

The 2nd Clinical Data Management Training



Clinical Data Review

September, 2010 at SMMU, Shanghai

Agenda (**Why**, What, Where, When, How)

- 1 Purpose of Data Review
- 2 Data and Error Source
- 3 Types of Data Review
- 4 Perform Data Review
- 5 Key Messages

1. Purpose of Data Review (Regulatory)



ICH GCP requires:

- **2.10** All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
- **5.1.1** The sponsor is responsible and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s) .
- **5.1.3** Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

1. Purpose of Data Review (Individual Trial)

The ultimate goal is to provide **complete**, **accurate** and **integrate** data that serves as the base to draw correct conclusions.

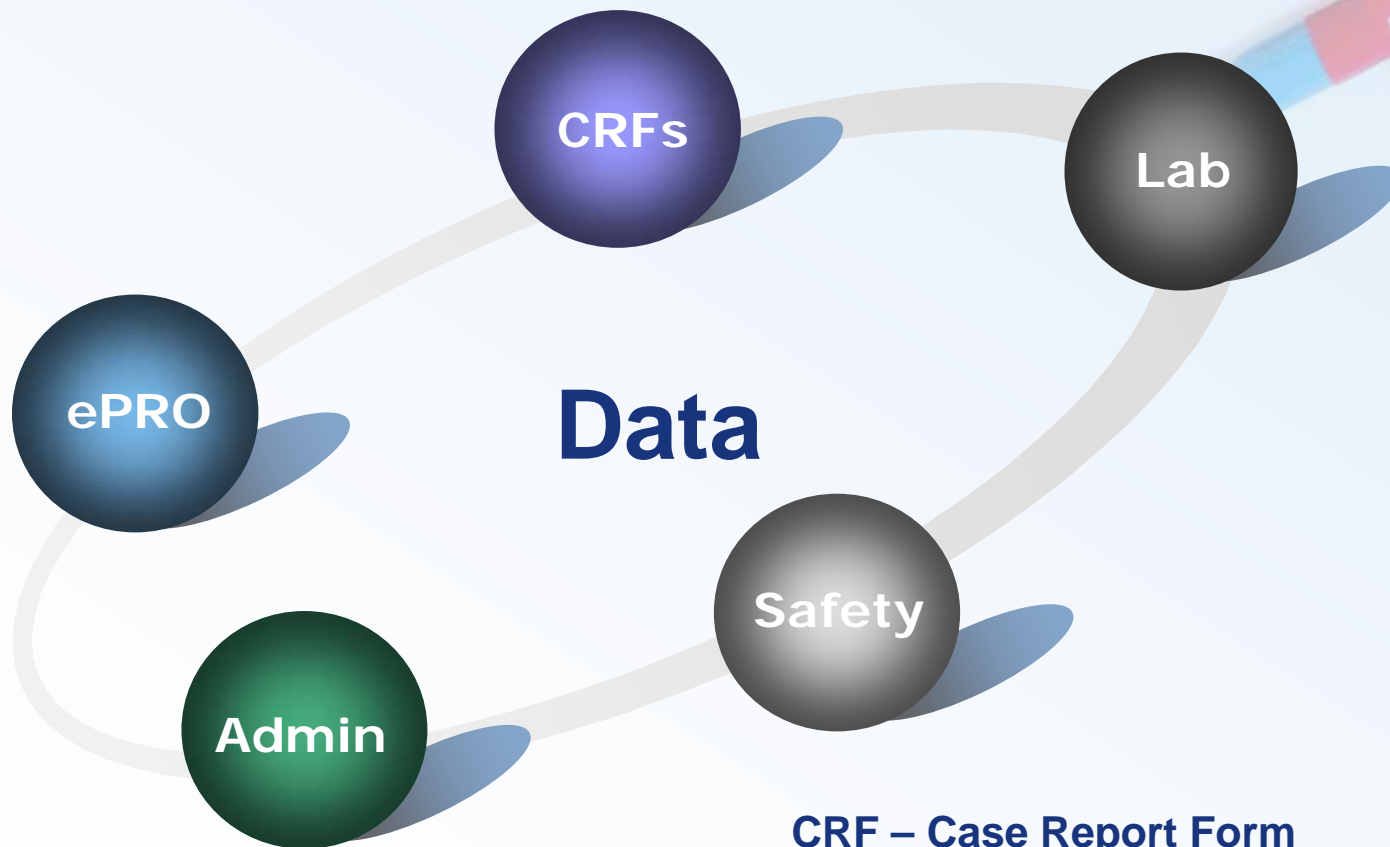
- No matter how much care is taken into collecting and entering data, discrepancies and data errors will invariably find their way into a clinical database.
- The **vast majority** of these data inconsistency and errors can be alleviated with careful data review and data cleaning.

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2.1 Data Source – What and Where



CRF – Case Report Form

Admin – Administration Data

ePRO – Electronic Patient Report Outcome

2.2.1 Error Type - Fraud

❖ Fraud

- Sponsor
- Investigator
- Patient



2.2.2 Error Type – Systemic Error



❖ Systemic error

- **Protocol deviation**
 - Oral vs. Axillary temperature
 - Fasting vs. non-fasting blood sample
 - Adverse event reporting
- **Poor CRF design**
 - Ambiguous questions
 - Double negative questions
 - Limited options for close question

2.2.2 Error Type – Systemic Error



❖ Systemic error

- **Measurement**
 - Un-calibrated sphygmomanometer
 - Different lab test method and reagent
- **Evaluator/analyst**
 - Lack of experience
 - Un-qualified
- **Data transfer between systems**
 - Missing record
 - Duplicate record

2.2.3 Error Type – Non-systemic Error

❖ Non-Systemic error

- Transcription error
- Other random errors



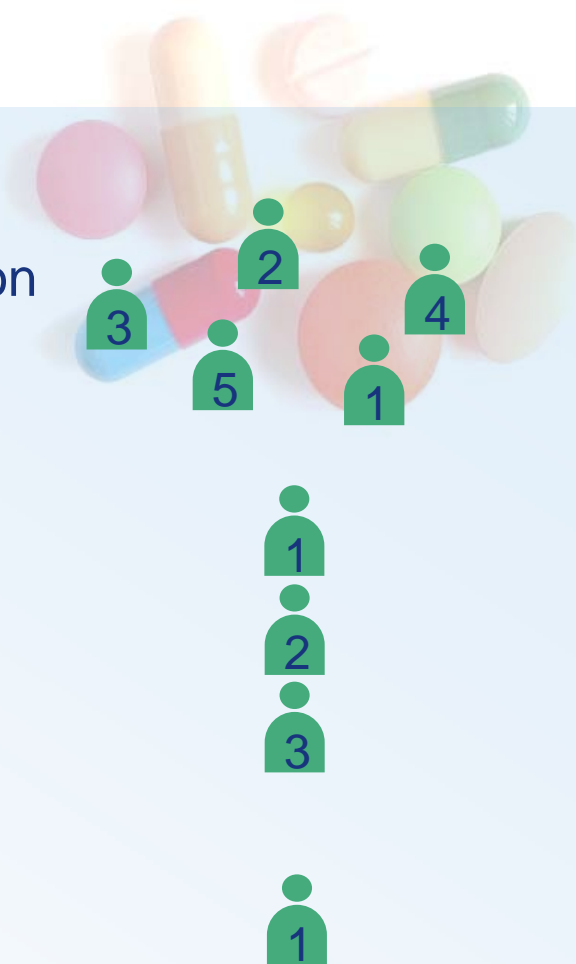
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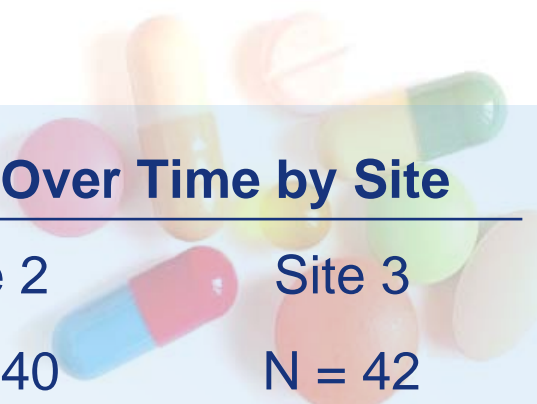
3.1 Data Review Type_Subject Set

- ❖ **Aggregate grouped data** across a study population (e.g. tabular summaries, bar charts, scatter plots)
- ❖ **Line listings of data** for a group of subjects (e.g. a list of all the AEs for a single subject, or a list of all subjects with a specific AE term)
- ❖ **Clinical data over time of individual subject** (e.g. all medically relevant data for a subject displayed time-aligned)



Example 1

Summary of Oral Temperature (Celsius Degree) Over Time by Site



Visit	Summary	Site 1	Site 2	Site 3
		N = 45	N = 40	N = 42
Baseline	N	45	40	42
	Mean	36.2	35.5	36.8
	Min - Max	35.3 - 37.6	34.8 - 37	35.4 - 38.6
Visit 1	N	45	39	40
	Mean	36.5	35.3	36.4
	Min - Max	35.5 - 37	35 - 36.8	36 - 37.2

Example 2

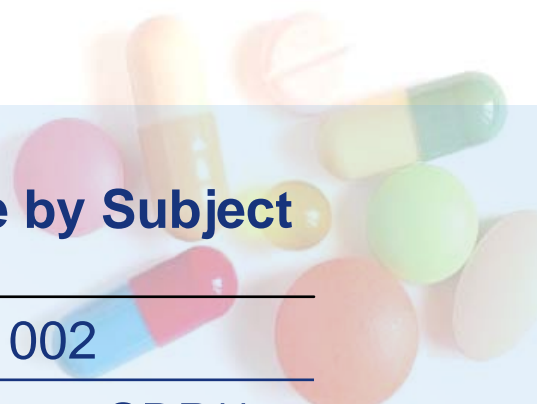


Listing of Adverse Events by Subject

Site	Subject	Adverse Event	Date of Onset	Intensity	Outcome	Date Resolved
ABC	1001	FATIGUE	14-Apr-08	MODERATE	Resolved	19-Apr-08
		ANEMIA	09-May-08	MODERATE	Resolved	13-Jun-08
		ANOREXIA	10-Mar-08	MODERATE	Resolved	22-Mar-08
		CONFUSION	11-Sep-08	MODERATE	Resolved	16-Sep-08
		ANEMIA	28-May-08	MILD	Resolved	19-Aug-08
		DRY MOUTH	19-Aug-08	MILD	Resolved	05-Feb-09
		DRY SKIN	07-May-09	MODERATE	Resolved	21-Dec-09
		LOST APPETITE	10-Mar-08	MODERATE	Ongoing	

Example 3

Listing of Blood Pressure (mmHg) Over Time by Subject



Subject	1001		1002	
	DBP*	SBP**	DBP*	SBP**
Baseline	79	128	84	130
Visit 1	78	125	85	125
Visit 2	83	121	68	118
Visit 3	91	150	79	122
Visit 4	89	142	89	123
Visit 5	80	124	80	124
Visit 6	78	120	82	125

*Mean of 3 Diastolic Blood Pressure readings

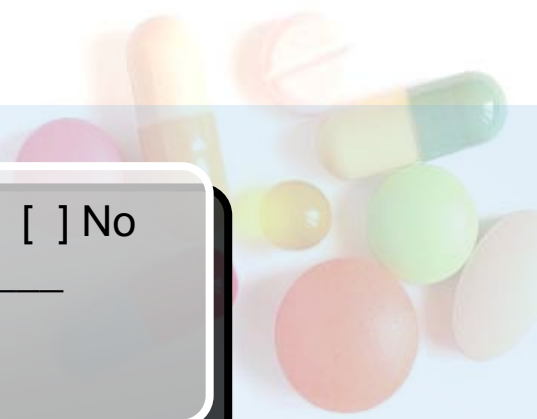
**Mean of 3 Systolic Blood Pressure readings

3.2.1 Data Review Type_Method



❖ Data Quality Review

- Synonym: electronic data review / edit check review / logic check review
- Edit checks are programmed and discrepancies triggered by system
- Mainly apply to individual patient data
- Errors can be detected by computer and an algorithm can be defined
- Carefully designed edit checks can greatly increase efficiency and data quality by automating many data review processes
- Examples (see next slide)



Context Logic

Was a blood sample drawn at this visit? [] Yes [] No
If yes, date of blood sample collection: __/__/____

If Yes is checked, date should be present.
If No is checked, date should be blank.

Range check

Blood Pressure ____/____ (SBP/DBP)

Systolic BP is expected to be 100 – 200
Diastolic BP is expected to be 60 – 110
SBP should be greater than DBP

Consistency Check

Weights at Month 1, Month 2, and Month 3

Weight changes more than 20% compared with last month



Duplicate Check

Lab test performed at Visit 1, Visit 2, and Visit 3

Lab test data of performed, lab test results are same for Visit 1 and Visit 3.

Overlapping Check

Drug A 20mg Start: 01Jan09 Stop: 01Jun09

Drug A 20mg Start: 01May09 Stop: 01Oct09

Same medication, sort by start date, and start date is prior to the stop date of previous record

Completeness Check

Date of birth: ___/___/___

Date of birth must be provided.



**Cross
Check**

Sex: Male Female

Was a pregnancy test performed? Yes No

If Female, pregnancy test question should be answered.
If Male, the question should not be answered.

**Reconcile
with other
data**

Reconcile with external lab data

Inconsistent birth data, date of sample collection,
mismatched record, duplicate records, etc

**Reconcile
with other
data**

Reconcile with safety DB (serious adverse event)

Inconsistent birth data, onset date, intensity, outcome,
mismatched record, etc

3.2.2 Data Review Type_Method

❖ Medical Review

- Synonym: clinical review / science review / manual review
- Apply to all kinds of subject data (individual, group, aggregate)
- Medical judgment is needed and an algorithm cannot be defined
- Examples (see next slide)





Example

Anti-hypertension drug is recorded

No hypertension is recorded in medical history or reported as adverse event

Example

Tylenol is recorded being used for diabetes

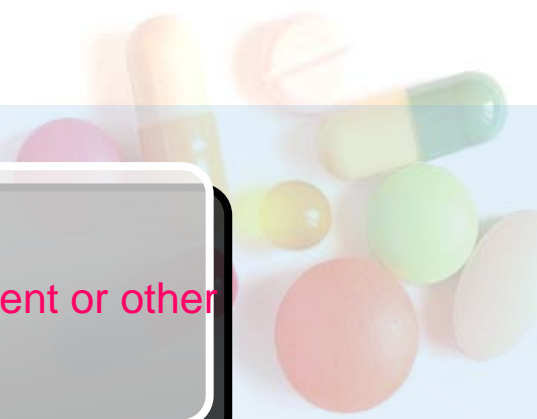
Tylenol is not indicated for diabetes

Example

ECG result: [] Normal [X] Abnormal

Specify abnormality: [Complete atrioventricular block]

No relevant medical history or adverse event reported



Example

Out of normal range value

Need to review medical history and adverse event or other data to determine if the value is valid or not

Example

Weight changed from baseline or previous visit

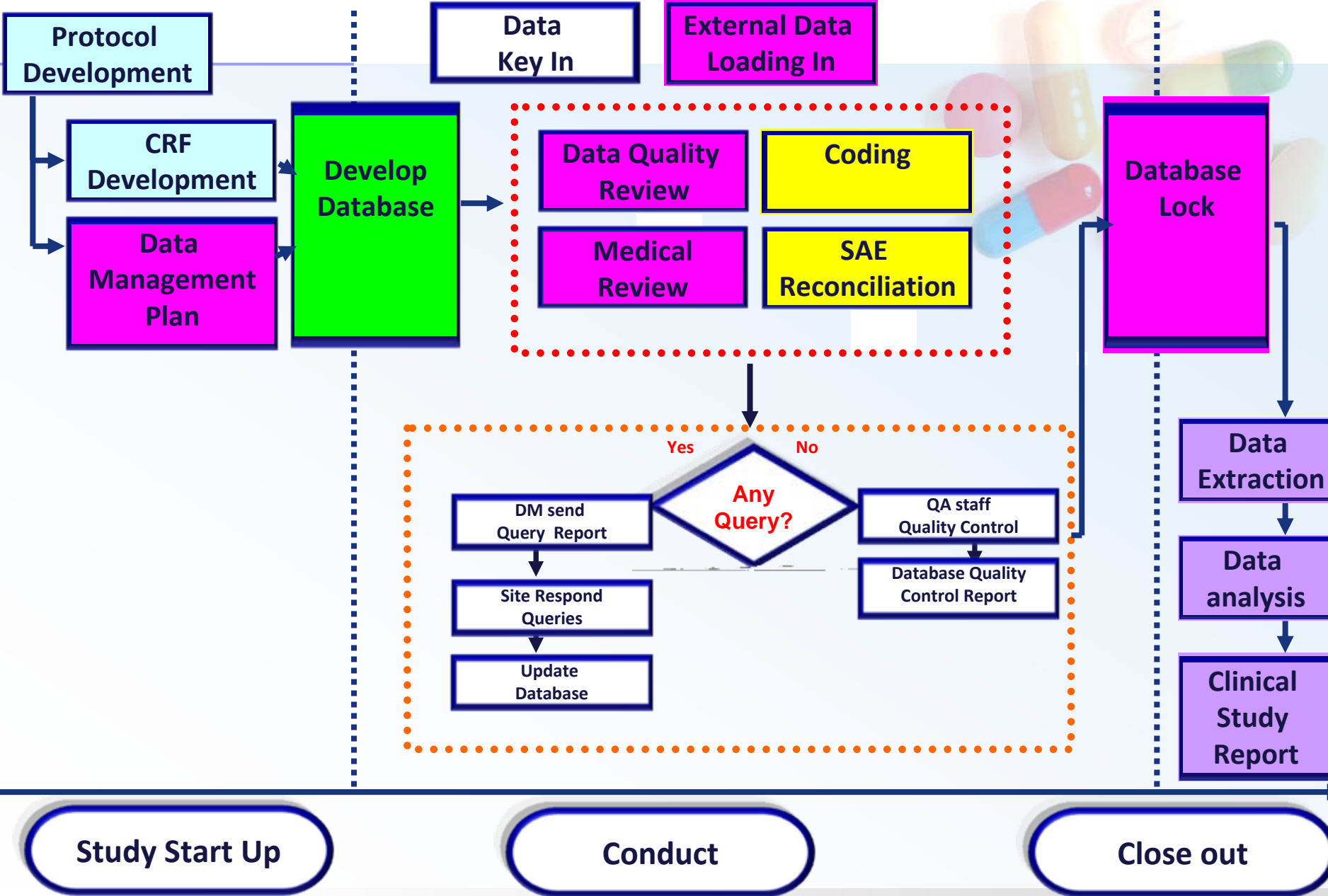
Need to review the variance in weight is due to medical history or result from adverse event (e.g. worsening HF)

Example

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4.1 Perform data review – Start Up

❖ Start Up

- No data review activities
- Develop Data Review Plan

❖ Conduct

- Data collection starts
- Majority data review work is conducted

❖ Close Out

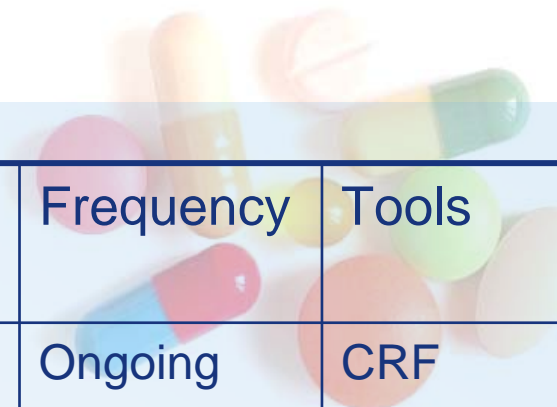
- Minimum data review work may be needed
- Database is locked and frozen



4.1.1 Develop Data Review Plan

- **DRP is intended to**
 - describes the objectives of data review and
 - document the key data review activities (frequency, tools and reports used, etc) and
 - define the roles and responsibilities of each study team member in the data review process
- **For each data review activity, DRP will define:**
 - Type of Data
 - Purpose
 - Roles and Responsibilities
 - Frequency
 - Tools





Type of Data	Purpose	Process/ Role & Responsibility	Frequency	Tools
CRF data Central lab data Other data defined in DVC	To check data are complete, logical and correct	DM: <ul style="list-style-type: none">● Continuous review discrepancies generated by the validation specifications● Monitoring the quality of discrepancy management;	Ongoing	CRF DVC Study Reports
Key data for efficacy data and signal detection	Focused medical data review and signal detection	Science: Performs medical data review and detection of potential signals and risk management.	Monthly Additional timepoint/ongoing	CRF I-Review Study Reports

4.1.1 Develop Data Review Plan (DRP)

- **Fully understand**
 - Protocol
 - CRF and other data source
 - Working scope and contract (CRO)
- **Define critical data**
- **Two main components:**
 - Data Validation Check
 - Medical Review Checklist



4.1.1 Develop DRP – Define Critical Data



Data used to make decisions in clinical trials must be accurate. Decisions about dosages, risk of adverse event and risk-benefit profiles of the treatment are made using these data.

- Study objectives
- Primary and secondary efficacy endpoint
- Primary and secondary safety endpoint

Critical data are defined by statistician, clinical science, and reviewed and agreed by the study team

4.1.1 Develop DRP – Determine data review type

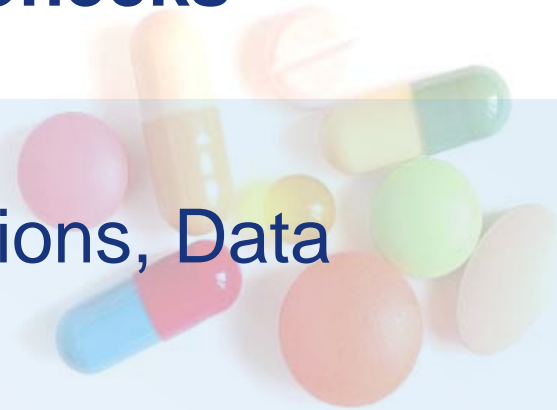
Use the appropriate, efficient method and tools to perform data review

- Study complexity / Study population
- Clinical database limitations
- Nature of data error
 - Some edit checks may be less feasible or efficient than a manual review (e.g. free text data fields);
 - Some data irregularities may be more appropriately identified by biostatisticians than through edit checks or manual reviews;
 - Some unexpected data trends may be indicative of systemic problems with data collection or processing and may not be easily identified by an edit check or manual review.



4.1.1 Develop DRP - Data Validation Checks (DVC)

- Synonym: Edit Check Specifications, Data Validation Guidelines, etc
- The DVC is a document containing the specifications of all **automatic validation checks programmed** to ensure data is accurate and complete within a study



4.1.1 Develop DRP - Data Validation Checks (DVC)

DVC usually include:

- Edit Check No.
- CRF Section/Domain
- Applicable Visit / Page
- Question
- Description
- Error Message Text
- Validation Procedure Name
- Testing Information (status, dummy data location, tester initial and date, reason for failure, action)

Additional columns may be needed per company's standard





VITAL SIGNS

Heart Rate (Seated): bpm

Respiration: /min

Height: in

Weight: . lb

Arm Circumference: . in

Oral Temperature: . °F

DVC Example



Check No.	CRF Section	Question	Applicable visit	Description	Error Message Text	VP Name
VS001	Vital Signs	Heart Rate	All	Heart rate should be between 50 – 100 beats per min inclusive.	Heart Rate is not within the expected range. Please review and amend or verify as correct.	V_VS_HR_01
VS002	Vital signs	Weight	All	Weight should be between 40 and 150 inclusive.	Weight is not within the expected range. Please review and amend or verify as correct.	V_VS_WT_01
VS003	Vital signs	Height	Screening	Height should be between 140 and 200 inclusive.	Height is not within the expected range. Please review and amend or verify as correct.	V_VS_HT_01

4.1.1 Develop DRP – Medical Review Checklist



Medical Review Checklist usually include:

- CRF Section/Domain
- Applicable Visit / Page
- Question
- Description (what should be reviewed and checked)
- Tools or reports

To facilitate manual review, some study-specific data listings, reports and tools are needed.

DEMOGRAPHICS

Date of Birth:

//
dd mmm yyyy

Race:

Caucasian Black Asian Hispanic/Latin
 Other, please specify _____

Gender:


Male Female

If **"Female"**, please complete below:

Pregnancy Potential:

- Post-menopausal for at least 2 years
- Surgically sterile
- Able to bear children

Screening (Visit 1)

PHYSICAL EXAMINATION			
Body System	Not Done	Assessment	If Abnormal, please specify
1.Skin	<input type="checkbox"/>	<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal	
2.HEENT	<input type="checkbox"/>	<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal	
3.Neck	<input type="checkbox"/>	<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal	
4.Lymph nodes	<input type="checkbox"/>	<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal	
5.Thorax	<input type="checkbox"/>	<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal	

Medical Review Checklist - Example



CRF Section / Domain	Applicable Visit / Page	Question	Description	Tools or Reports
Demography	Screening / Page 1	Race, Other	Check the specification is valid and not included in any of the pre-defined Race	Listing of Demography by Subj.
Physical Examination	Screening, Visit 10 / Page 1, 38	Abnormalities	Check the specification of abnormalities is valid and belongs to the correct body system	Listing of Abnormalities of Physical Examination

4.2 Perform data review – Conduct



❖ Start Up

- No data review activities
- Develop Data Review Plan

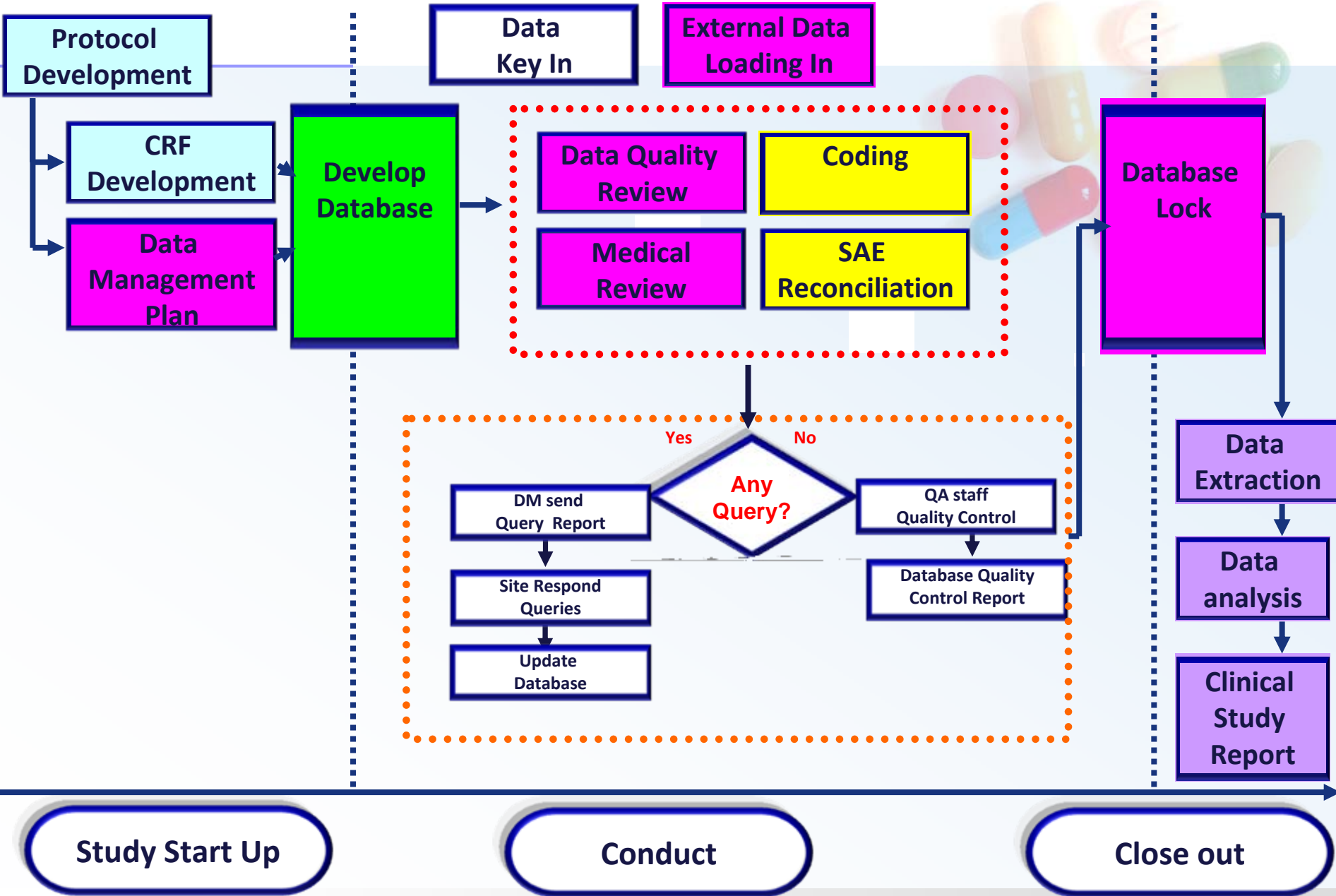
❖ Conduct

- Data collection starts
- Majority data review work is conducted

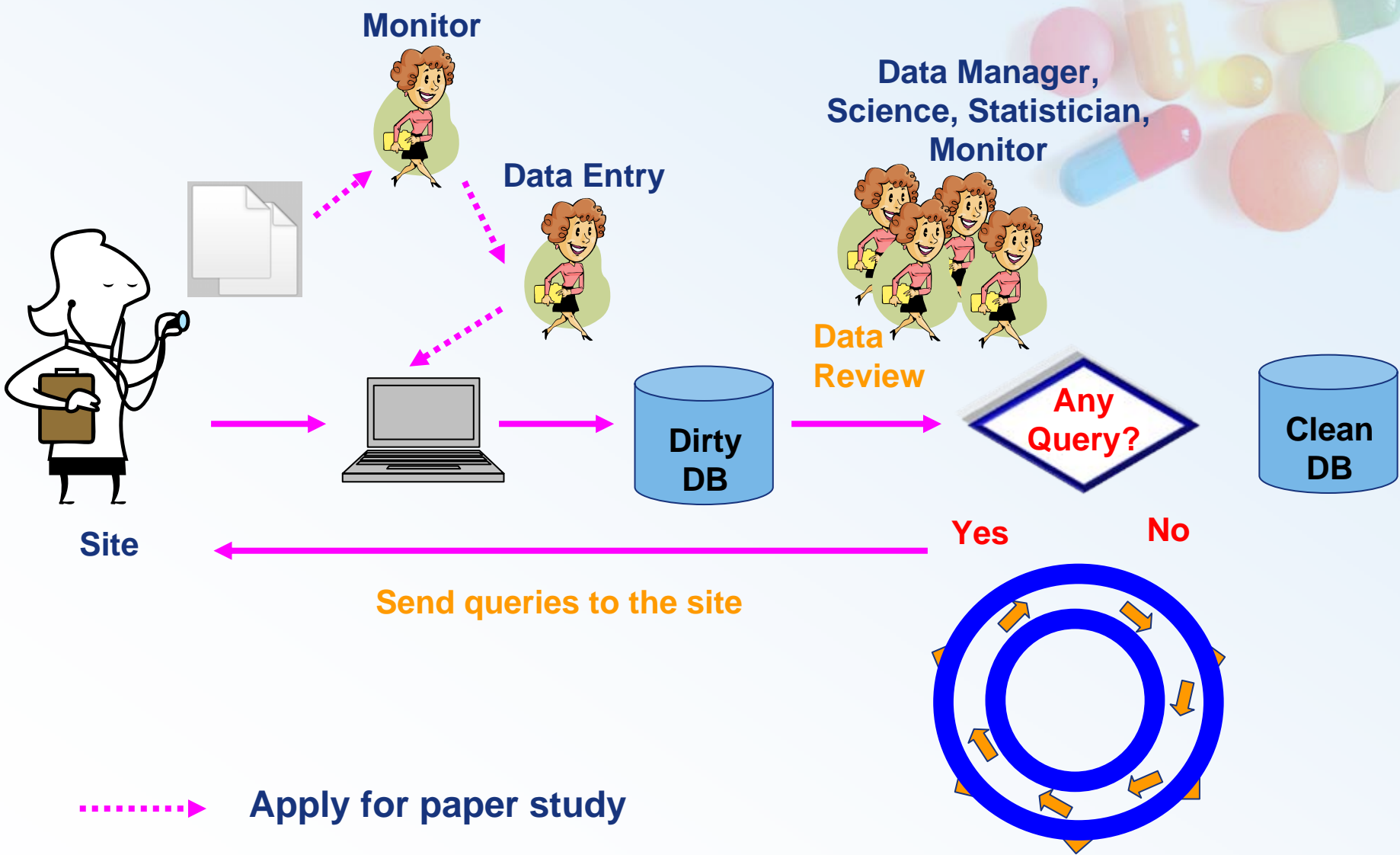
❖ Close Out

- Minimum data review work may be needed
- Database is locked and frozen

DM FLOW



Discrepancy Management



4.3 Perform data review – Close Out



❖ Start Up

- No data review activities
- Develop Data Review Plan

❖ Conduct

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❖ Close Out

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5. Take-home Key Messages



- Purpose – deliver data that fits the quality level and serve as the basis for correct conclusion and interpretation
- Understand the data and error source and concentrate on the critical data
- Develop Data Review Plan before the review activities start and the efficient and appropriate data review method
- Data quality is a shared responsibility across functions and departments which needs teamwork and joint efforts

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Thank You !

Question?

