensive analysis of available pre- and post-market clinical data
  - May be specific to device in question or related devices
  - Should address clinical claims and all labeling, particularly warnings/precautions

Clinical Evaluation – General Principles

- What is the scope of a Clinical Evaluation?
  - Should be defined prior to undertaking, based on relevant Essential Principles that need consideration from a clinical perspective
  - Considerations include:
    - Are there any design features or target populations that require specific attention?
    - Can data from comparable devices be used?
    - What data source(s) and type(s) can be used?

Clinical Evaluation – General Principles

- Who should perform it?
  - Someone with “suitable qualifications”
  - Must be justifiable choice
  - Should possess knowledge of:
    - Device technology and application
    - Research methodology
    - Diagnosis and management of target conditions

Clinical Evaluation – General Principles

- How is it performed?
  - Three discrete stages:
    - Identification of pertinent data (may include citation of pertinent standards where appropriate)
    - Appraisal of each individual dataset in terms of relevance, quality, applicability, etc.
    - Analysis of individual data sets with conclusions drawn for the subject device
  - As outlined on previous slide with figure

Clinical Evaluation – Sources of Data

- Literature searching
  - For subject device or comparable devices
  - Should follow a predefined protocol and have a final report
- Clinical experience
  - e.g. surveillance reports, adverse event databases, compassionate use
  - Requires some caution re: useability
- Clinical Investigations

Clinical Evaluation – Appraisal of Data

- Each piece of data needs to be objectively reviewed for quality and relevance
  - Then need further appraisal as to the contribution to establishing safety and performance

Clinical Evaluation – Analysis of Data

- Do appraised data sets collectively demonstrate clinical performance and safety of device in question?
- Relative weighting of datasets must be factored in, but all datasets should be included in analysis
- How do combined data demonstrate/fail to demonstrate safety and performance?

Clinical Evaluation – Report

- A Clinical Evaluation Report should be prepared to outline the process and conclusions
- Should be sufficient to be read as a stand-alone document by an independent third party
- Should be signed and dated by the evaluator(s) and accompanied by justification of choice of evaluator(s)

Clinical Evaluation Guidance – Appendices

- Include:
  - Suggested Literature Search Report format
  - Possible methodology for literature screening
  - Sample criteria for data appraisal
  - A sample method of appraisal
  - Suggested Clinical Evaluation Report format

Clinical Investigations Document

- Put forward to Steering Committee at this meeting for advancement as Proposed Draft

Clinical Investigations Document

- Provides guidance on use of Clinical Investigations as a tool for gathering Clinical Data not available through other means
- Provides general direction on standards for conducting study, basic principles of study design, etc.

Clinical Investigations Document

- Introduction and Scope Statements
  - Points to ISO 14155 as standard for the conduct of a Clinical Investigation and the contents of a Clinical Investigation Plan
  - Indicates that guidance was drafted primarily with use in pre-market applications in mind, but that some concepts will be broadly applicable to post-market clinical follow-up studies as well

Clinical Investigations – General Principles

- When do you undertake one?
  - When necessary to provide the clinical data not available through other sources (e.g. preclinical or literature) required to demonstrate conformity to Essential Principles
    - Can be clarified by:
      - Reviewing relevant Essential Principles,
      - Performing risk management activities
      - Conducting a clinical evaluation

Clinical Investigations – General Principles

- How does risk analysis factor in?
  - Helps determine what clinical evidence may be required for a particular device
  - Where risk analysis and clinical evaluation indicate that there are residual risks that cannot be adequately addressed through other means
  - See ISO 14971

Clinical Investigations – General Principles

- When is it justified?
  - Should avoid unnecessary experimentation on human subjects
  - Therefore, only perform a clinical investigation when:
    - It is necessary (as outlined above)
    - It is properly designed
    - It is ethical
    - Proper risk management procedures are followed
    - Compliant with all legal and regulatory requirements

Clinical Investigations – Principles of Design

- Design should aim to ensure that necessary clinical data are obtained
- Many factors may influence extent of data requirements
- As a general rule, devices based on new technologies or extending an intended use beyond current experience are more likely to require data derived from a Clinical Investigation

Clinical Investigations – Principles of Design

- Examples of specific considerations for device study designs:
  - Clear statement of objectives
  - Appropriate study populations
  - Minimization of bias
  - Identification of confounding factors
  - Appropriate controls where necessary
  - Design configuration
  - Type of comparison (e.g. non-inferiority)

Clinical Investigations – Principles of Design

- Design should maximize clinical relevance of data while minimizing confounding factors
  - Randomized, controlled, double-blind studies are historical “gold standard” but this design can seldom be appropriately applied to a device trial

Clinical Investigations – Principles of Design

- Statistical considerations very important
- Statistical plan must be prospectively defined and based on sound scientific principles and methodology
- Design should ensure that statistical evaluation reflects a meaningful and clinically significant outcome

Clinical Investigations – Principles of Design

- Conduct of the study:
  - A properly conducted clinical investigation, including compliance to the clinical investigation plan and local laws and regulations, ensures the protection of subjects, the integrity of the data, and it suitability for demonstrating conformity to the relevant Essential Principles
  - ISO 14155 outlines Good Clinical Practice for medical device investigations

Clinical Investigations – Principles of Design

- Outcome of an investigation should be documented in a final Study Report
  - This report forms part of the clinical data that is included in the clinical evaluation process

Clinical Investigations – Ethical Considerations

- Should follow Declaration of Helsinki
- Should be used only when data cannot be obtained through other methods
- Design and endpoints should be adequate to address residual risks
- Should follow a scientific and ethical investigational process not exposing subjects to undue risks or discomfort
- Undergo ethics review and regulatory oversight in conformity to local requirements

Impact of SG5 Documents

- N1 document provides a set of definitions that can be universally applied to the discussion of clinical evidence
  - Consistent terminology for everyone involved

Impact of SG5 Documents

- N2 document provides guidance surrounding the concept of clinical evaluation
  - What information should be satisfactory to support a device's presence in the marketplace
  - Outlines the elements to include in the process & what does and does not constitute clinical data

Impact of SG5 Documents

- N2 document provides guidance surrounding the concept of clinical evaluation
  - How the clinical evaluation report forms part of the clinical evidence
  - If the document is followed, the format and content of the resultant report should be considered acceptable by reviewers

Impact of SG5 Documents

- N3 document provides guidance surrounding the design and conduct of clinical investigations
  - When a study is required/justified
  - Appropriate design and conduct
  - How the results are integrated into clinical evaluation process

Current Work Items for SG5

- Adapt Clinical Evaluation document to address IVDs
  - What does “Clinical Evaluation” really mean for IVDs?
  - Being undertaken with co-operation of IVD Subgroup of SG1

Current Work Items for SG5

- Clinical Investigation document
  - Publication as draft for public comment

Current Work Items for SG5

- Post-Market Clinical Follow-Up Document
  - When should Post-Market Clinical Follow-Up Studies be considered?
  - How do they fit in to the “big picture”?
  - Document will be out for public comment soon

Going Forward

- Continued liaison with ISO TC 194 to examine areas of common interest
- Proposed New Work Item regarding Clinical Investigation Adverse Event reporting
- Assess whether there other new topics should be addressed

THANKS!

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