Clinical Data Management

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What is Clinical Data Management

Clinical Data Management is involved in processing the clinical data, working with a range of computer applications and database systems for

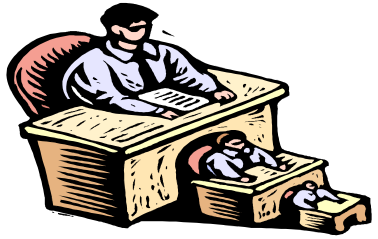
-collection,

-cleaning

-management of subjects details and trial related datas

-archiving the data.

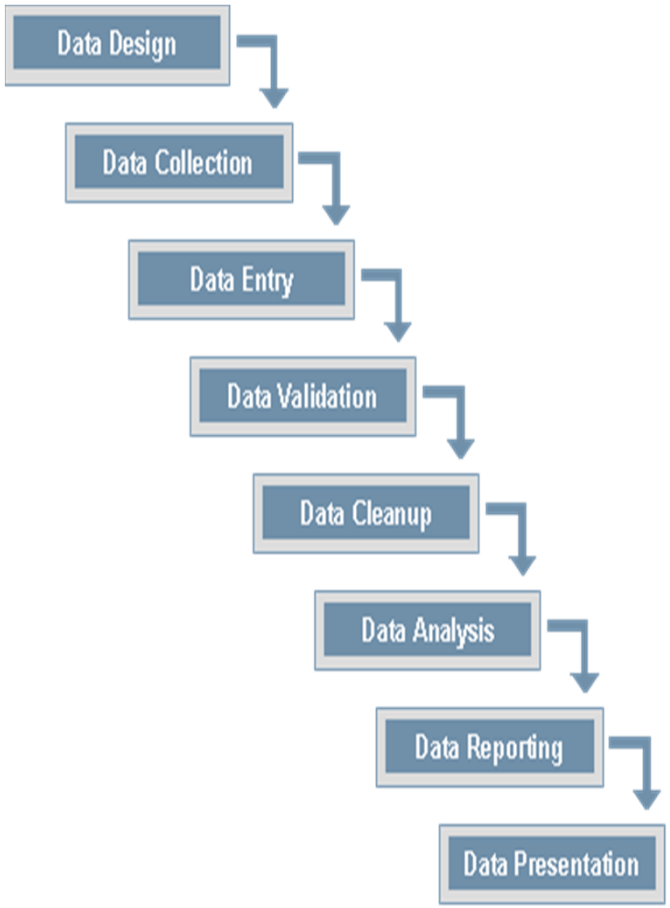
Subject Data



Data Manager

Clinical Trial Data

- **During the clinical trial, the investigators collect data on the patients' health for a defined time period. This data is sent to the trial sponsor, who then analyzes the pooled data using statistical analysis.**



Why CDM

CDM is a vital vehicle in Clinical Trials to ensure:

- **The Integrity & quality of data being transferred from trial subjects to a database system**
- **That the collected data is complete and accurate so that results are correct**
- **That trial database is complete and accurate, and a true representation of what took place in trial**
- **That trial database is sufficiently clean to support statistical analysis, and its subsequent presentation and interpretation**

Clinical Trials Multidisciplinary Team

At The Site

1. Clinical Investigator
2. Site coordinator
3. Study Nurse
4. Pharmacist
5. Phlebotomist

At The CRO

1. Project manager
2. Pharmacologist/Medical Monitor
3. Clinical Research Manager/Associate
4. Monitor
5. Regulatory affairs team
6. IT
7. Clinical supply

At Central Lab

1. Lab Head
2. Lab Coordinator

AT Clinical Data Management

- Clinical Data Manager
- Database Administrator
- Database Programmer
- Clinical Data Coordinator
- Clinical Data Associate
- Statistician

At Pharmacovigilance Team

1. Clinical Safety Surveillance Associate (SSA)

At QA/QC

1. Auditor/Compliance

Guidelines as per Good Clinical Practice (GCP):

- **All clinical research data should be recorded, handled, & stored in a way that allows its accurate reporting, interpretation & verification. (ICH GCP 2.10, 4.9, 5.5, 5.14 & ICH E9 3.6 & 5.8)**
- **Quality assurance & quality control systems with written standard operating procedures should be implemented & maintained to ensure that research are conducted & data are generated, documented & recorded, & reported in compliance with protocol, GCP & applicable regulatory requirements. (GCP 5.1.1)**

What is Clinical Data:

- Most valuable asset for a clinical trial.

- Serves as a basis for regulatory submission and approval, labelling and marketing of a compound

- Sources:
  - Subject-investigator interaction at sites
  - Laboratories reports

Who Can Collect Data?

- **Investigators**
- **Nurses**
- **Research team(Study Coordinators)**
- **Subject**
- **Subject's family**

Where Are the Data?

In the source documents

What is a Source Document?

- **It is the First Recording**

- **What does it tell?**

  1. It is the data that documents the trial

  2. Study was carried out according to the protocol.

Lists of Source Documents

- **Letters from referring physicians**
- **Medical Record**
- **Original Lab reports**
- **Pathology reports**
- **Surgical reports**
- **Physician Progress Notes**
- **Nurses Notes**
- **Original radiological films**
- **Tumor measurements records**
- **Patient Diary.**

What Do You Collect from source document?

- Demographical data
- Eligibility
- Study agent given
- Concurrent therapy
- Assessments/tests/exams
- Adverse Events
- Response according to protocol

Responsibilities of CDM

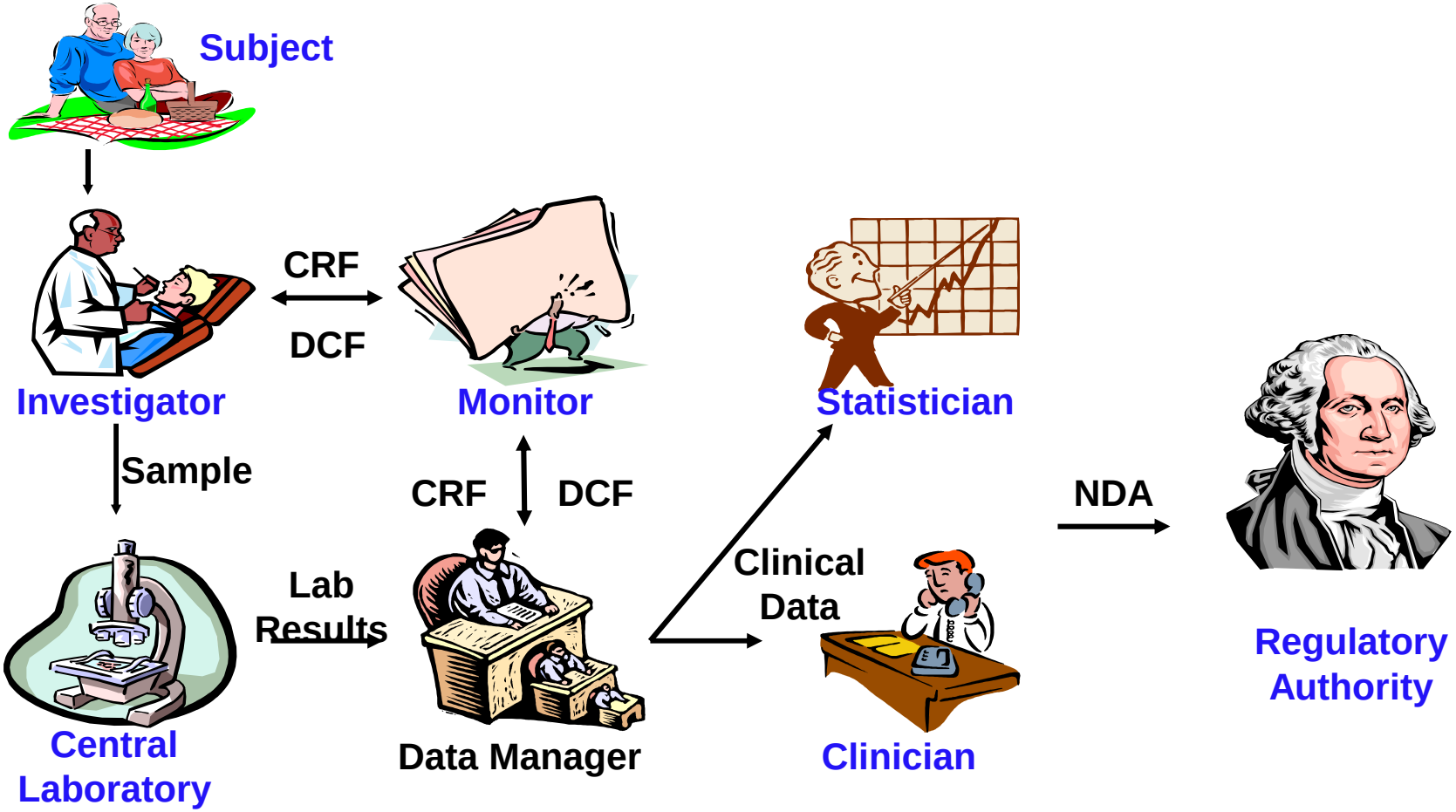
Study Setup
- CRF design and development (paper/e-CRF)
- **Database built and testing**
- **Edit Checks preparation and testing**

Study Conduct
- Data Entry
- Discrepancy Management
- Data Coding (using MEDRA and WHODD dictionaries)
- Data review (Ongoing QC)
- SAE Reconciliation
- Data Transfer

Study **Closeout**
- SAE Reconciliation
- Quality Control
- Database Lock
- Electronic Archival
- Database Transfer

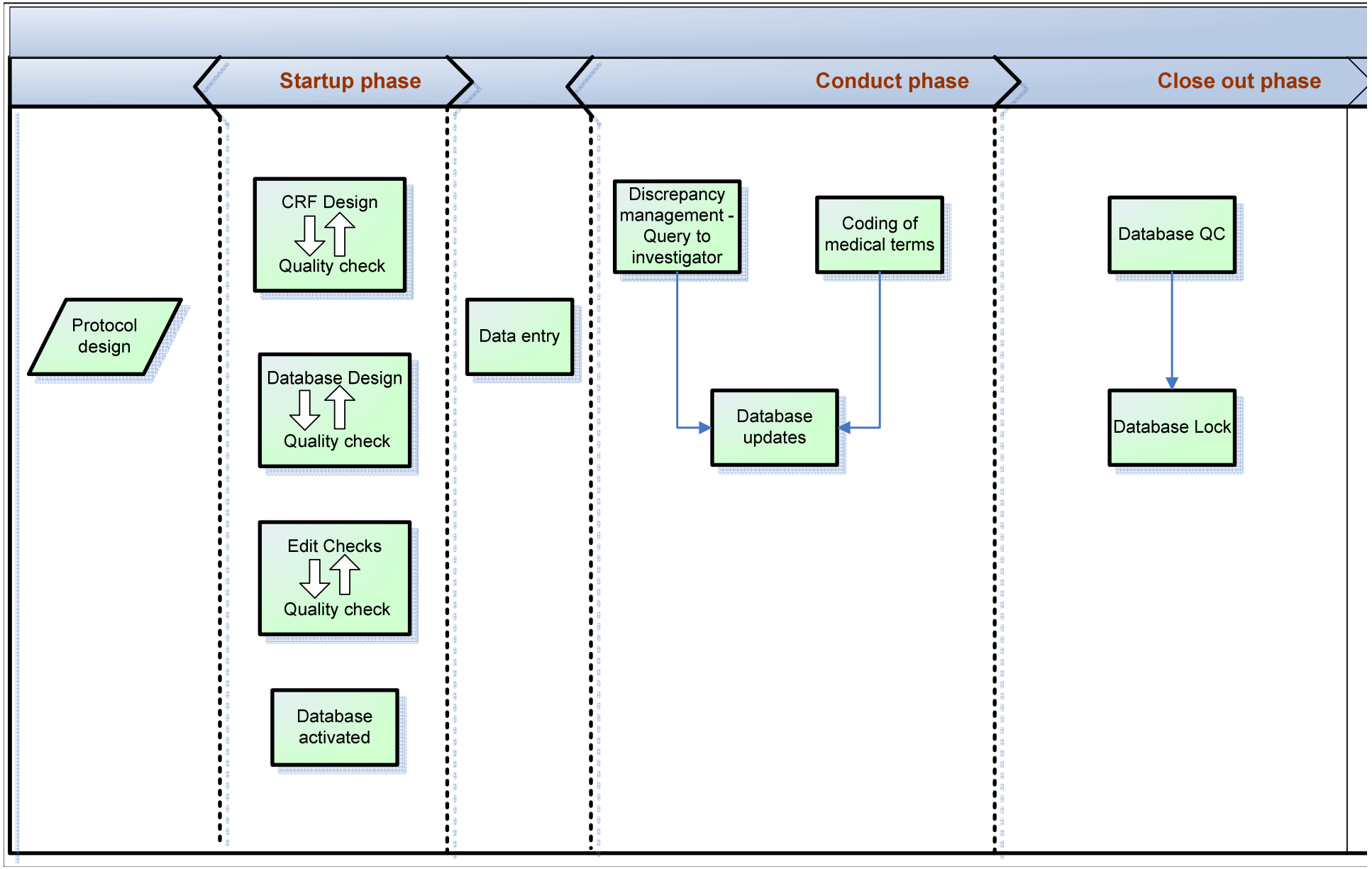
Don’t let poor data management steal your trial !

CDM Process

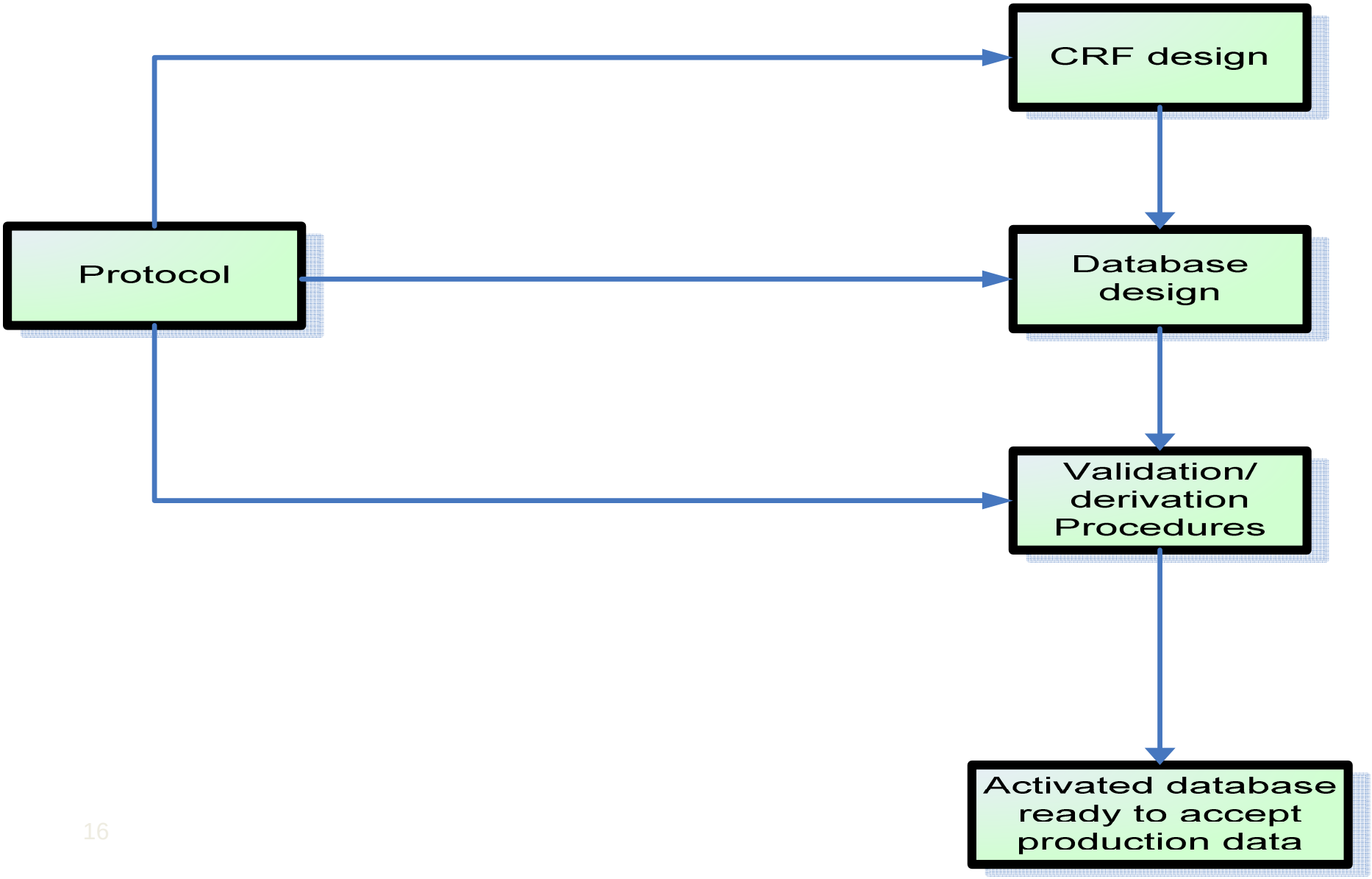


*CRF: Case Report Form
DCF: Data Clarification Form
NDA: New Drug Application

CDM Process Overview



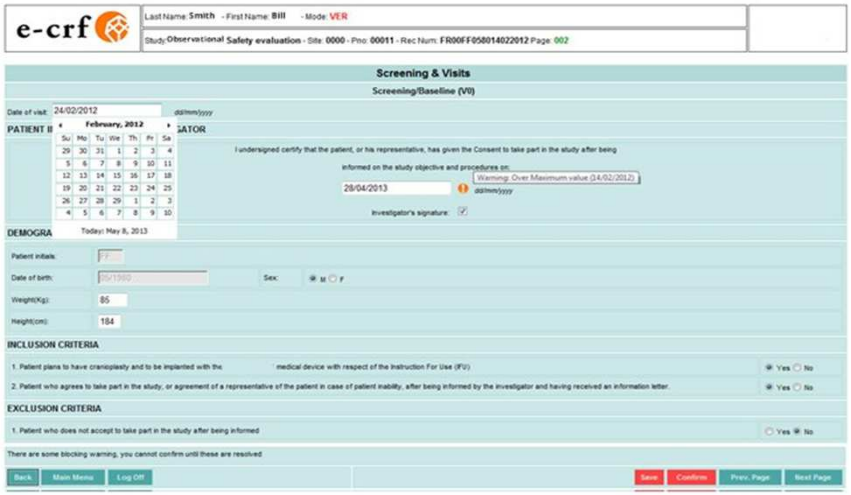
Study Start Up Process Review



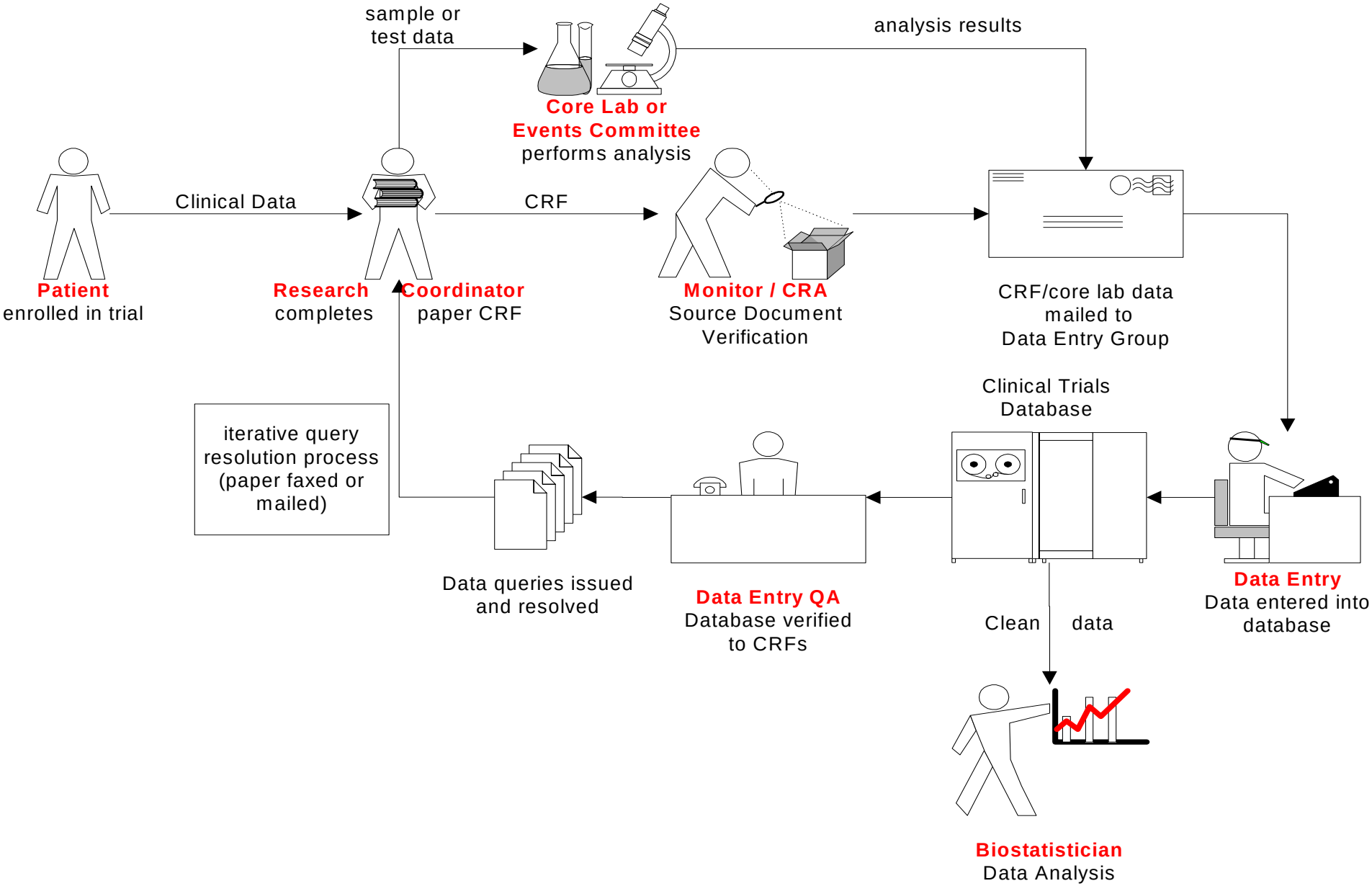
Collection of Clinical Trial Data

– Case Report Form :
  - Paper (Collected by monitor from Site)

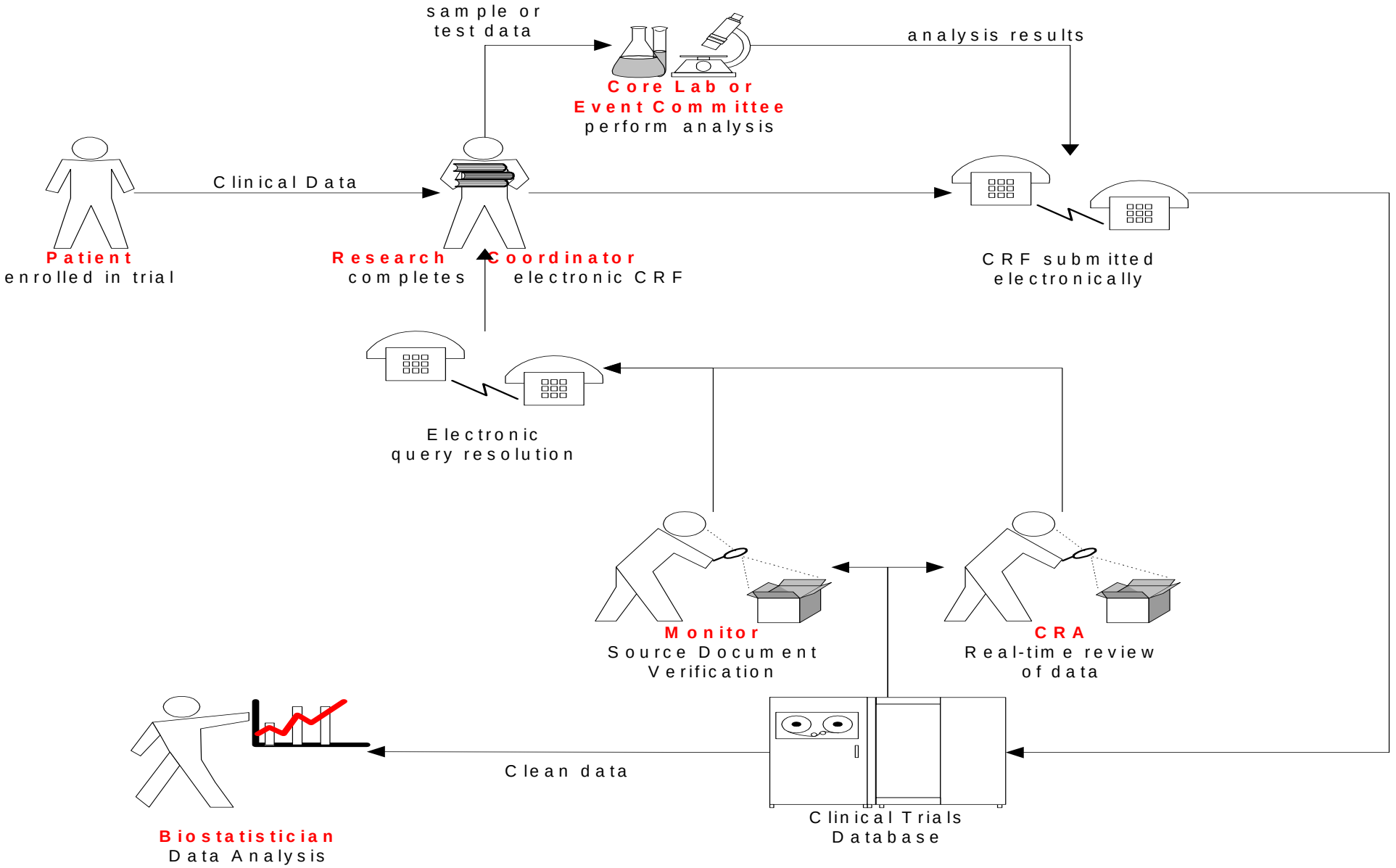
  - Electronics(Entered from site in Electronics Data Capture system)



Paper based data collection



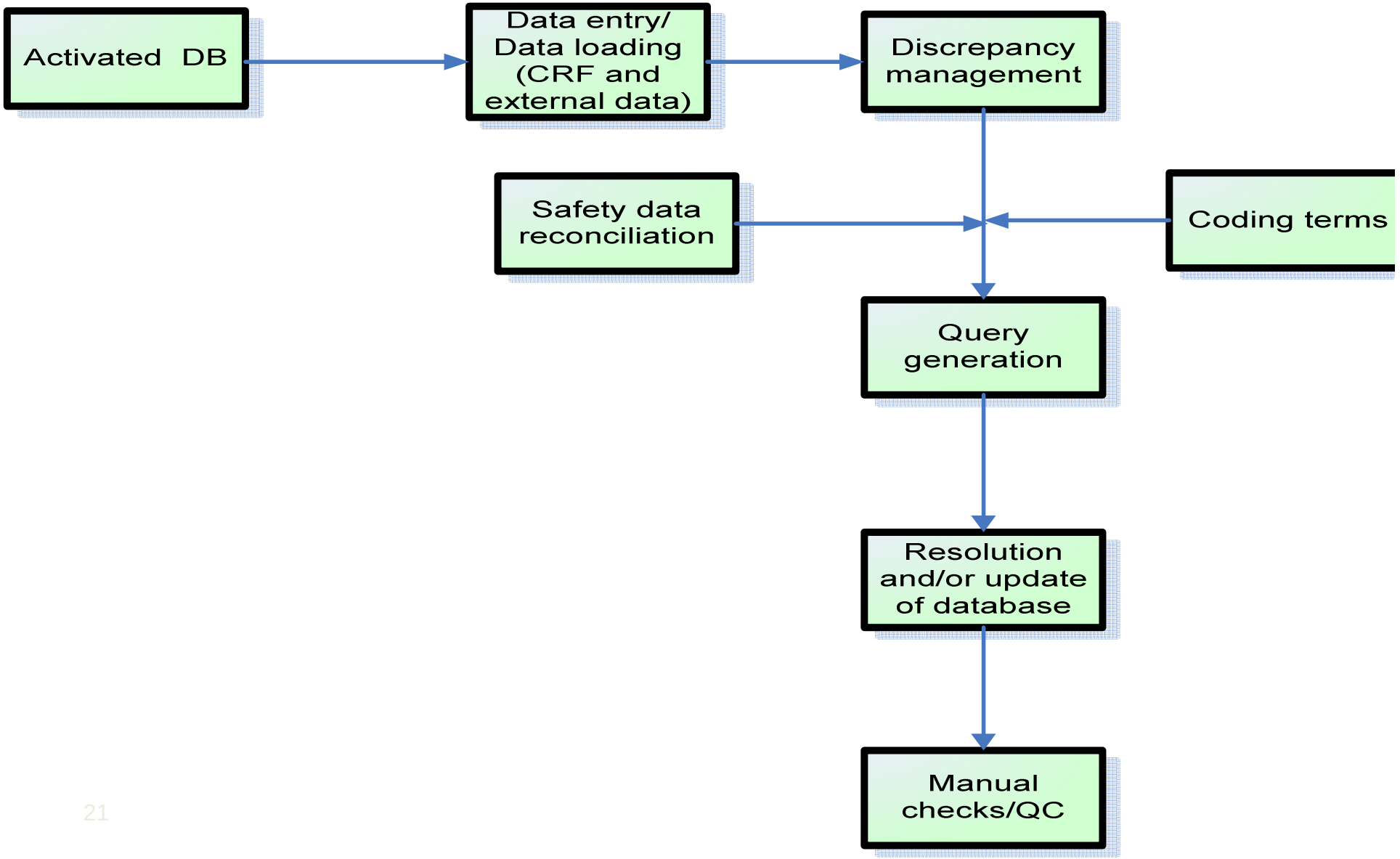
Electronic data collection



Validation Checklist:

Validation Checklist describes in detail which data shall be checked and queried if necessary. The programming of the checks occurs according to this checklist. Before the programming starts, the sponsor will be asked to give approval of this Validation Checklist.

Study Conduct Process Review



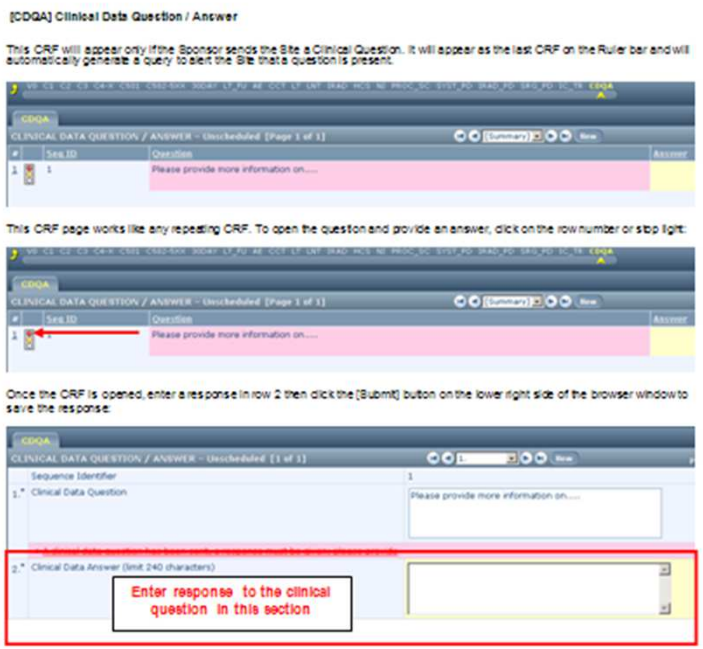
Data Discrepancies

Data Query:
A query is raised when a discrepancy or an inconsistency is noted during image review & during computer edit-check. Subsequent changes in data must be supported by paper Data Clarification Form (DCF) or e-DCF.

Data Discrrepancies:
- **Internal audits/monitoring**

- **Sponsor audits/monitoring**

- **Corrections documented**



Medical Coding

The medical coding for a study is done as per the project specific protocol requirement. The dictionaries used for a study are:

Adverse Events: MedDRA (Medical Dictionary for Regulatory Activities)

Medications: WHODD (World Health Organization – Drug Dictionary)

Manual coding is performed using Thesaurus Management System (TMS) which is integrated with our Clinical Data Management System (CDMS).

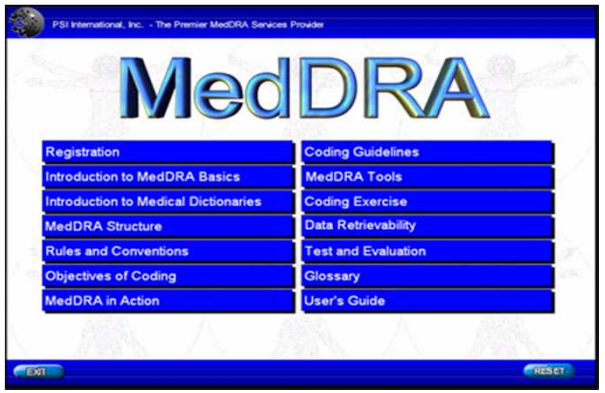
Code	Long Name
1	Abdomen
755	Abdomen, left
429	Abdomen, left lower quadrant
428	Abdomen, left upper quadrant
756	Abdomen, right
427	Abdomen, right lower quadrant
426	Abdomen, right upper quadrant

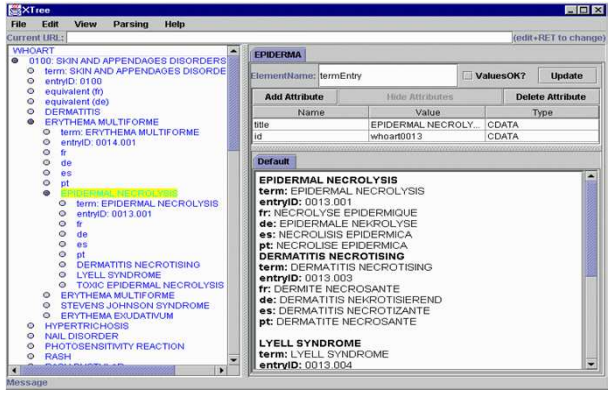
Code	Long Name
371	Ablation
378	Ablation, Bone Marrow
377	Ablation, Laser
275	Acupuncture
242	Adenoidectomy

Code	Long Name
2	Abdomen, Pendulous
3	Abdominal Swelling
3187	Ability to achieve and maintain erections
4	Abnormal Involuntary Movement

Data Dictionaries

- MedDRA
  - An International Conference on Harmonization (ICH) initiative, is a standardized dictionary of medical terminology
- WHO: WHOART, drugs
  - World Health Organization Adverse Reaction Terminology
- FDA COSTART
  - Coding Symbols for a Thesaurus of Adverse Reaction Terms

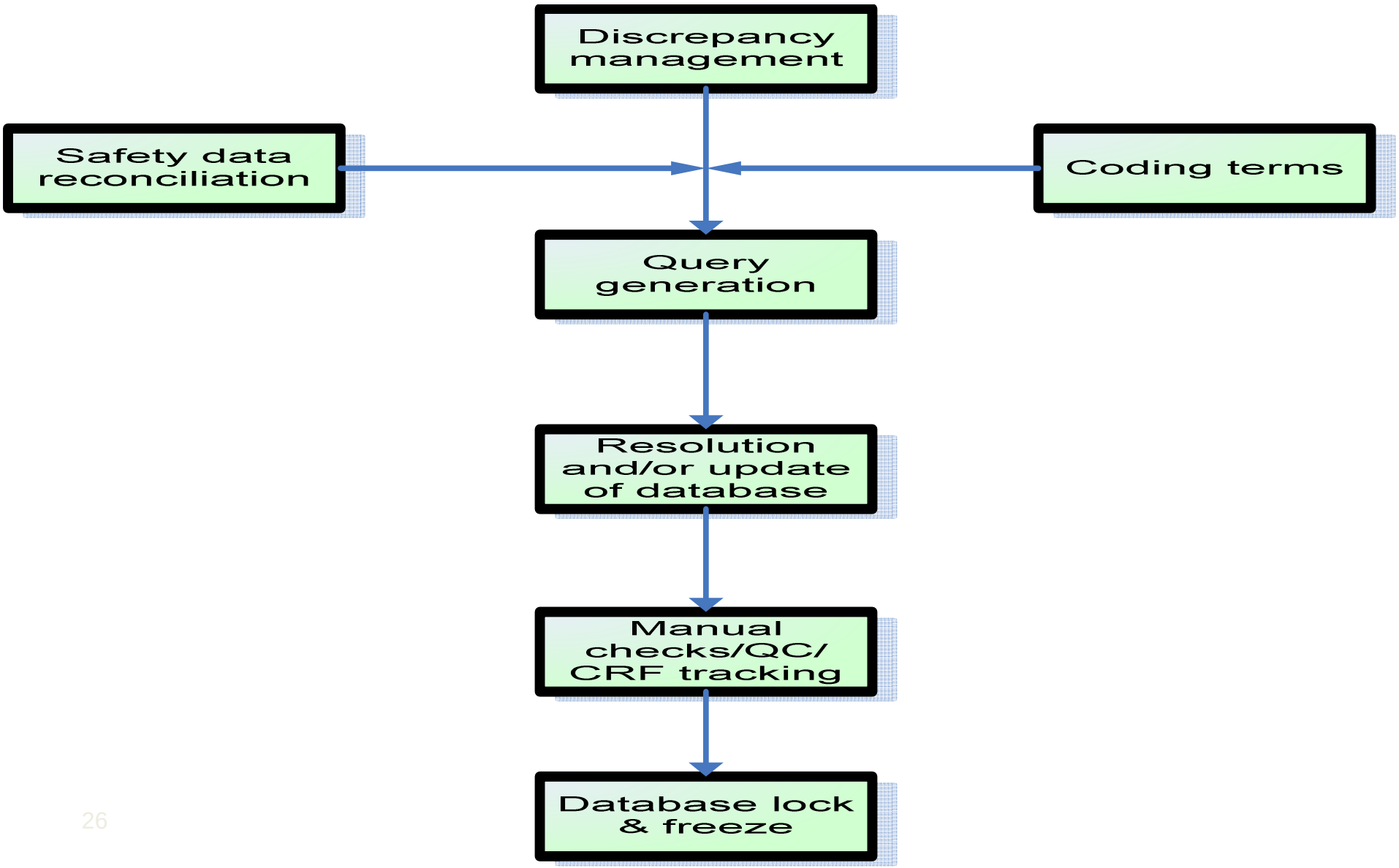




SAE Reconciliation

- Serious Adverse Event (SAE) data reconciliation is the comparison of key safety data variables between Clinical Data Management System (CDMS) and Master Drug Safety Database (MDSD). Reconciliation is performed to ensure that events residing in both systems are consistent.

Study Close out Process Review



Quality Control

- Quality Should be maintained for overall study by performing Quality checks at intervals for all data points prior to database lock.
- QC helps to ensure that all the data processed is accurate, clean and Correct.

Database Lock

The database lock for a study is done to ensure no manipulation of study data during the final analysis which is done once all Data Management activity are completed.

This includes:

-All discrepancies closed,

-DCFs received and updated,

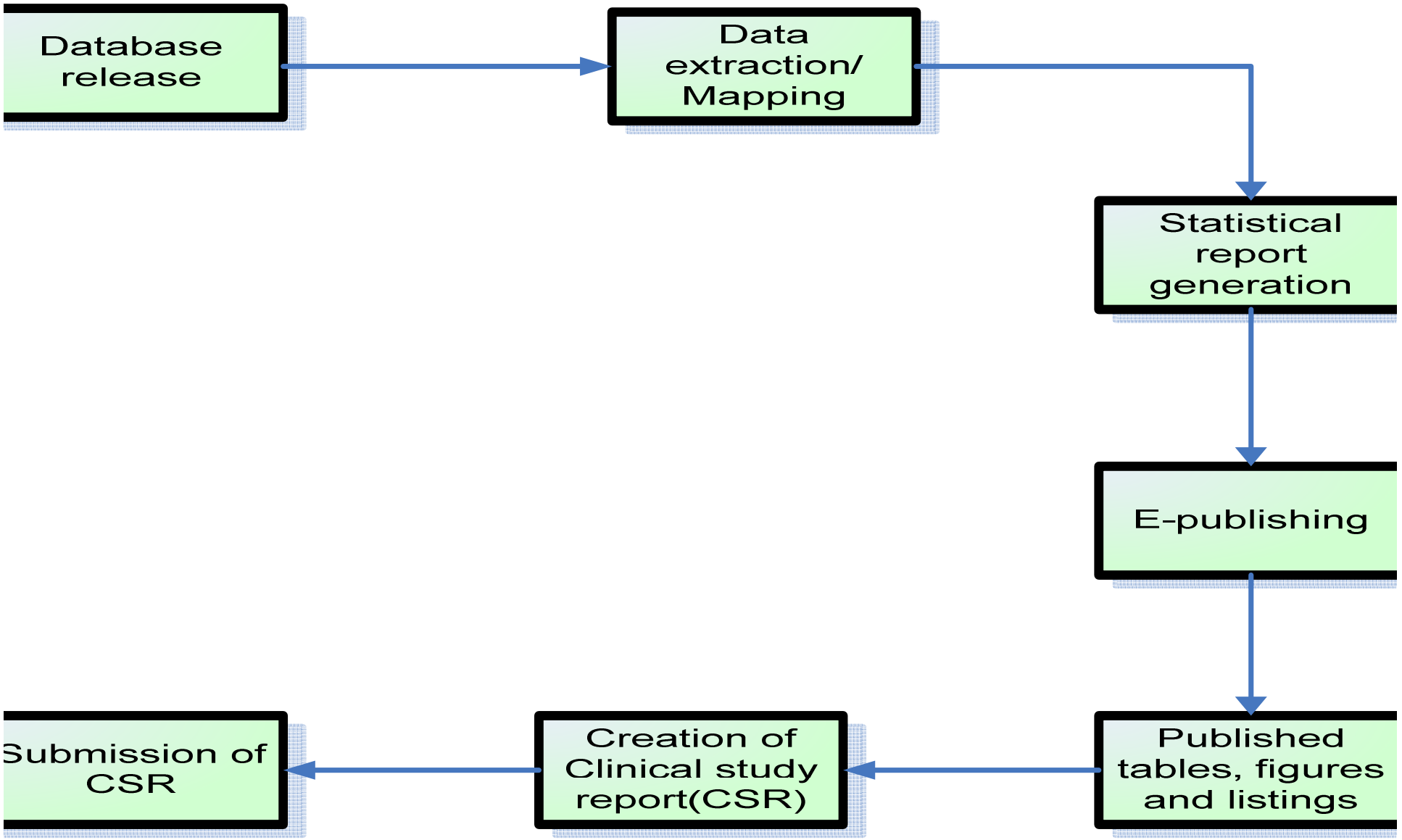
-Coding complete,

-SAE Reconciliation process complete

Archiving

- **Clinical data**
- **CRF or eCRF images in PDF form**
- **Regulatory documents**
- **Audit trail**
- **Transfer specifications**

Analysis & Reporting Process Review



Data storage needs to be SECURE and EFFICIENT.

Response Evaluation Criteria In Solid Tumors (RECIST)

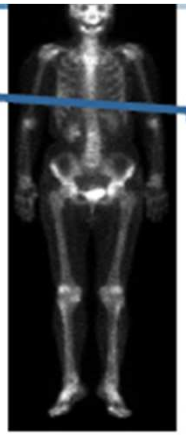
RECIST-INTRODUCTION

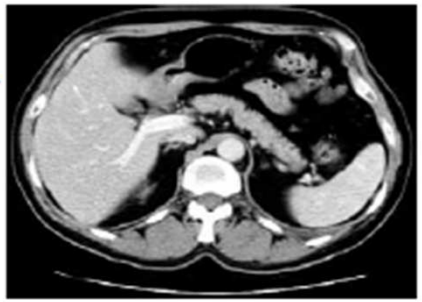
- **Response Evaluation Criteria In Solid Tumors** (**RECIST**) is a set of published rules that define when patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatments for solid tumors.

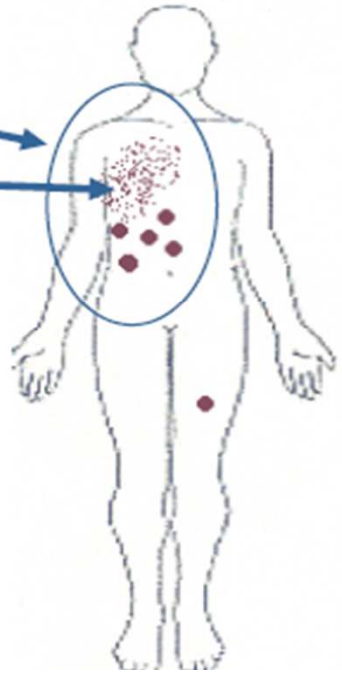
- Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumors are using RECIST.

ASSESSMENT

- Briefly review all scans/imaging provided for the subject's visit
- Determine the overall disease burden of the subject
  - Are there "good" target lesions to select?
  - Is the disease burden restricted to specific areas of anatomy?
  - Are there many non-targets?
  - Are there lesions to be evaluated in a lung window?
  - Are there any bone lesions?
- Begin selecting/categorizing target lesions and non-targets
- Consider lymph node rules







RECIST : Response Evaluation

➢ **Baseline Evaluation :**

- **Assessment of overall tumor burden and measurable disease :** Only patients with *measurable disease at baseline should be included in protocols where objective tumor response is the primary end point.*
- **Baseline documentation of "target" and "non target" lesions :**

✓ Measurable lesions up to a maximum of two lesions per organ

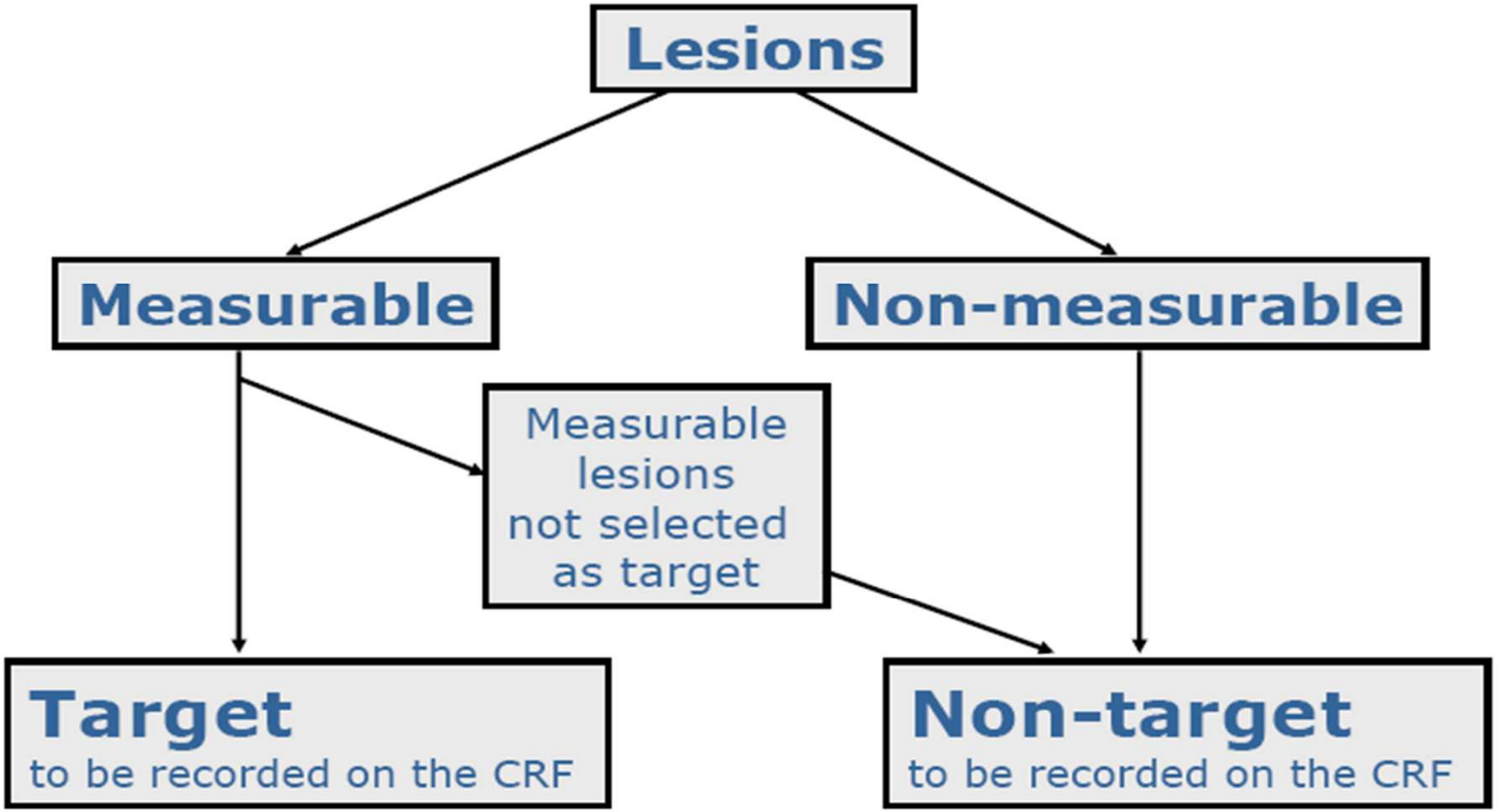
✓ 5 lesions in total, representative of all involved organs

✓ Recorded and measured at baseline.

✓ A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter.

✓ All other lesions / sites should be identified as non target lesions and recorded.

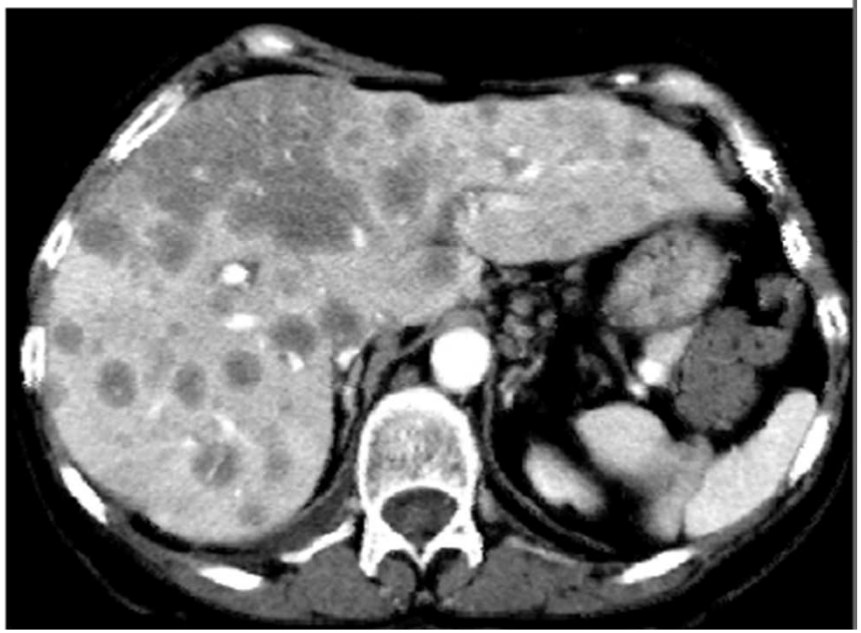
✓ Measurements of these lesions are not required.


Lesions
Measurable
Non-measurable
Measurable lesions not selected as target
Target
to be recorded on the CRF
Non-target
to be recorded on the CRF

RECIST 1.1-MEASURABLE LESION

Baseline selection of target lesions:

- All lesions up to a maximum of **five lesions total** and a maximum of **two lesions per organ** representative of all involved organs should be identified as target lesions



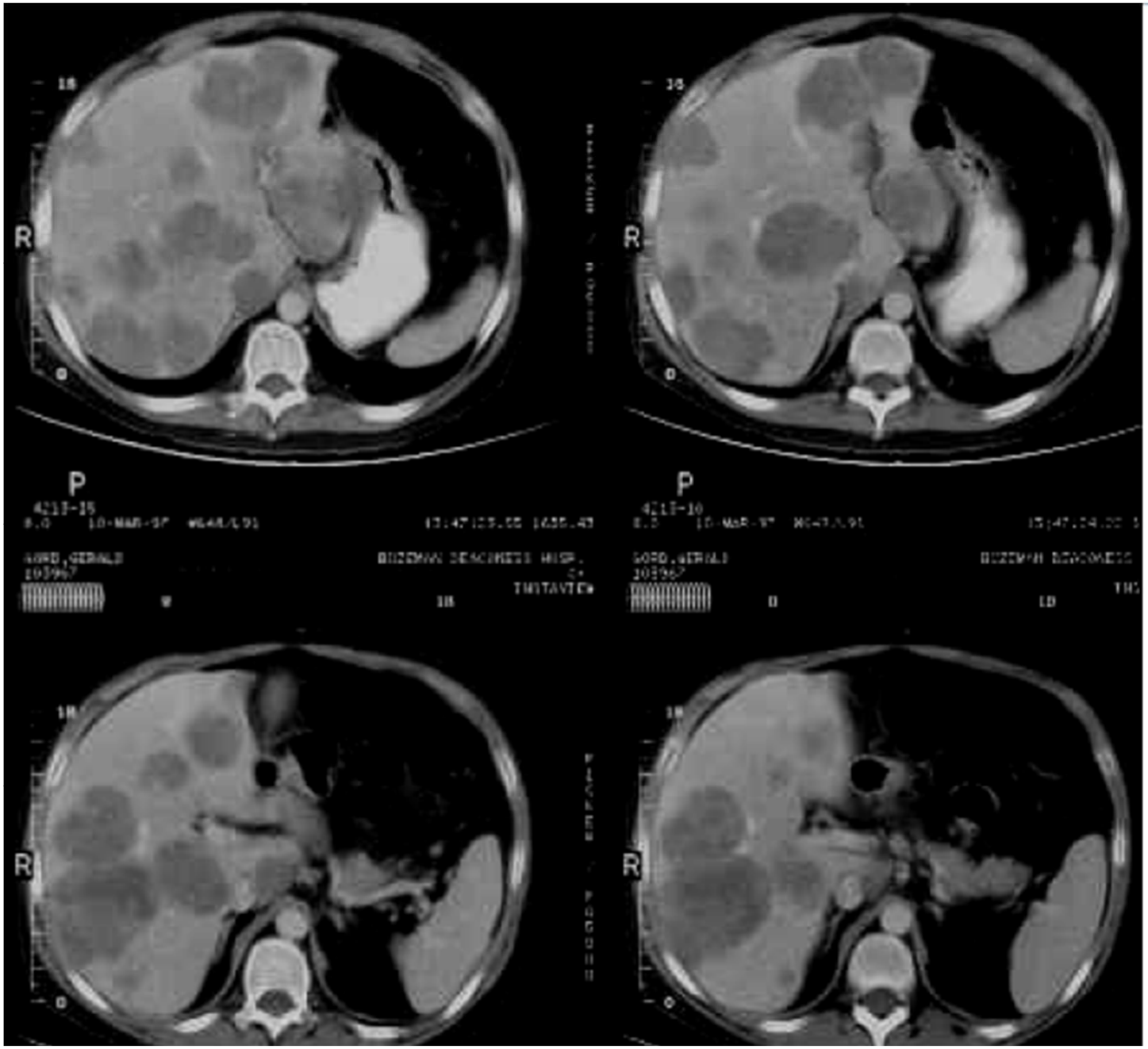
Measurable Lesions

- Accurately measurable in at least **<u>one dimension</u>** (longest dimension)
    - **≥10 mm (CT + MRI)**
    - **≥15 mm Lymph nodes**
    - **→ no less than double the slice thickness**
    - *10mm caliper measurement by clinical exam (when superficial)*
    - *20mm by chest X-ray (if clearly defined and surrounded by aerated lung)*
- Quantitative assessment

Non-Measurable Lesions

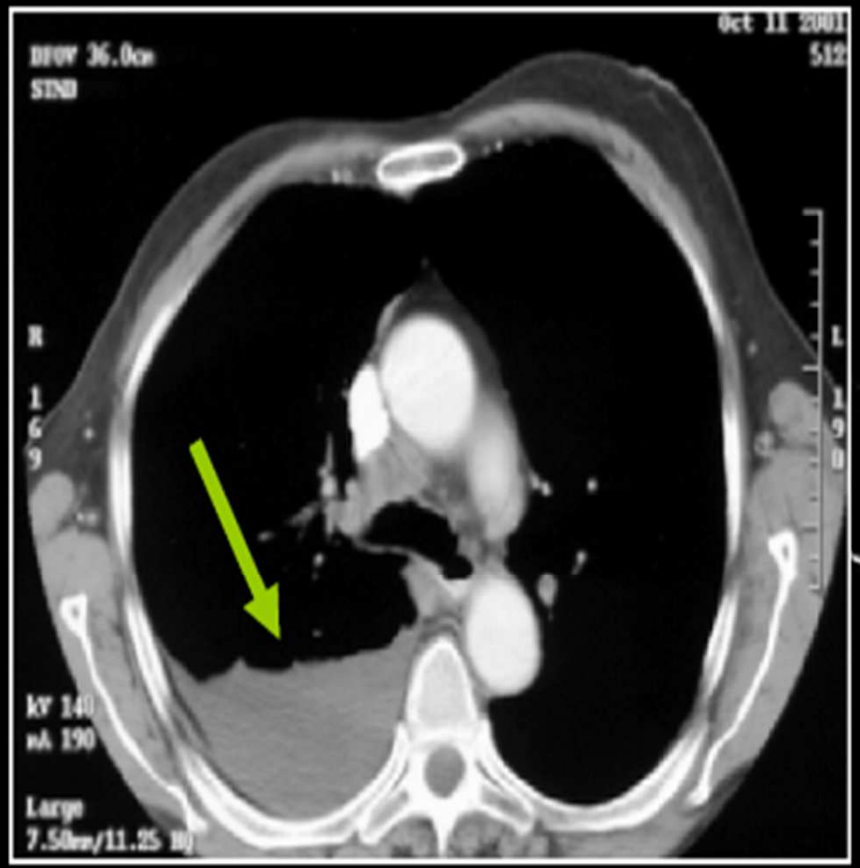
- Lesions too small to qualify as targets (<10mm)
- Lymph nodes smaller than measurable size (short axis 10 to <15mm)
- All other lesions including:

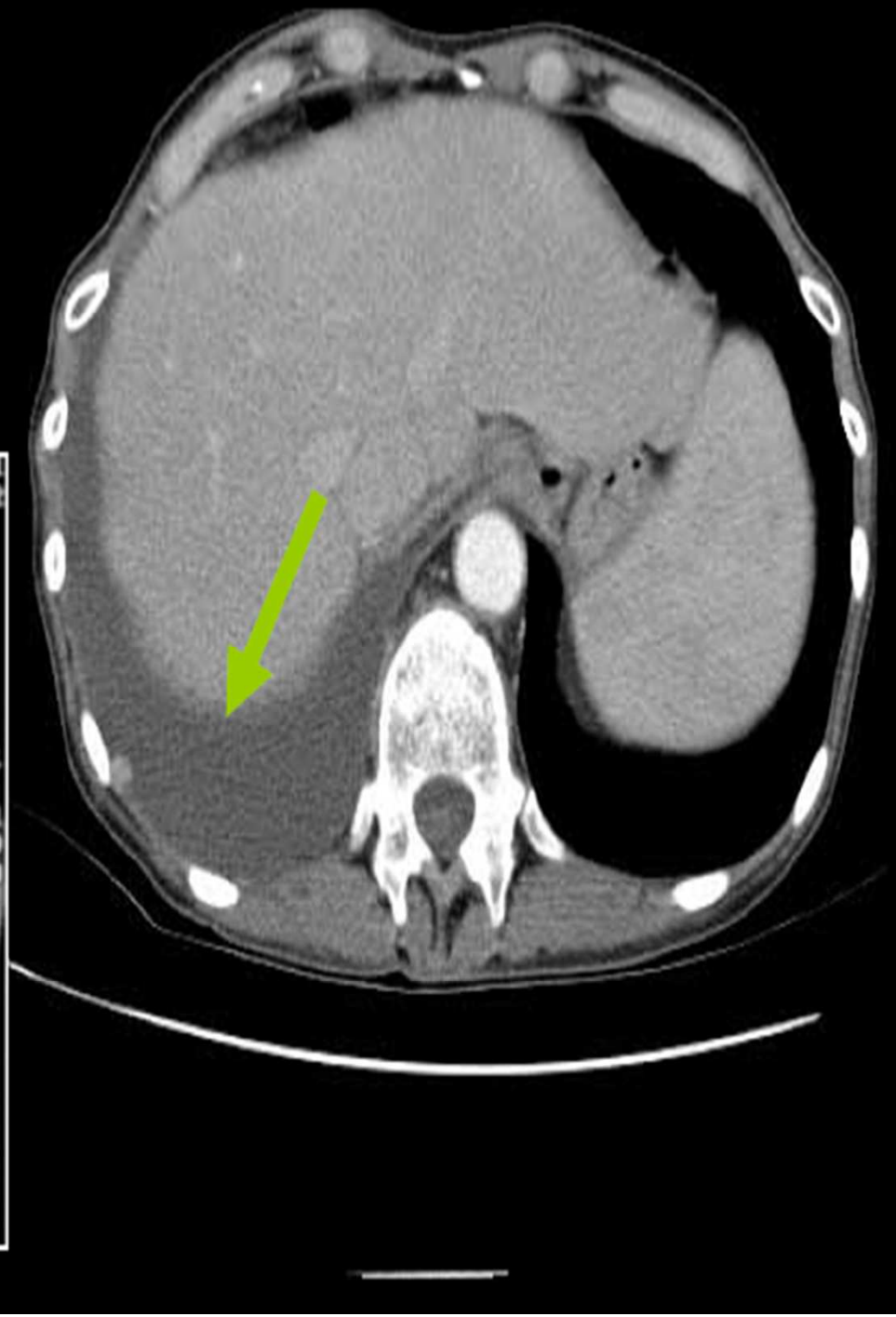
1. Bone lesions,
2. Leptomeningeal disease,
3. Ascites, Pleural/ Pericardial effusion,
4. Inflammatory breast disease,
5. Lymphangitis cutis / pulmonis,
6. Abdominal masses that are not confirmed and followed by imaging techniques,
7. Cystic lesions.



Select lesions that can be accurately measured throughout all follow-up scans

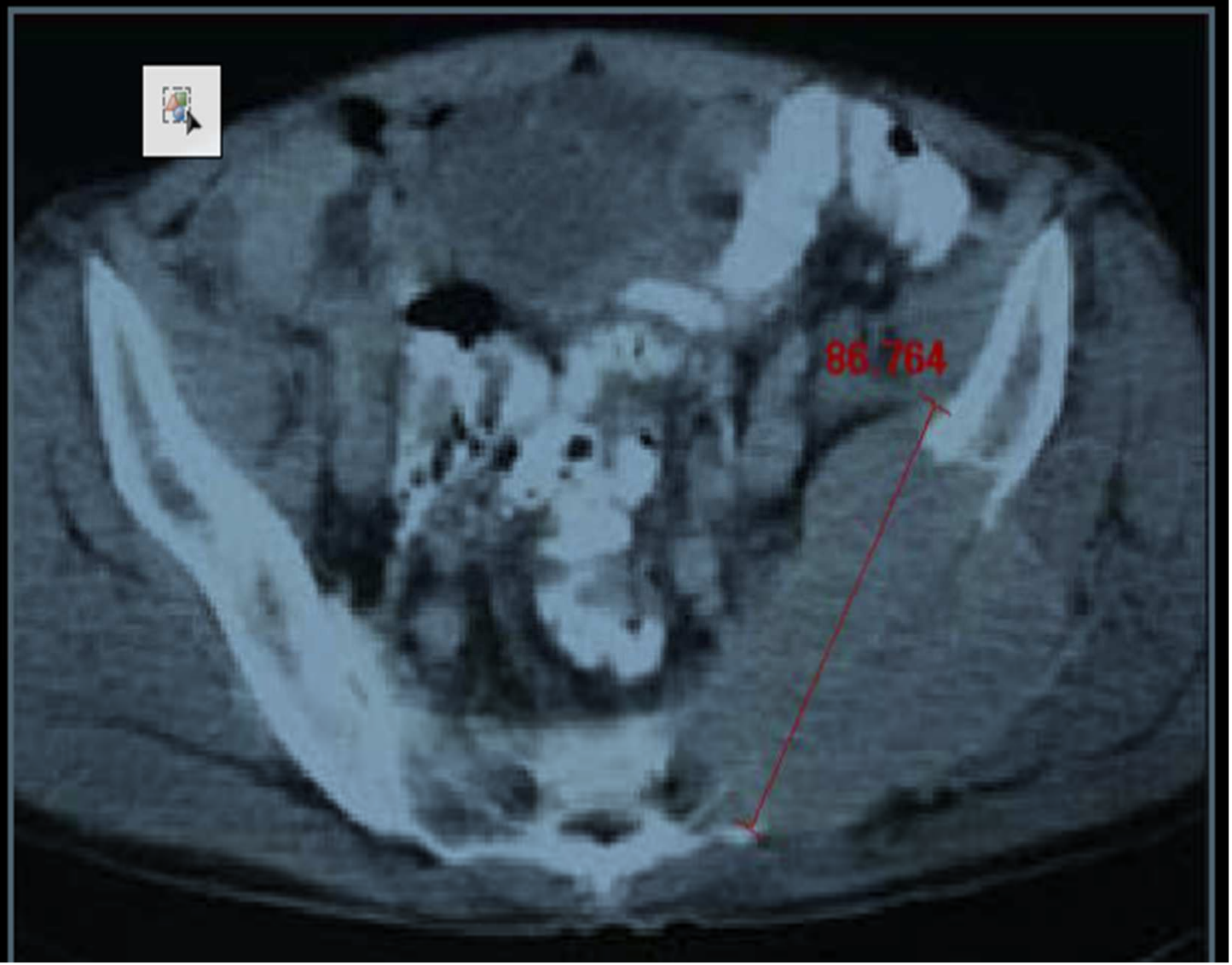
Pleural effusion, ascites are **non-measurable**





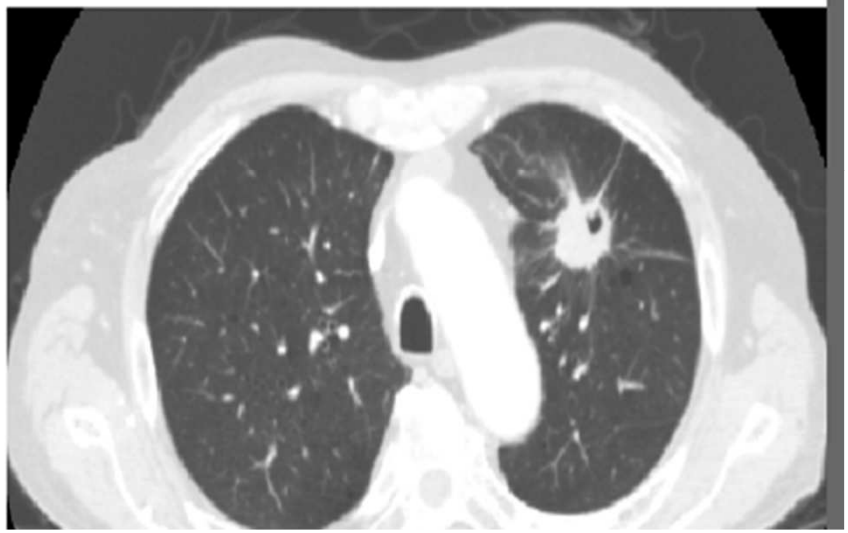
Blastic, sclerotic bone
lesion is **non-measurable**

Lytic bone lesion with soft tissue mass is **measurable**



Timepoints:

- **Baseline / Screening:**
  - within 21 days prior to treatment
- **Follow-Up:**
  - every 6 weeks (± 3 days)
- **End of Treatment/ early discontinuation:**
  - After 4 weeks (discontinuation due to PD, or early discontinuation)



IMAGING MODALITIES

- **CT Scan:**

Investigation of Choice.

Minimum size of lesion should be no less then double the slice thickness to avoid “partial volume“ effect.

Longest diameter should be selected for target lesion.

IV /Oral Contrast to be given.

Both Soft tissue and lung window are included.

IMAGING MODALITIES-Cont.

- X-Ray:

Should be done full inspiration with PA view.

Constant film to tube distance to be maintained.

Clearly defined lesion with surrounded normal lung tissue.

- USG:

Not ideal as it is subjective and entire examination cannot be reproduced for independent review at later time.

Hardcopies of the film don’t represent true and accurate reflection of the event.

- MRI

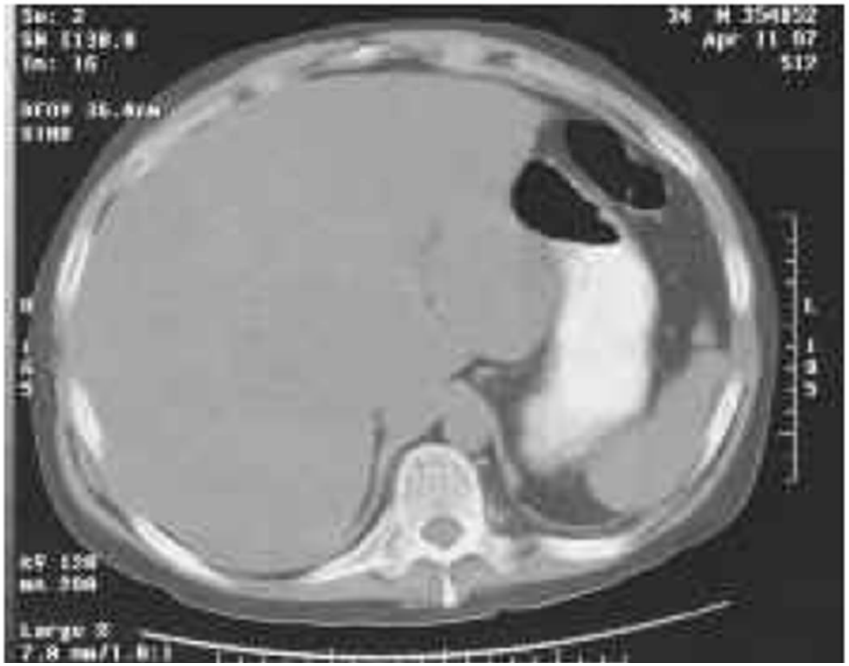
MRI should be done where CT is not feasible or medically contraindicated.

IMPORTANCE OF CONTRAST

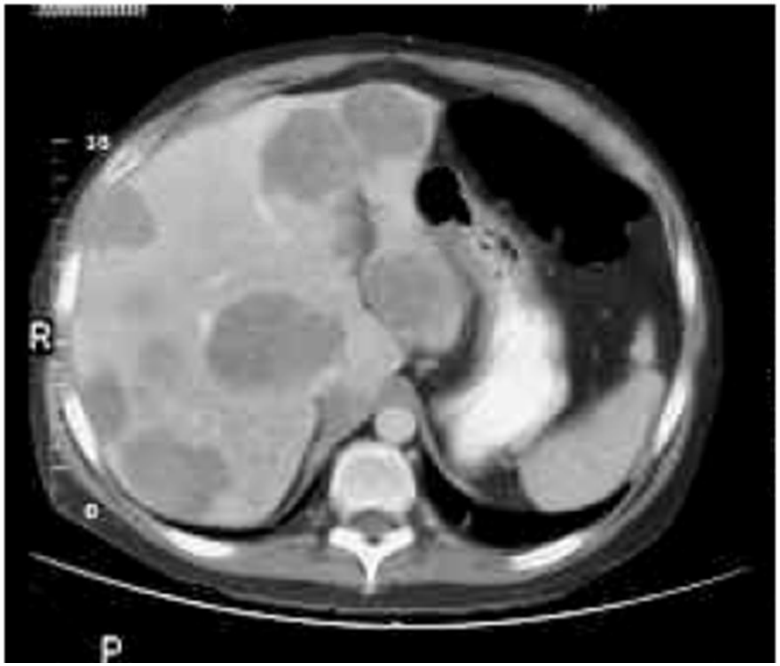
IV contrast should be consistently administered

- If no IV contrast, lesion assessments may not be possible or may be inaccurate
- Enter a comment on Image Transmittal Form (ITF) noting contraindications to IV contrast

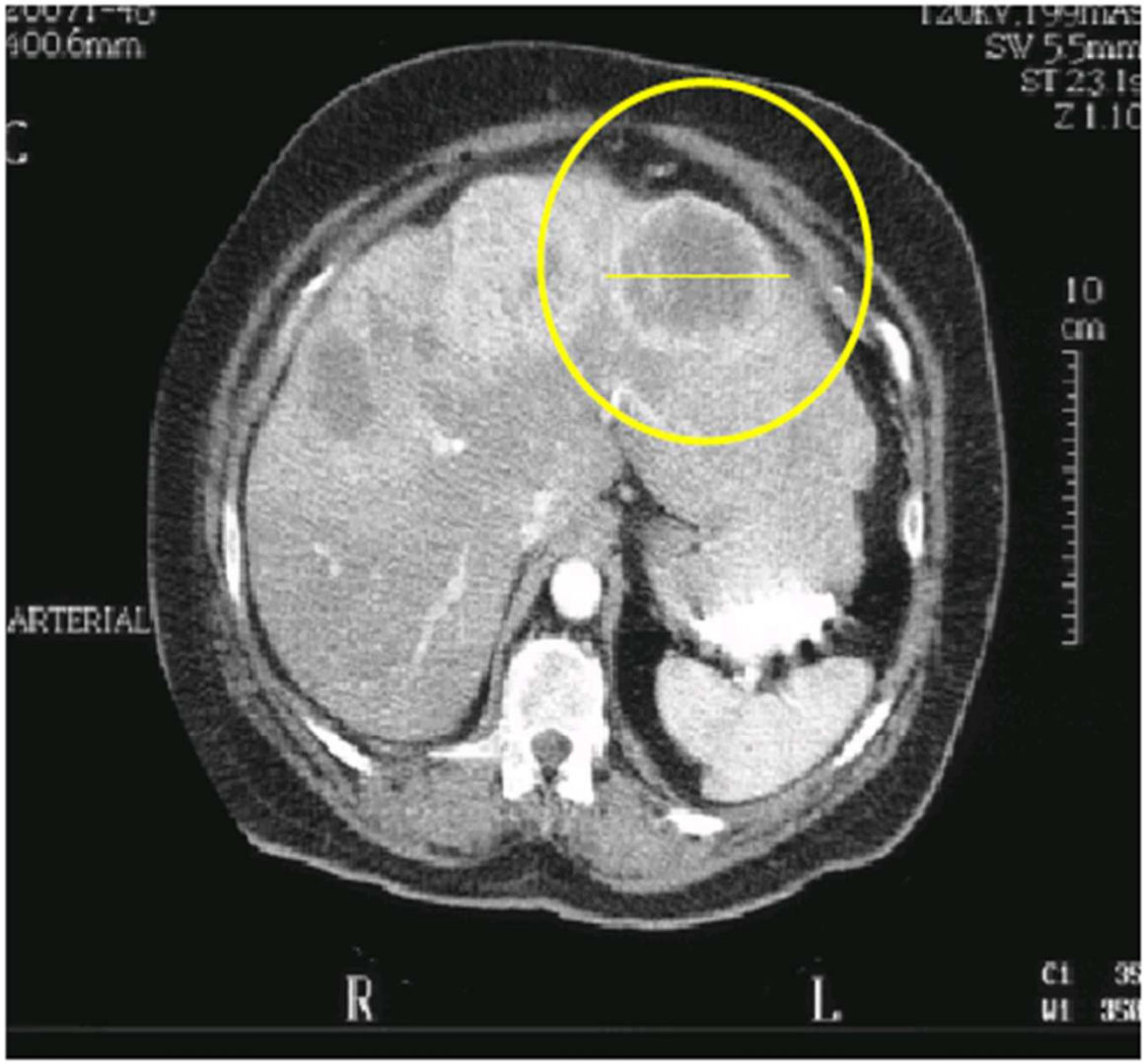
No IV Contrast



IV Contrast

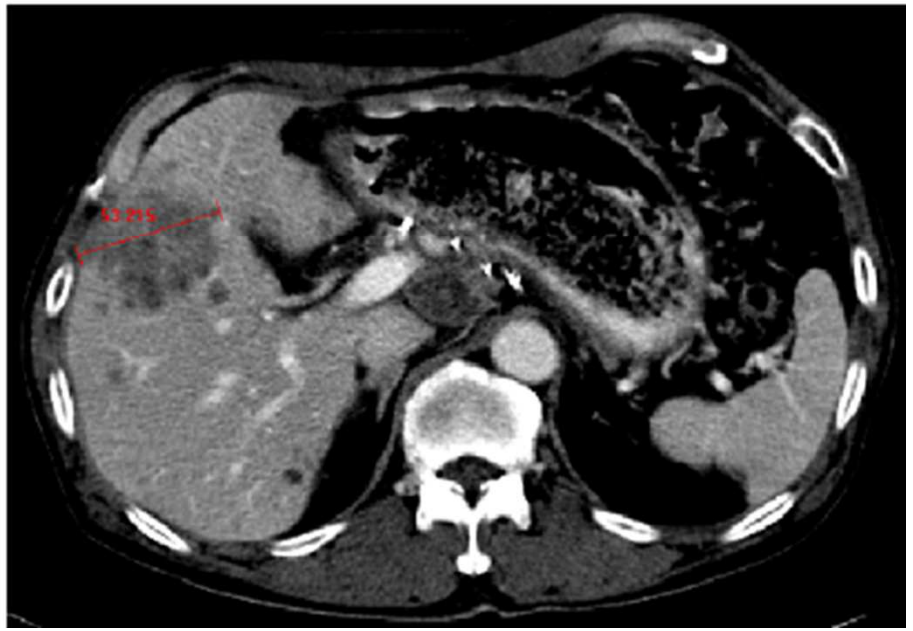


- Include the hypervascular "enhancing rim", if present, in the longest diameter measurement



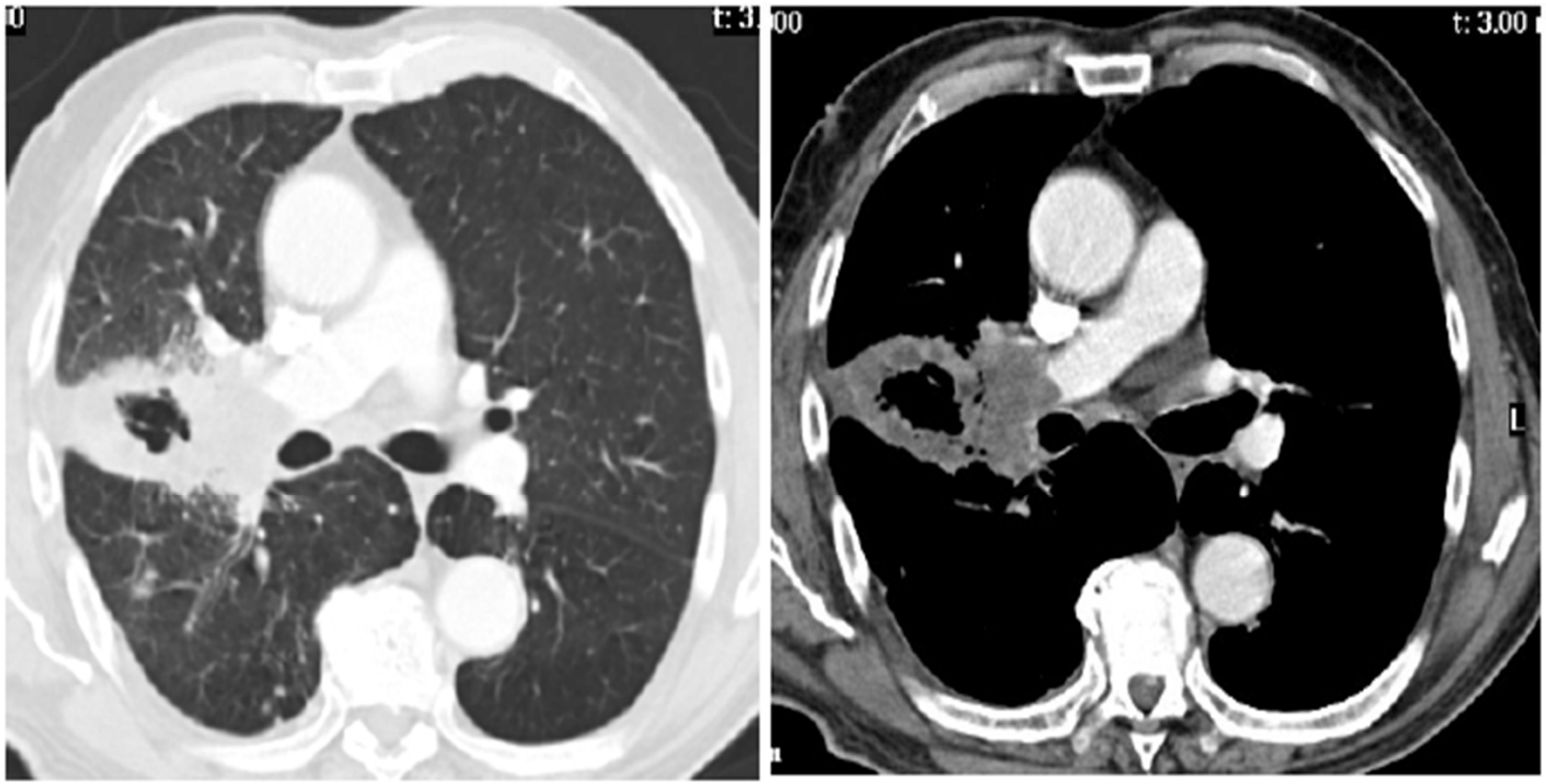
TARGET MEASUREMENT RULE

- Choose the slice where the target lesion is largest
- Always measure the longest diameter of the target lesion
- Target nodes measured in the SHORT axis
- → SOD (no longer SLD)
- Liver lesions by CT should be preferably measured on **portal venous phase** images



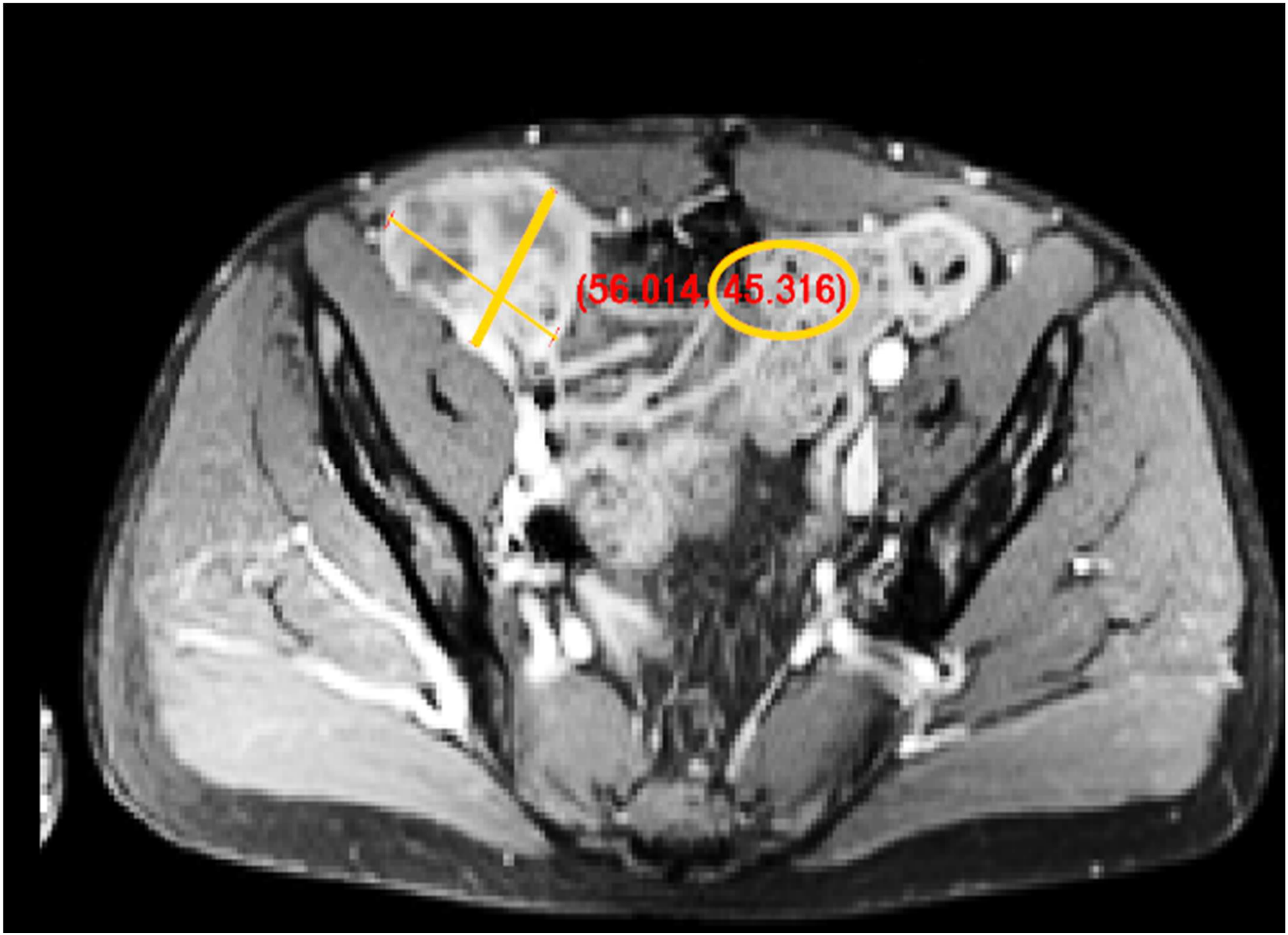
Measurable Lesions

- Accurately measurable in at least **one dimension** (longest diameter)
- Must be: tumour, large enough, well defined.



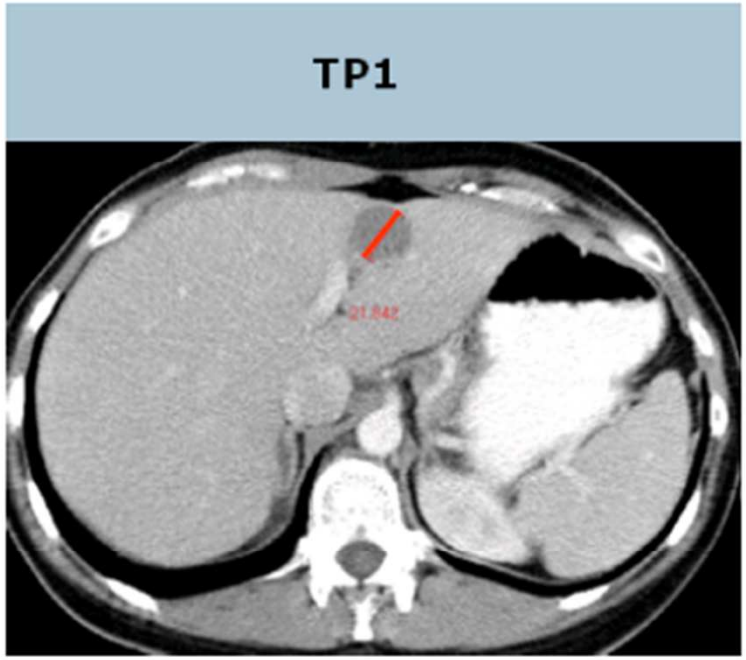
Assessment of Lymph Nodes:

- **Normal**: short axis **<10mm**
- **Non measurable** = non-target: short axis **>10mm - <15mm**
- **Measurable** (possible target): short axis **≥15 mm**
  - Target nodes measured in the SHORT axis (perpendicular to longest diameter)
    - More reproducible and predictive of malignancy
  - Short axes of target nodes to be added to the SOD


(56.014, 45.316)

TARGET MEASUREMENT AT FOLLOW UP

- Choose the slice where the target lesion is largest, **even if it is different from baseline**



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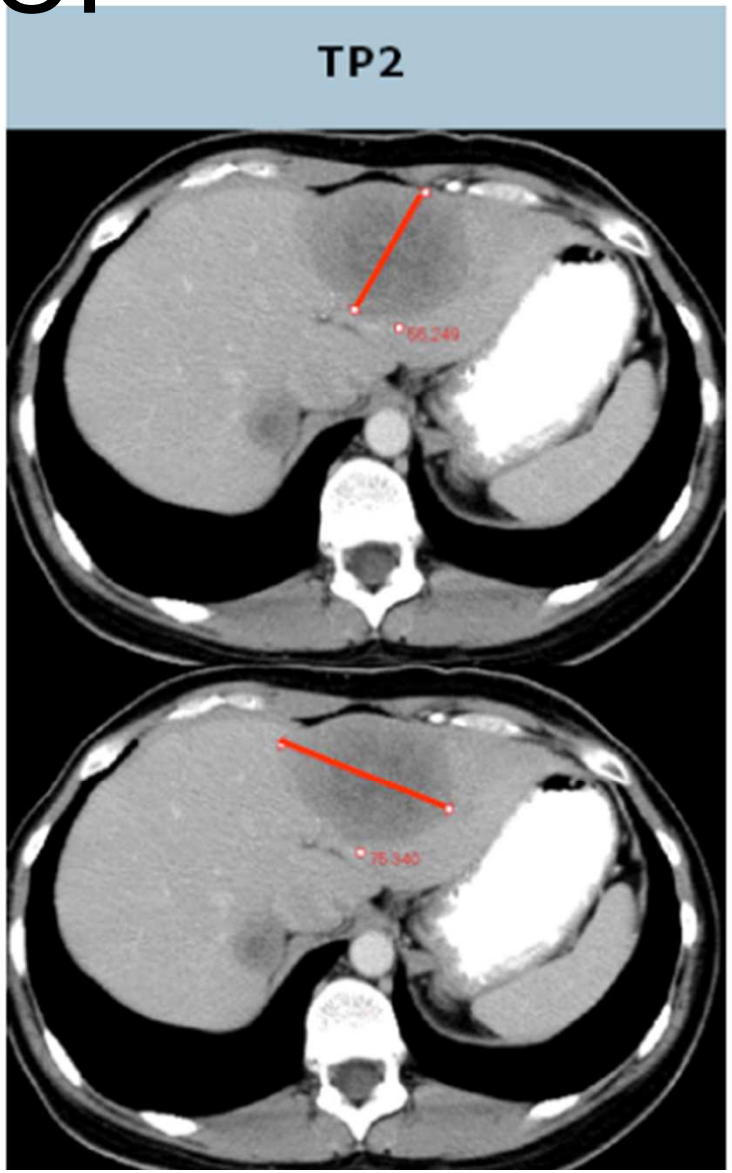
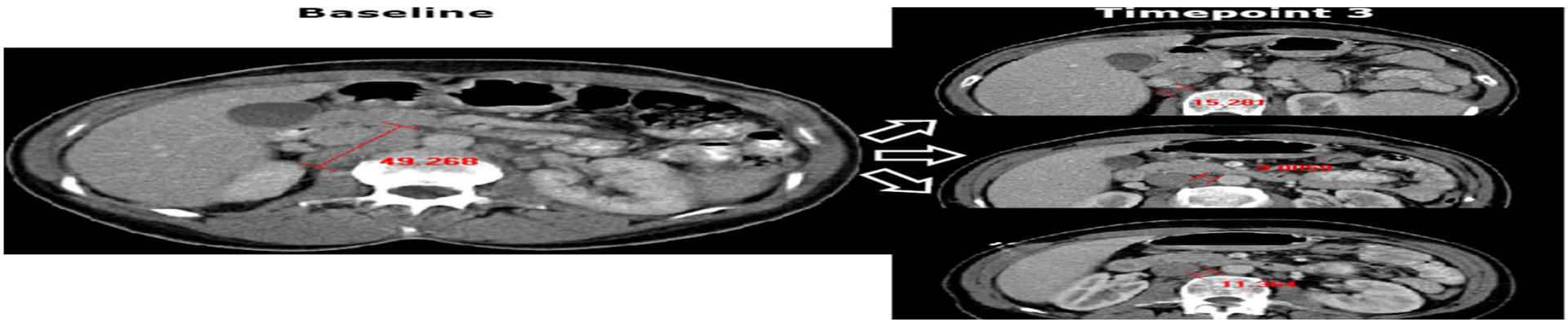


- The longest diameter of the lesion should be measured **even if the actual axis is different from baseline**

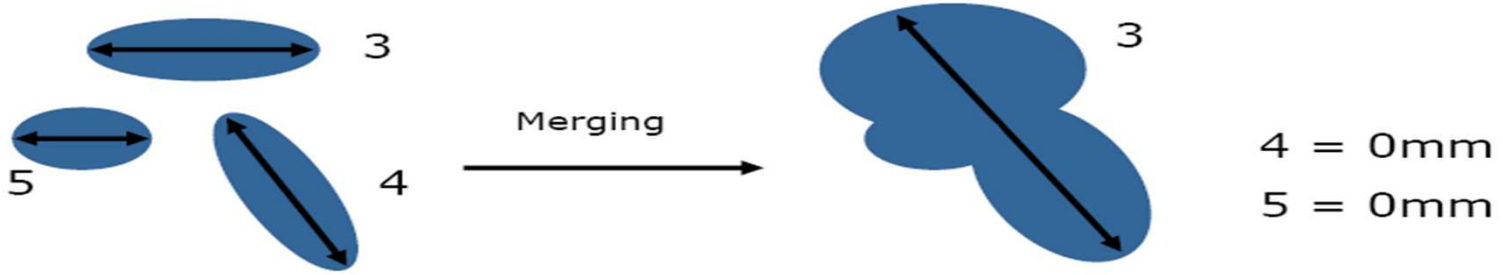
SPLITTING LESIONS

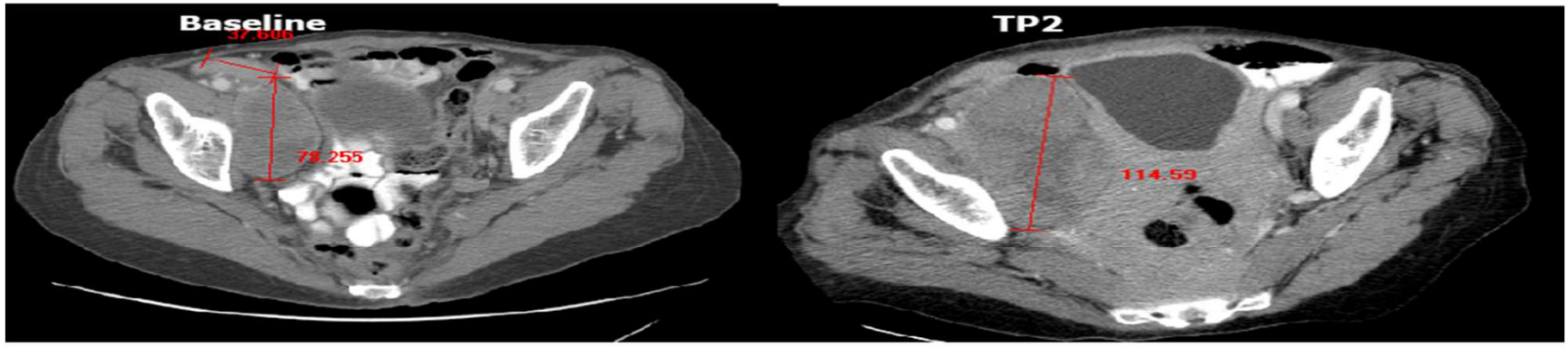
- If a target lesion separates, each lesion should be measured separately and contribute to the SOD
- The child lesion(s) shall be labeled separately to the "parent" lesion *(e.g., #3 → #3 + #3a +#3b)*
- The individual longest diameters of all the resulting lesions shall contribute to the SOD



MERGING LESION

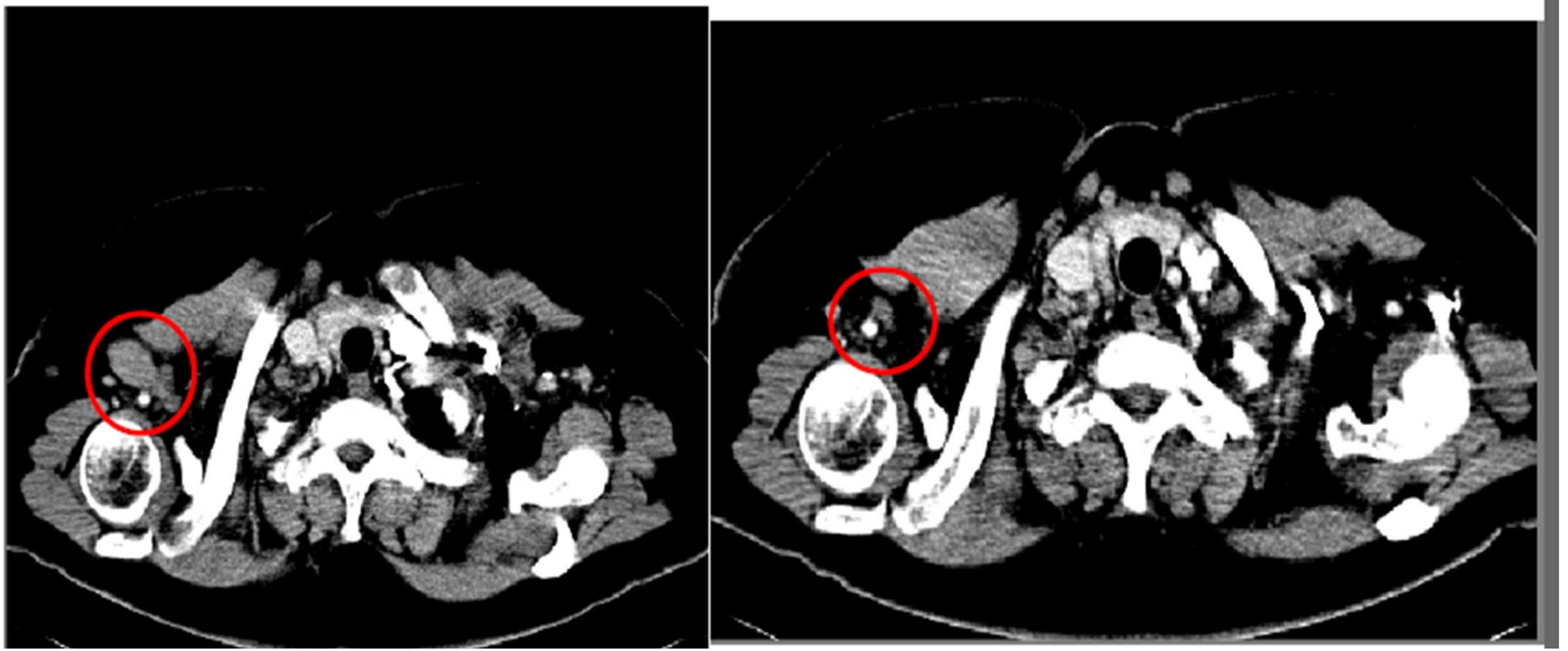
- If lesions become confluent, calculate and record the longest diameter of the resulting mass





The individual longest diameters of all the resulting lesions shall contribute to the sum of diameters (SOD)

- Any pathological lymph nodes must have decreased in size to have a **short axis of <10 mm**
  → the SOD will potentially not be “0 mm”



RECIST : Response Evaluation

- **Response Criteria**

1. Evaluation of *target lesions* :

✓ Measurement of the longest diameter only for all target lesions.

✓ Complete response : Disappearance of all target lesions.

✓ Partial response : At least a 30% decrease in the sum of the longest diameter of target lesions

✓ Stable disease : Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

✓ Progressive disease : At least a 20% increase in longest diameter of target lesions. (ref. smallest sum longest diameter)

Tumor Response Evaluation

➢ ***Evaluation of non target lesions*** **:**

- **Complete response** :
- Disappearance of all non target lesions.
- Normalization of tumor marker level.
- **Incomplete response/stable disease**:
- Persistence of one or more lesion (s).
- Elevated tumor marker level above the normal limits.
- **Progressive disease** :
- Appearance of one or more new lesions.
- Unequivocal progression of existing non target lesions.

Tumor Response Evaluation

➢ **Evaluation of best overall response :**

- Best response from the start of treatment until disease progression/ recurrence.

Target	Non- Target	New	Overall response
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Y/N	PD
Any	PD	Y/N	PD
Any	Any	Yes	PD

Not Evaluable (NE)

- An assessment cannot be made due to **poor image quality** or missing target lesions
- When **no imaging**/measurement is done at all at a time point, the patient is not evaluable (NE) at that time point
- If only a subset of lesions' measurements (**incomplete imaging**) are made at an assessment, usually the case is also considered **NE** at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

NEW LESION

- Lesions that appear after BL = new lesion.
  Irrespective of size, in the same organ or different organ, which was not imaged at BL = new lesion.
- Lesions that re-appear after CR assessment are considered new = PD
- In the setting of PR or SD, if a lesion disappears and reappears at a subsequent time point it should continue to be measured. Response will depend upon the status of other lesions. The lesion should simply be added into the sum.
- Lymph nodes that were normal size at prior time point and grow or regrow are considered new lesions (>10mm)
  - 5mm⇧ absolute!

RECIST Criteria .. Disadvantages

- Variability in image acquisition.
- RECIST makes no provision for total volume of disease.
- RECIST excludes bone and mediastinal structures, and hematologic malignancies.
- Number of target lesions may not account for the full burden of disease.
- The edges of irregular or infiltrating lesions are often difficult to identify.
- Its difficult to distinguish peritumoral fibrosis from tumour spread at times.
- Parameters chosen for evaluation must be relevant to the biological action of the treatment being assessed.

RECIST Criteria .. Disadvantages

- Measurements difficult in spherical tumors viz. gastric and breast tumor.
- Mammography and Barium swallow not included.
- Consideration of site of metastatic lesion.
- Exclusion of target lesions having a diameter of less than 2.0 cm.
- Uni-dimensional measurement has a lower correlation with tumor volume value than the bi-dimensional measurement.

Take home message

- Measurable tumor lesions must be accurately measured at least one dimension with a minimum size of
  - 10mm by CT Scan where slice thickness 5mm
  - 10 mm caliper measurement
  - 20mm by chest x-ray
  - >/ 15 mm lymphnodes in short axis as target lesions.

- CT preffered over X-Ray chest .
  - MRI in selected case
- When more than one measurable lesions present at baseline,all lesions up to maximum 5 lesions total and maxm.2 les ion per organ to be identified

- **TAKE HOME MESSAGE**

  - Target lesions should be based on size(Lesion based on longest diameter)
  - Lymph nodes measured based on short axis diameter
  - Lymph node <10 mm:-non pathological
  - Lumph node >15 mm :- pathological
  - Negative PET at base line ,+ve at follow up are signs of PD
  - No PET at baseline,+ve at follow up
  - If positive pet correspoond to new site of disease;PD
  - If positive PET not confirmed as new site- Follow up CT

CT

Reporting Adverse Event and Serious Adverse Event

What is an Adverse Event (AE)?

- **Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research.**
- **An AE may be expected or unexpected, related or unrelated to the subject's participation in the research, local or non-local, and serious or not serious.**

- **The study investigator is responsible for determining the status of an event.**

What is a Serious Adverse Event (SAE)?

An *SAE* is an event that results in any of the following outcomes:

(1) fatal (death);

(2) life-threatening;

(3) inpatient hospitalization or prolongation of existing hospitalization;

(4) persistent or significant disability/incapacity;

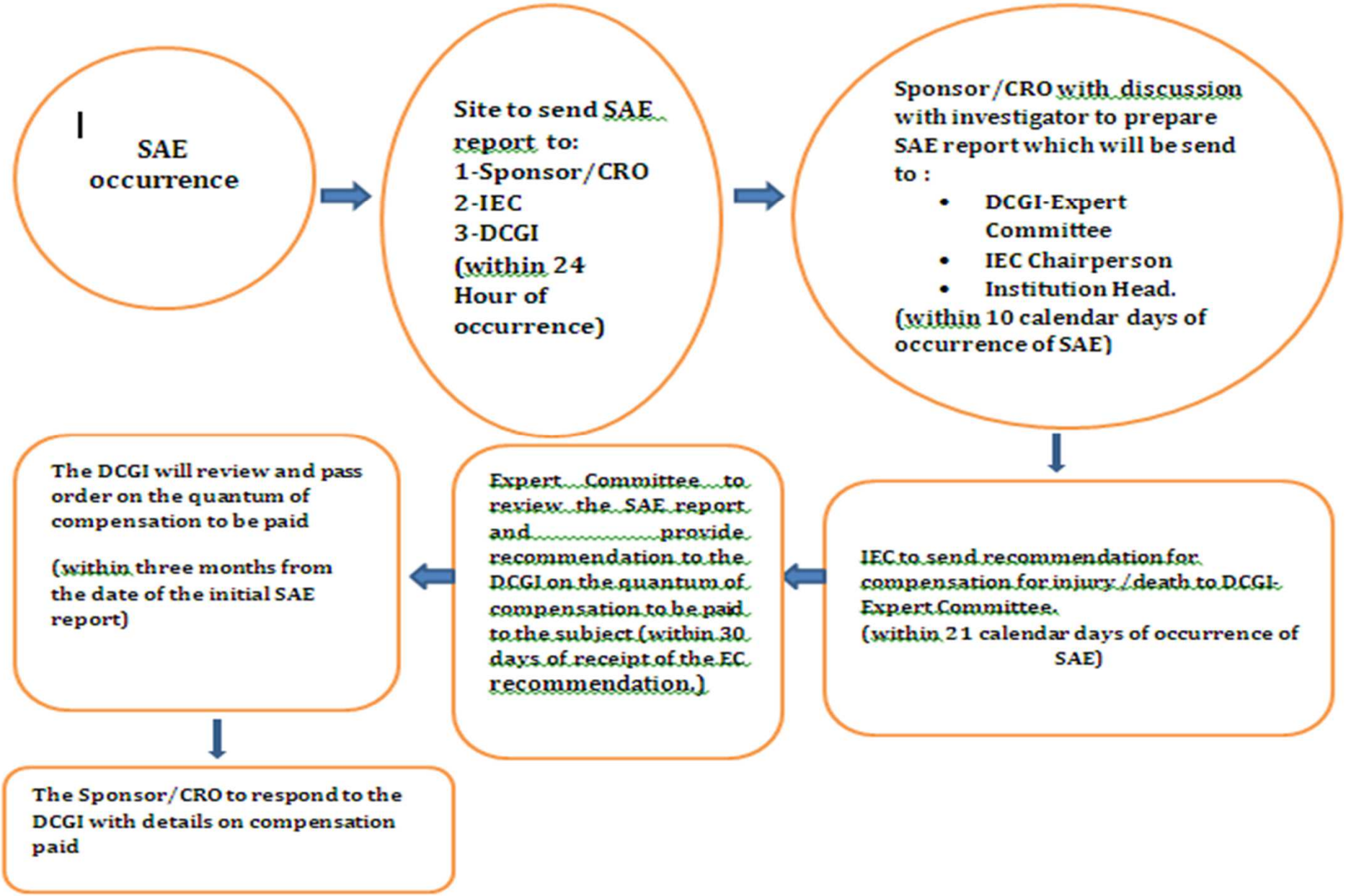
(5) congenital anomalies or birth defect; or

(6) any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

AE reporting

- All the AE at site and outside the side need to be captured in source document at site and the same need to be transcribed into the CRF.
- The site may notify the same to the IEC.

SAE reporting



Common Toxicity Criteria Adverse Events (CTCAE)

Background:

- 1982/1983: Common Toxicity Criteria (CTC) used to aid in the recognition and grading severity of adverse events (AE) of **chemotherapy**

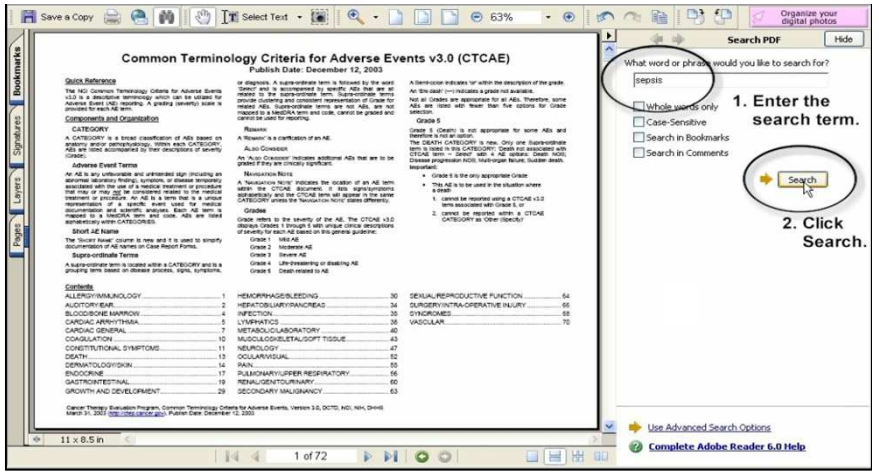
– List of AE terms commonly encountered in oncology and each AE is accompanied by a grading (severity) scale

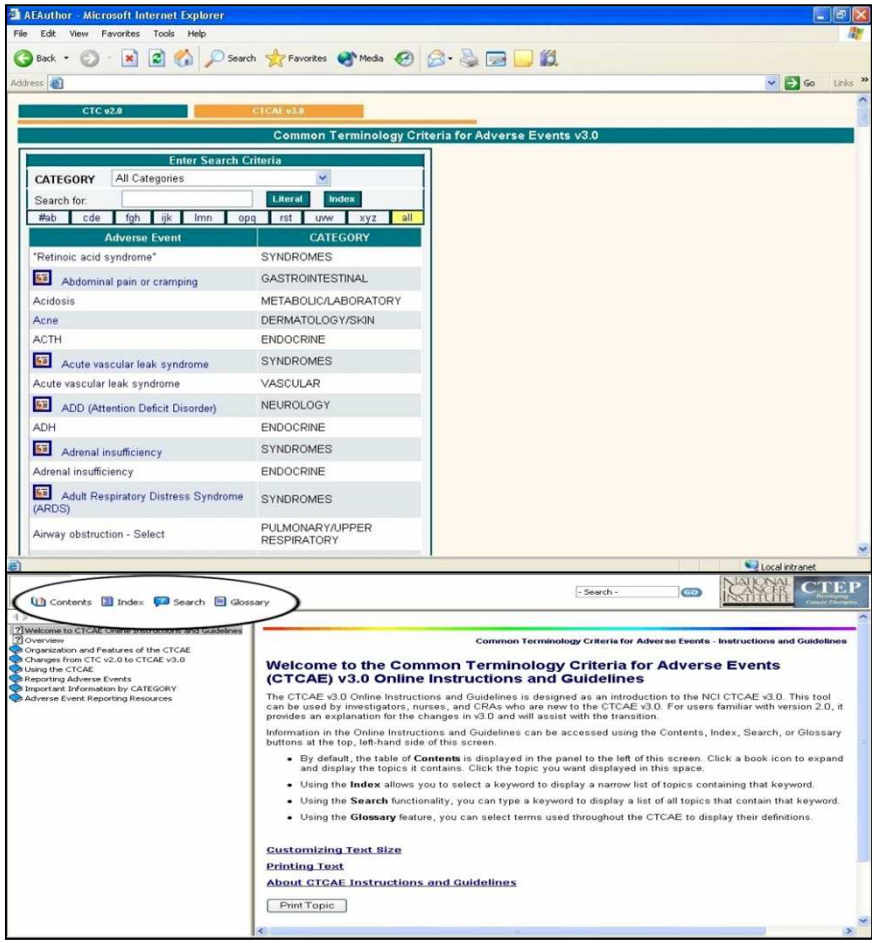
– Fundamentally intended to be an agreed upon terminology for the designation, reporting and grading of AEs that occur in oncology research

Available Tools

The following are the tools available for determining correct AEs.

- Section 1: CTCAE v3.0 Document Search
- Section 2: CTCAE Dictionary and Index
- Section 3: CTCAE Online Instructions and Guidelines
- All tools are available from the CTEP Home Page at http://ctep.cancer.gov






Thank You!