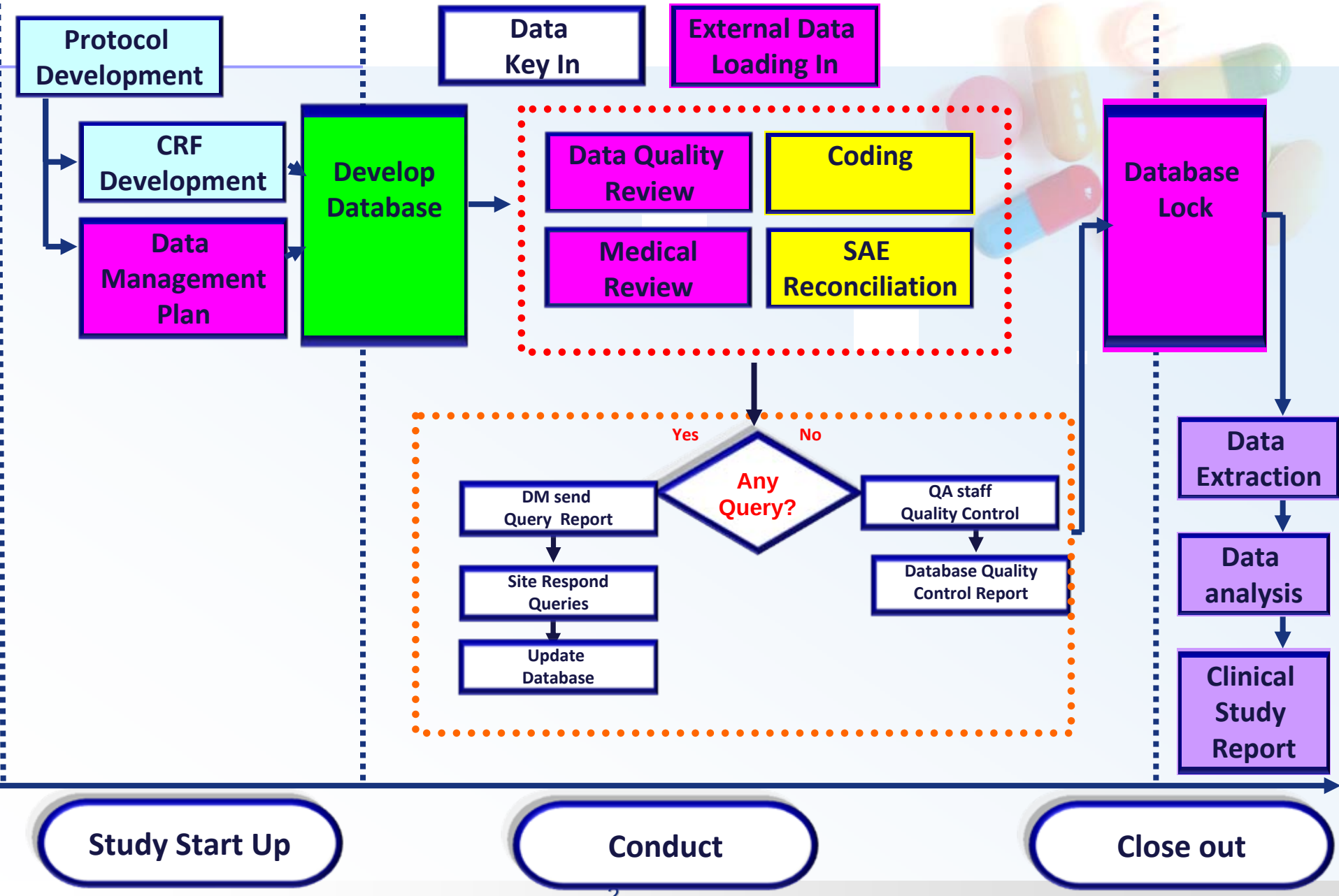
Protocol Introduction --- DM Perspective

September, 2010 at SMMU, Shanghai

DM Flow


Protocol Development
CRF Development
Data Management Plan
Develop Database
Data Key In
External Data Loading In
Data Quality Review
Coding
Medical Review
SAE Reconciliation
Yes
No
Any Query?
DM send Query Report
Site Respond Queries
Update Database
QA staff Quality Control
Database Quality Control Report
Database Lock
Data Extraction
Data analysis
Clinical Study Report
Study Start Up
Conduct
Close out

Outlines

1. Protocol Development
2. DM Perspective
3. Case Study
4. Take Home Messages

What is Protocol?

A protocol is a document that describes a clinical trial in detail and provides information and rules for the conduct of the trial to those involved

Statistical Analysis Plan: Table/Listing/Figure

Clinical Study Report: Conclusion for Efficacy/Safety

Questions?

- Author?
- Reviewers?
- Readers/Implementers?

Science (Clinician) Perspective

- Response variable selection and measurement (When and how long)
- Defining the intervention (control arm)
- Study design
- Eligibility criteria (population)
- Patient management procedures
- Monitoring for safety and benefit

Statistical Perspective

- What is the study hypothesis?
- Sample size estimate
- Data analysis approaches

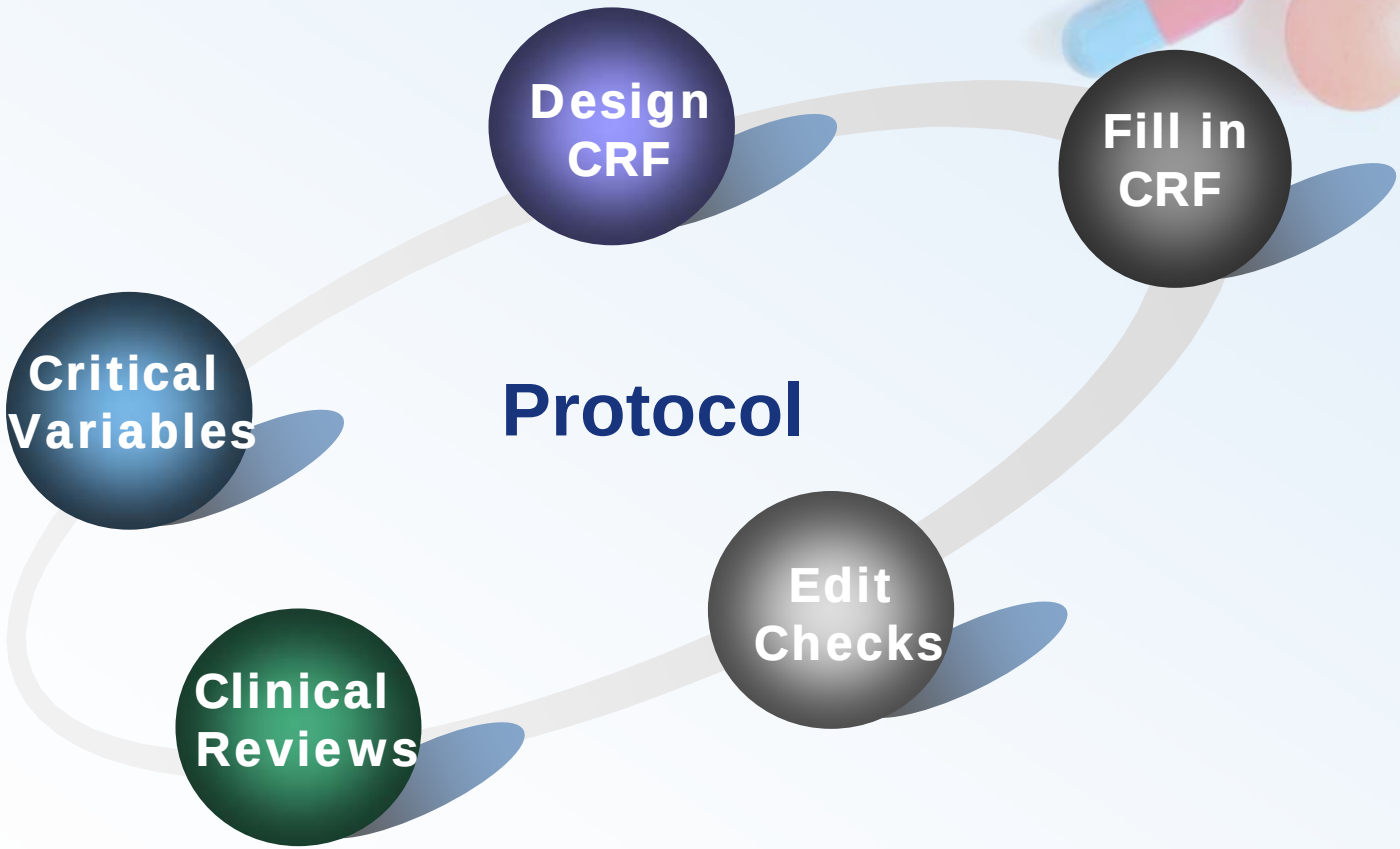
Chemistry, Manufacturing, and Controls (CMC)
Clinical / Antimicrobial
Clinical / Medical
Clinical Pharmacology
Combination Products
Concept Papers
Current Good Manufacturing Practices (CGMPs)/Compliance
Drug Safety
Electronic Submissions
FDAAA (Food and Drug Administration Amendments Act)
Generics
Good Review Practices
Individual Product Bioequivalence Recommendations
Industry Letters
International Conference on Harmonisation - Efficacy
International Conference on Harmonisation - Joint Safety/Efficacy (Multidisciplinary)
International Conference on Harmonisation - Quality
International Conference on Harmonisation - Safety

Adaptive Design Clinical Trials for Drugs and Biologics (PDF - 424 KB)	*Draft*	2/25/2010
Allergic Rhinitis: Clinical Development Programs for Drug Products (PDF - 68 KB)	*Draft*	6/2000
Antianxiety Drugs--Clinical Evaluation (PDF - 2 MB)	**Final**	9/1977
Antidepressant Drugs--Clinical Evaluation (PDF - 2 MB)	**Final**	9/1977
Assessment of Abuse Potential of Drugs (PDF - 138 KB)	Draft	1/26/2010
Available Therapy (PDF - 176 KB)	**Final**	7/22/2004
Calcium DTPA and Zinc DTPA Drug Products - Submitting a New Drug Application (PDF - 157 KB)	**Final**	8/13/2004
Cancer Drug and Biological Products - Clinical Data in Marketing Applications (PDF - 39 KB)	**Final**	10/11/2001
Chronic Cutaneous Ulcer and Burn Wounds -- Developing Products for Treatment(PDF - 205 KB)	**Final**	6/1/2006
Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment (PDF - 153 KB)	*Draft*	11/8/2007
Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the Treatment of Osteoarthritis (PDF - 40 KB)	*Draft*	7/07/1999
Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA) (PDF - 369 KB)	**Final**	1/1999
Clinical Evaluation of Analgesic Drugs (Withdrawn per August 5, 2003, Federal Register Notice)	**Final**	Withdrawn 8/5/2003

DM Perspective (Questions?)

- Why DM need to read protocol?
- Which parts you will pay particular attention? Why?

Protocol's influence on DM work



Trial Objectives and Purpose

Describe the overall objectives and purpose of the study. This should include both primary and any secondary objectives

- Review and keep objectives in mind as the rest of the protocol is discussed
- Requirements detailed in other sections should support the objectives

Example:

- EFFICACY

  Primary:

  - **Progression free survival**

  Secondary:

  - Objective response rate (CR + PR).
  - Disease control rate (CR+PR+SD)
  - Duration of response.
  - Overall survival.

Example (cont.)

Assessment of tumor response will take place during the last week of every 2nd cycle (or every 6 weeks), at the time of study treatment discontinuation (regardless of reason).

Assessment of tumor response will take place every 6 weeks for both comparative arm and treatment arm until investigator determined disease progression or death. ….

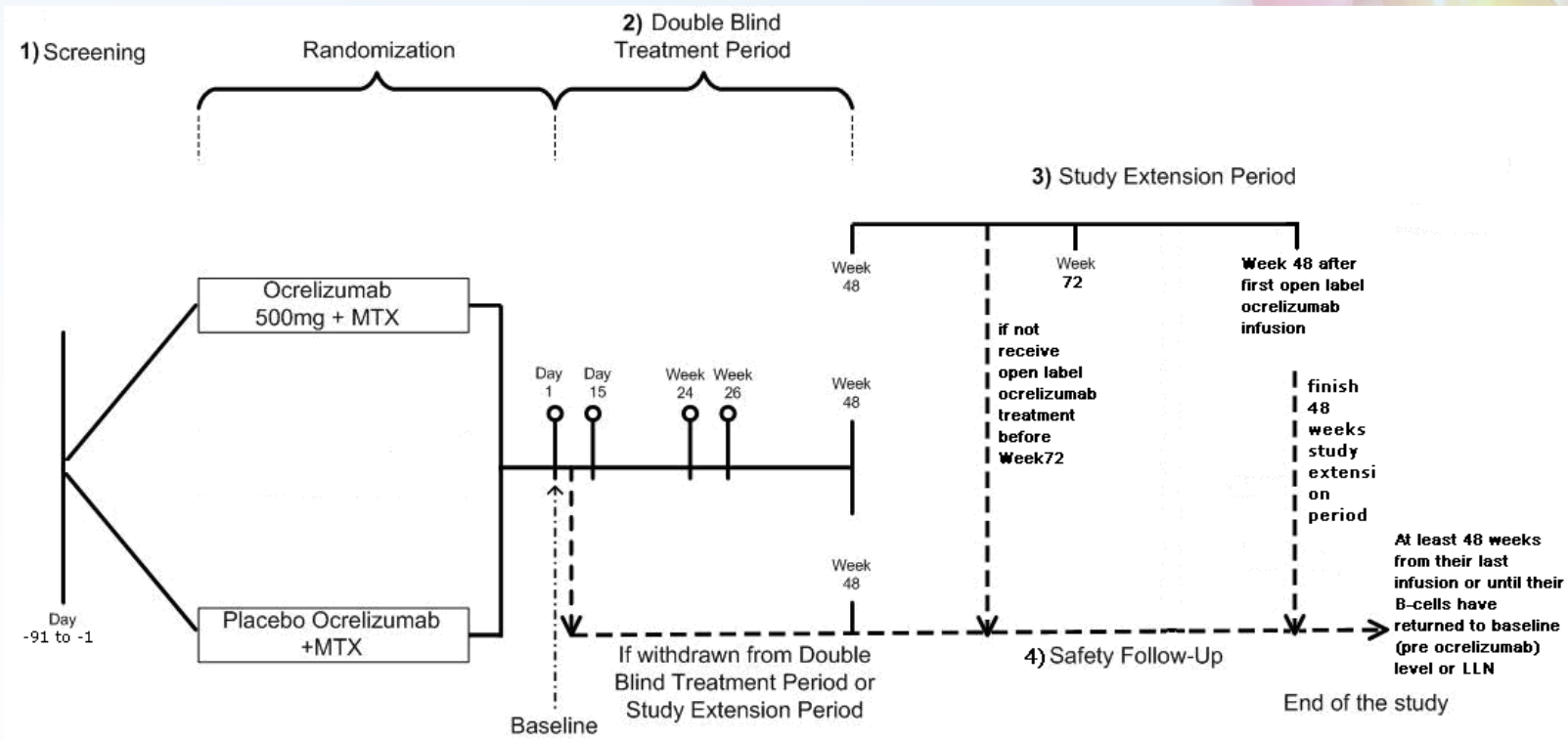
> ‘Should the patient need to postpone chemotherapy due to toxicity, tumor assessment should not be delayed and should be conducted according to the original schedule of every 6 weeks from the date of randomization”

Trial Design

• The type/design of the study (e.g. Phase, randomized, double-blind, parallel group, etc.)
• A schematic diagram of the trial design, procedures and stages
• Expected duration of subject participation
• A summary description of the sequence and duration of all trial periods including follow-up, if any

- It is important to <u>understand</u> the details of this section, for example, overall study plan, dosing regimen, inclusion/exclusion criteria etc
- Make sure the study phases (start point and stop point) are clear and evaluate the impact on CRF design and data validation
- Discuss questions with the team

Example 1



1)	Screening: Day -91 to day -1
2)	Double Blind Treatment Period: Day 1 to week 48
3)	Study Extension Period: At week 48. May receive open label ocrelizumab. Eligibility ends at week 72.
4)	Safety Follow-Up: If at any time after the first infusion the patient or investigator decides that no further courses of study treatment or open label ocrelizumab are required, the patient must be followed for at least 48 weeks from their last infusion or until their B-cells have returned to baseline (pre ocrelizumab) level or LLN, whichever is the longer.

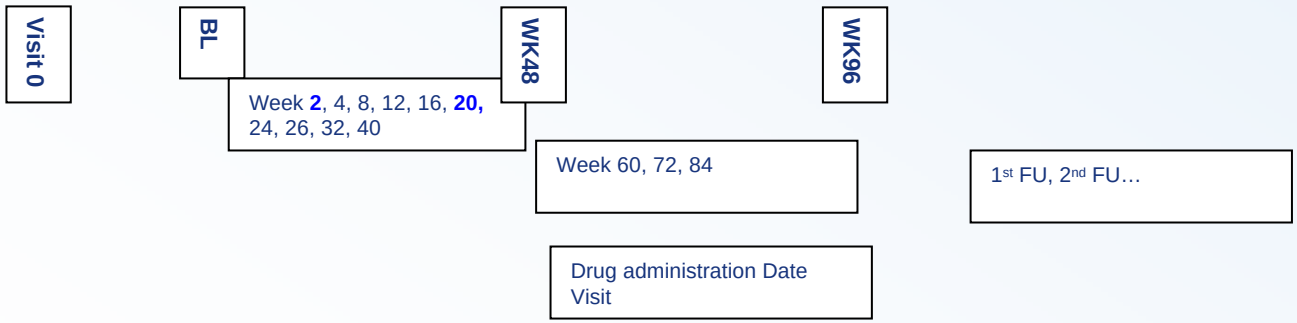
Blinded Infusion

Trial Design Matrix

	Screening	Double-blinded	Open phase	**Safety follow Up**
Placebo arm	Study cell	Study cell **Element: Two courses injection**	Study cell	
Ocre arm	Study cell	Study cell **Element: Two courses injection**	Study cell	

Branch: Randomization

Transition: treatment discontinuation



Study Population

- **IC/EC**
- **Randomization/screening**
- **ET**
- **ConMed**

- Objective or Subjective IC/EC? How to cross check with the data?
- Consider the impact of disease states on laboratory data - data from seriously ill patients is likely to take more time to review; broader windows may be needed for questioning abnormal results etc
- If re-screening, how will the site re-number the patient?
- ET? Re-supply? How to number the patient?
- Consider the concomitant medication, how to check?

Schedule Of Assessments

This section, describe all the procedures and treatments required at each visit, broken out by visit.
A study procedures flowchart/table that describes the activities and procedures to be followed at each visit.

- Consistency
- Don’t ignore the footnotes under the flowchart
- laboratory assessments
  - Detail
  - Itemised
  - Complete
  - Unscheduled
  - Timing
  - Central vs local
  - Transfer

Study procedures

- Clearly explained, especially if the procedure is relevant to the statistical analysis
- Study procedures should be consistent throughout the protocol:
  - Vital signs – maintain consistent measurement, e.g. supine and semi-supine throughout the study
  - Concomitant medication and special dietary requirements, are they allowed in the study?
  - Will information such as whether the patient smokes or has a meal at certain times be collected?
  - Are PK/PD measurements collected? How will this information be captured on the database? Will any PD parameters be captured on the CRF?

Investigational Product (IMP)

- Compliance
- Dosing regimen
- Are batch numbers clear if it is a bioequivalent study?

Assessment of Safety

- Noting rules regarding AE handling and follow-up, handling and follow-up of lab abnormalities, etc.
- Note if dose modifications are permitted and rules governing dose modifications
- Adverse events grading of severity (impact on CRF design and validations)

Statistics

- Review and note any endpoints, primary/secondary variables and which populations will be used to analyse each variable
- Note if there are plans for interim analyses and timings
- Data unblinding, will this only occur at the end of the study? Check timings of any database unblinding.

Quality Control and Quality Assurance

- Assure that this section contains the standard statement
- If plans a process that is different from the standard (e. g. the study is using EDC, a CRO for data management), provide corrected statement to the author)

Study Committee

- Note if a Safety Monitoring Board (DSMB) is planned and frequency of safety reviews - this will impact the timing of bringing data in house, cleaning and data extraction
- Note if any independent review of efficacy data is planned
  - How will this review be conducted?
  - Will the findings be recorded on the CRF, loaded electronically, or not captured at all?

Appendices

- Review the appendices for any scales, questionnaires, etc., referenced that may impact CRF design

Case Study

- Please answer the question below.
  - What is the study design?
  - What is the target population?
  - What is the primary efficacy hypothesis?
  - What are the procedures? (when and how to do what?)
  - What is safety evaluation? What is the definition of AE? SAE? Reporting/Follow up timeframe?
  - What information you have gotten from Appendix? Are they important?
  - Any problem you foresee from this protocol?

Take Home Message

a. Understands the protocol content
b. Understands and interprets primary and secondary hypotheses
c. Identifies critical data elements used for analysis and reporting.
d. Assures consistency internal to the protocol and the goals of the study/program.
e. Identifies gaps in protocol detail that are necessary for successful CRF design, database design, data cleaning and evaluation of study results and safety data reporting.
f. Challenges unnecessary data collection and contribution to study objectives

The 2nd Clinical Data Management Training

Thank You !