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U.S. FOOD & DRUG ADMINISTRATION

Unblinding – let me count the ways……..

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Learning Objectives

- To understand
  - Basics of how data flows through various systems as it is collected, integrated, transformed, analyzed and reported for clinical trials
  - There are many ways in which clinical trial data may be unintentionally unblinded
  - Premature unblinding of data that permits identification of subjects' treatment allocation may raise significant concerns related to the adequacy of data integrity and data quality for a clinical trial

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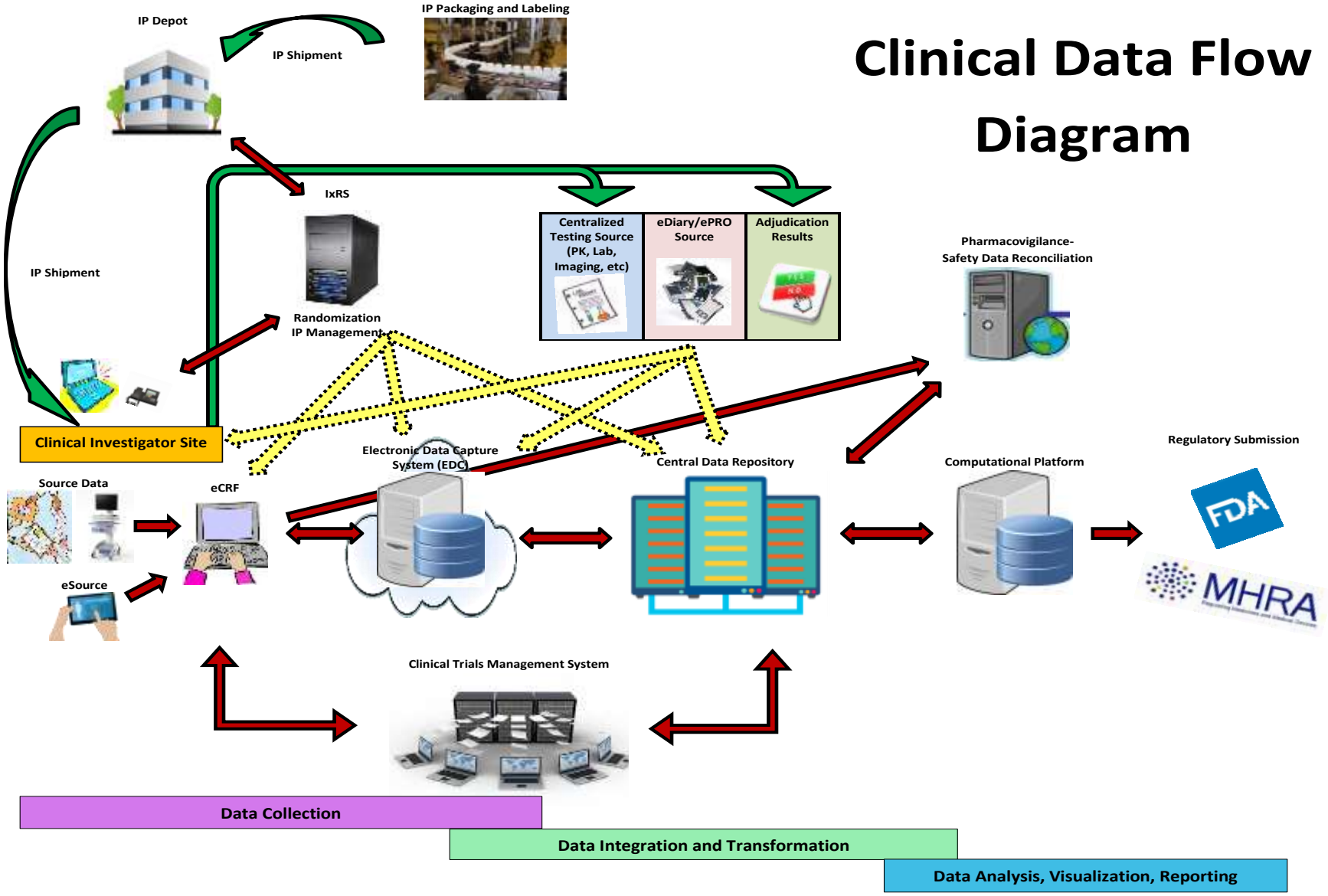
Clinical Data Flow Diagram



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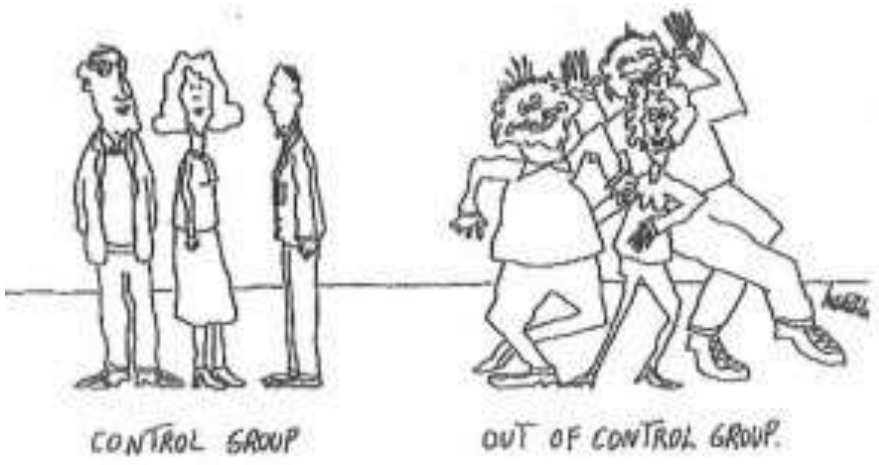
Why Blind?

- Reduce bias
- Prevent conduct of aggregate analyses by treatment group prior to database lock
- Protect the blind to maintain the integrity of the data



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Considerations

- Appearance of the Investigational Medicinal Product (IMP) – matching placebo possible?
- Obvious and known side effects
- Known effect on laboratory results
- Reports such as adverse events, IRT, internal reports
- Batch numbers/lots numbers, Kit numbers, Expiry dates
- Data Masking procedures
- User access

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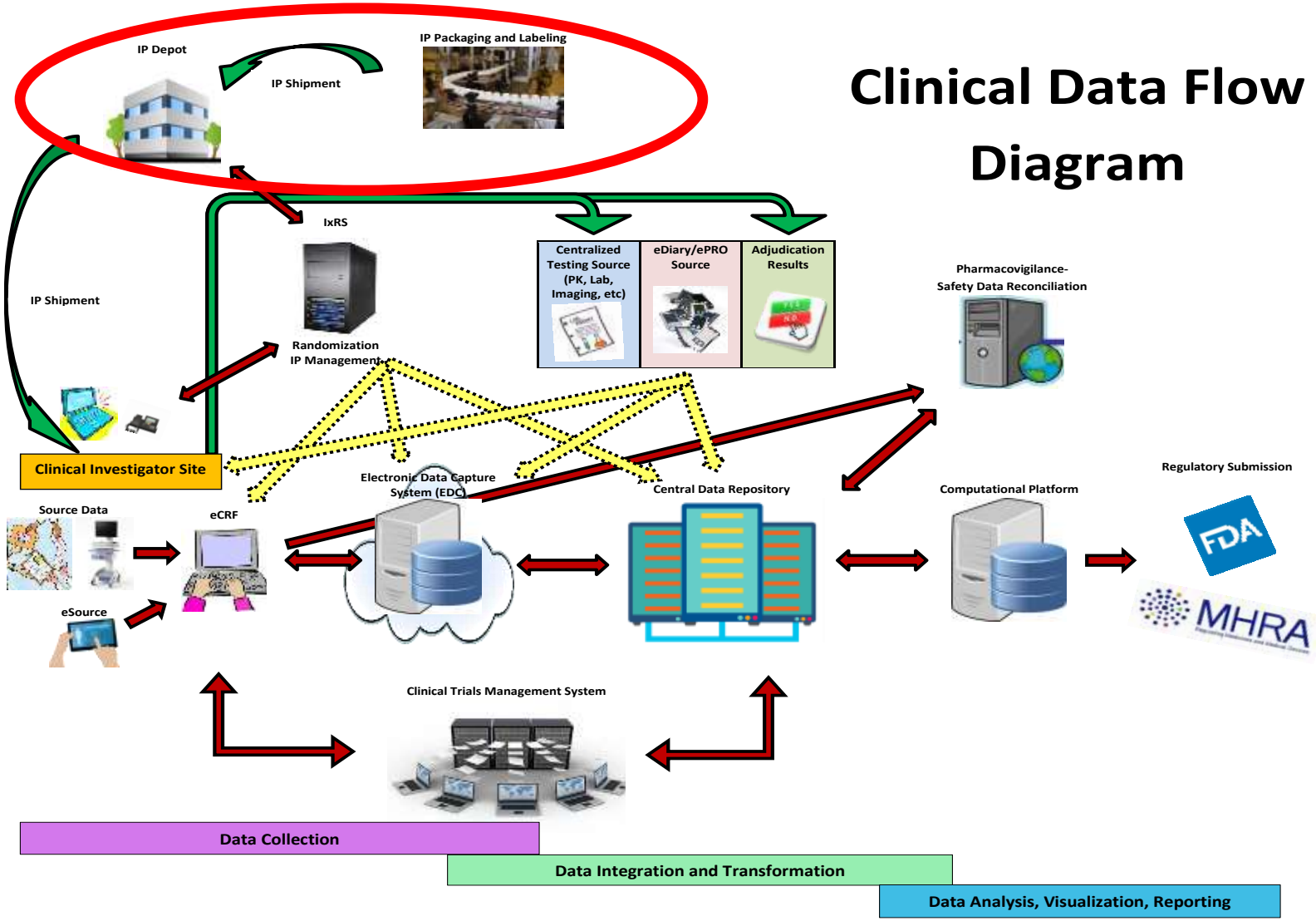
IMP Preparation and Labeling



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Examples – IMP Preparation and Labeling

- Numbering patterns may permit subjects, site staff, study team to guess treatment group
  - Batch numbers/lots numbers
  - Expiry dates
  - Kit numbering

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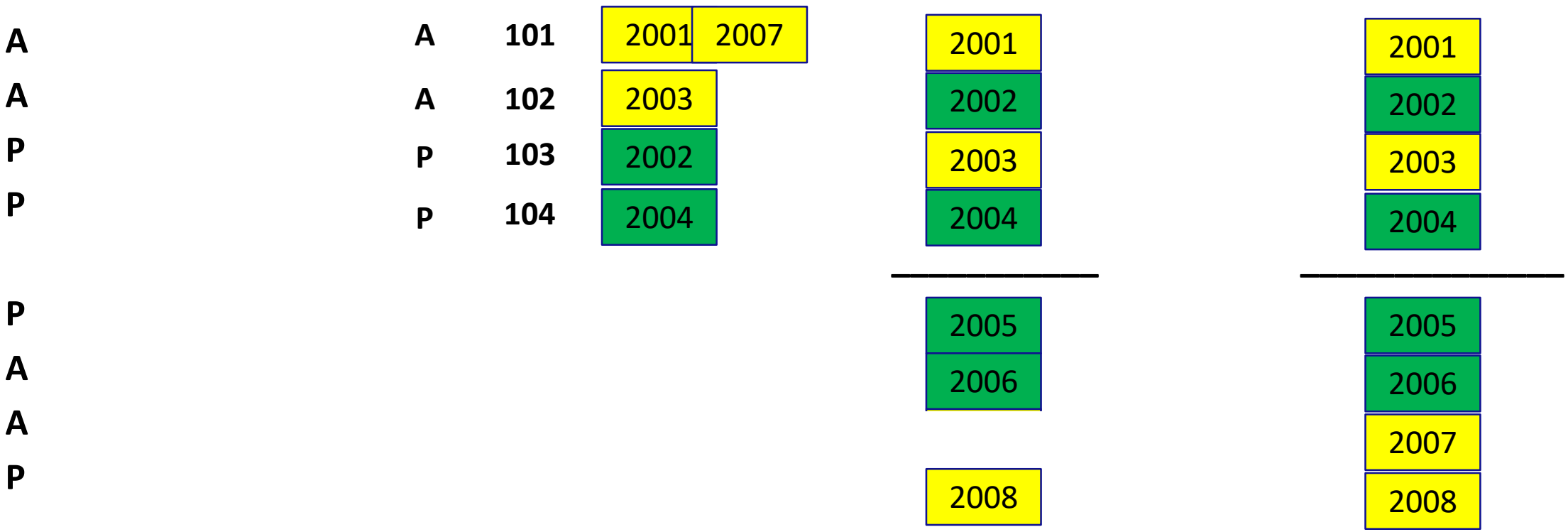
Example – Sequential Kit Numbering



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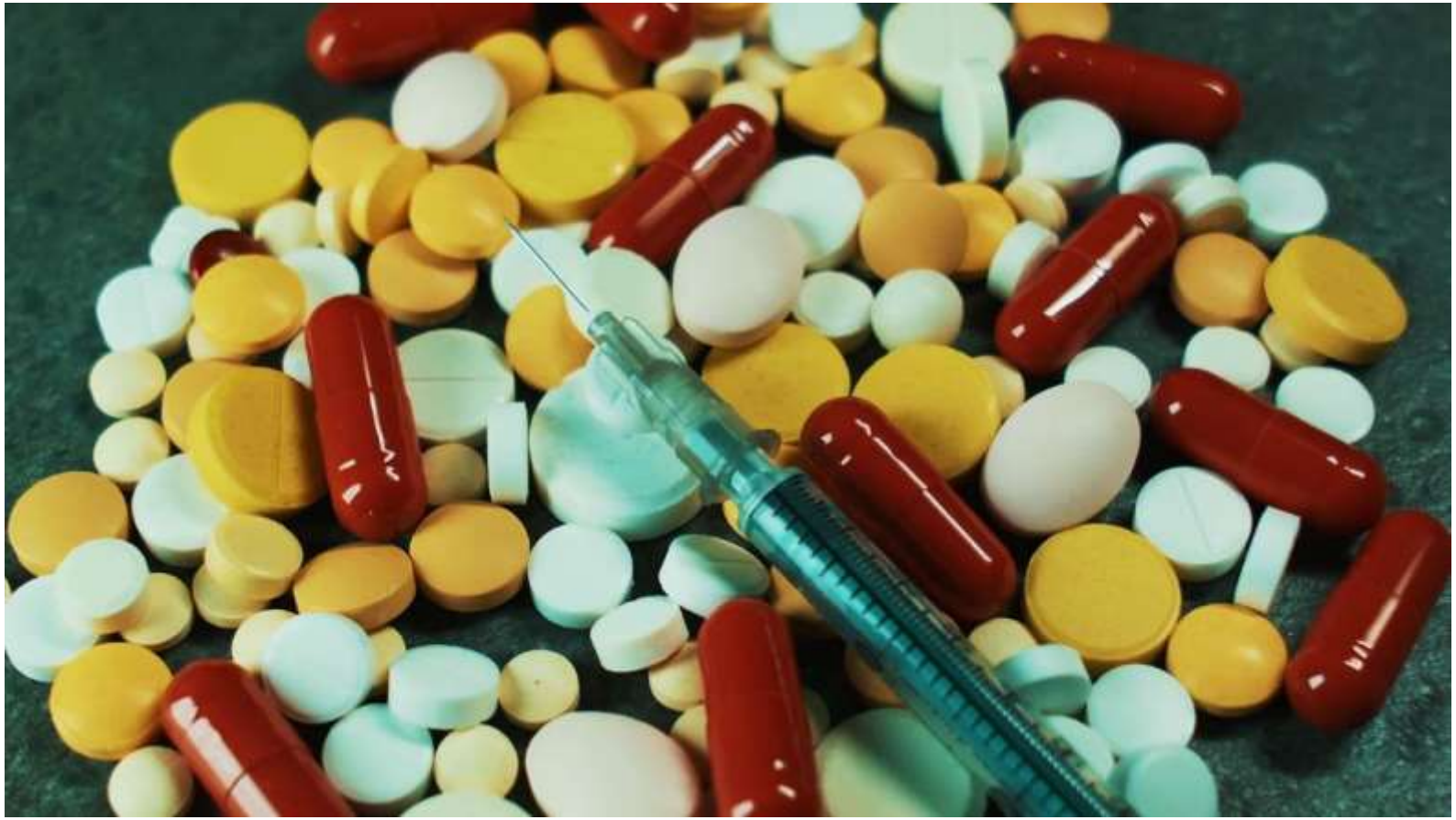
Investigational Medicinal Product Presentation



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Example – IMP

- The placebo was green lactose filled capsules, different to the active IMP which was a film coated tablet with letters stamped on one side and 80 stamped on the reverse.
- IMP was contained in a brown glass jar, from which the IMP could be immediately identified. The trial was a **double-blind cross-over** design, therefore, the patients received both medications, and thus could potentially easily differentiate between which was active and which was placebo.
- The primary endpoint was a patient completed outcome questionnaire, which the unblinding could easily have resulted in the introduction of bias when answering the questions.

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Example – IMP

- It was possible to determine the contents (either active or placebo) from the expiry date stated on the IMP label. The expiry date could then be checked against the certificates of analysis provided by the manufacturer (held in the site master file) therefore revealing the treatment assignment (envelopes dated 30/Mar/13 could be linked to the placebo and envelopes dated 30/Jun/13 could be linked to active).

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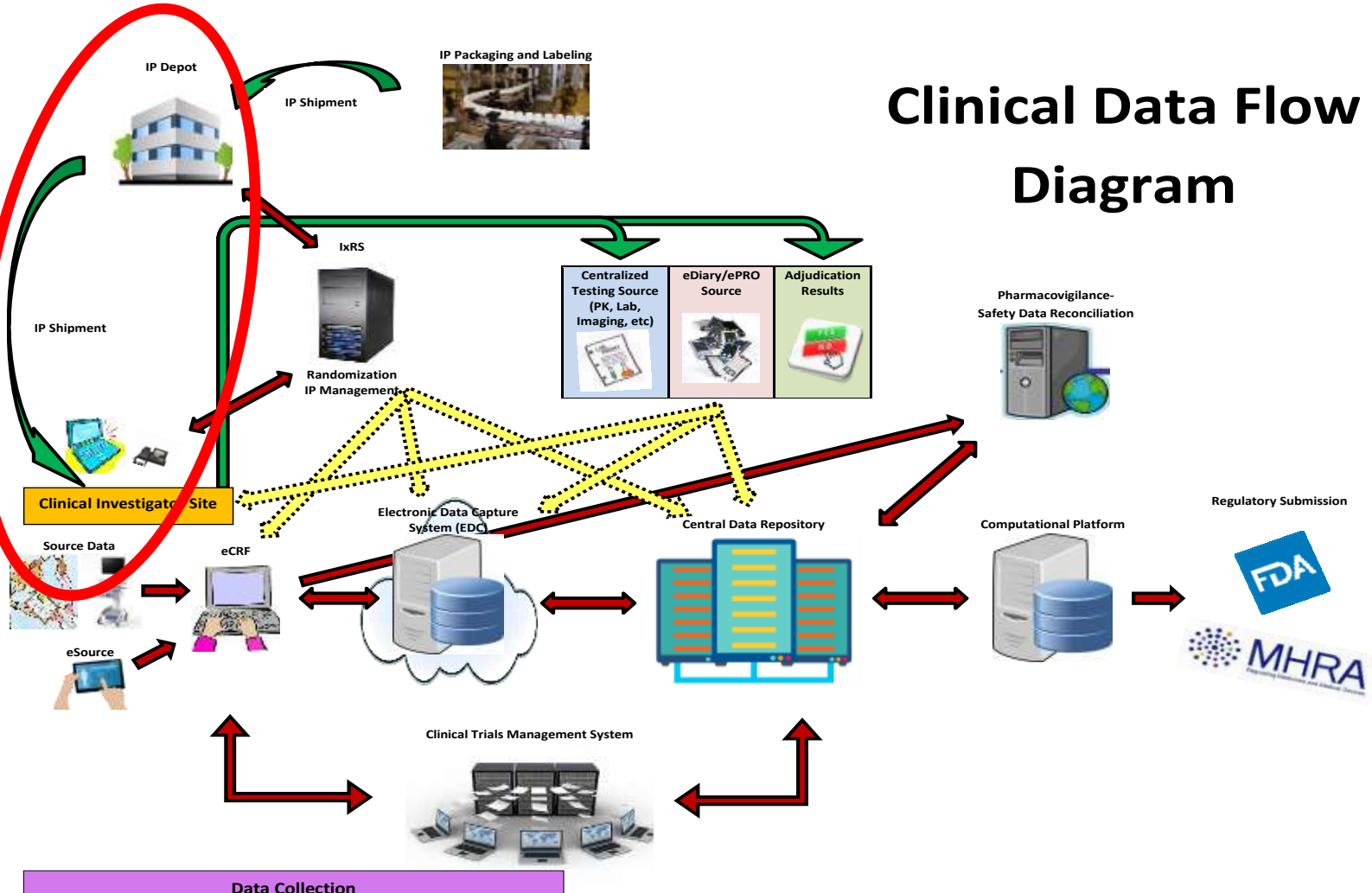
IMP Shipping Issues



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Examples – IMP Shipping Issues

- Documentation included in shipments to sites included Kit numbers by Lot/Batch numbers with actual expiry dates (can derive which subjects in different treatment groups by reviewing Certificates of Analysis in site files)
- Shipments containing unblinded IMP documentation or reports sent to blinded site staff instead of unblinded site pharmacy staff

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Example – Site personnel

- CRAs and study nurses
  - Prepared and randomized the (blinded) IMP

  BUT

  - Also performed blinded study assessments (reviewed test results, reported SAEs etc)

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Example – Site personnel

- Investigator site file contained cards showing treatment assignments, i.e. investigators had access to the randomization schedule
- The treatment assignment cards were also found stapled in the subjects' medical records
- Resulted in the treatment assignment of creams to 8 patch test areas' cards being available in the room where the investigator was making skin assessments

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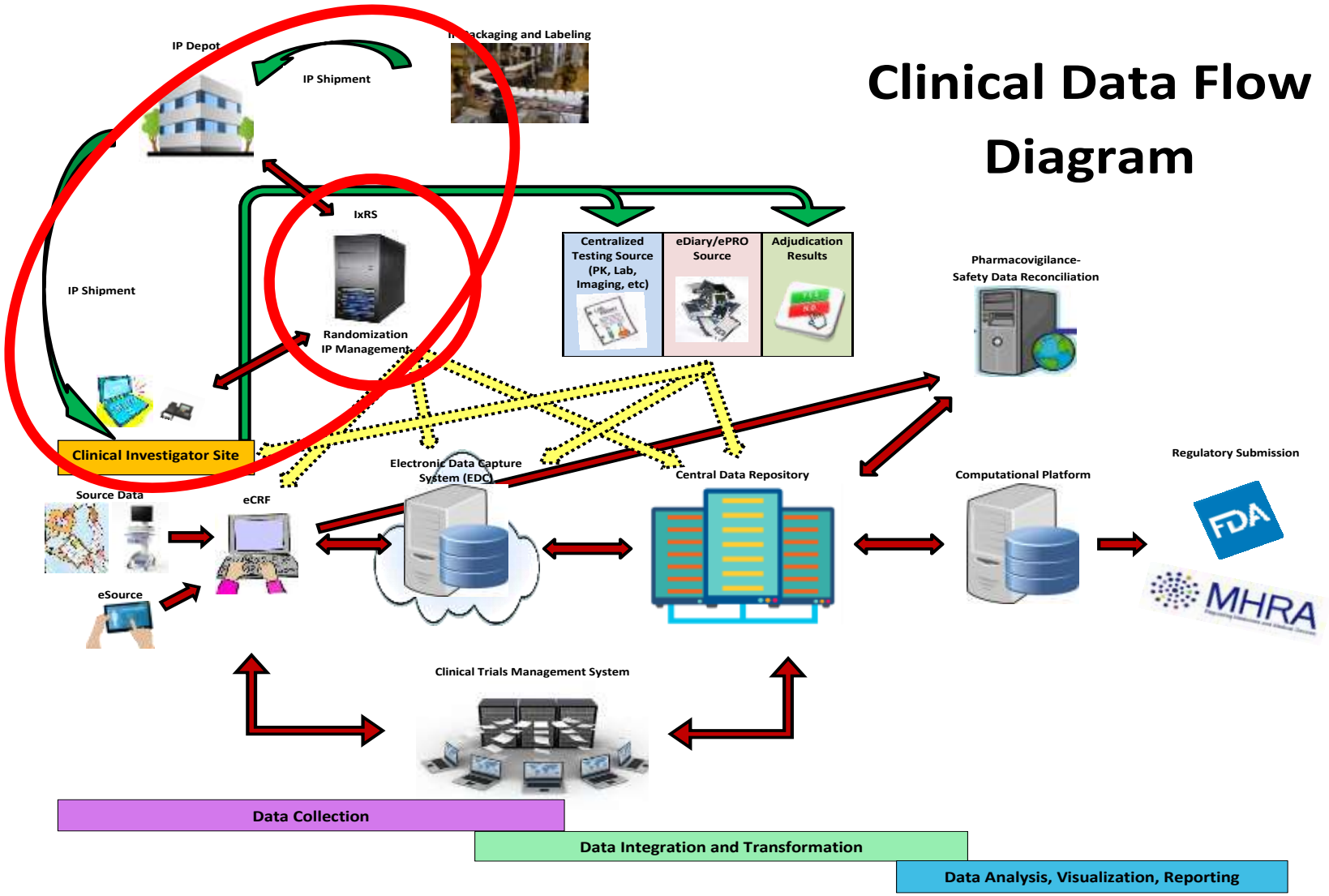
Interactive Response Technology Issues



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Example – IRT Reports

- Phase I double blind SAD and MAD, 8 cohorts
- IRT system allows users to view and download reports from the system
- Reports (and whether they are blinded or unblinded) are defined in the User Requirements Specification
- Both blinded and unblinded reports included the IMP Lot numbers – which unblinded the treatment allocation
- Not picked up until the 8th cohort
- Audit trail review showed that 3 study managers viewed the unblinded reports

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Example – IRT Reports

- Reports from IRT – blinded inventory report displayed the quantity of kits and the patient the drug was dispensed to
- One arm requires 2 kits of one medication type to be dispensed at each visit, so it was possible to determine the arm based on the number of kits
- Access to these reports was granted for site, sponsor and CRO
- Audit trail could not identify who had accessed these reports – the inventory report was filtered down from a consignment report which the audit trial showed, but not if the user had then accessed the inventory report from there
- 47 users had accessed the consignment reports
- System level or study specific build level?

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Example – IRT set up

- Double blind pain relief study, active v placebo; each subject individually unblinded by the research nurse at the end of their participation in the study to allow tapering of the IMP, and discussion on whether the subject wishes to continue on active IMP
- In-house IRT system
- Recruitment quicker than expected, IMP began to run out and a process was put in place to transfer IMP between sites to meet recruitment rates
- Delivery errors during site to site transfer meant that sites had incorrect kits; patients could not be dosed as the site did not have the correct kit to match the randomisation

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Example – IRT set up (cont.)

- Research nurse unblinded on a number of occasions when attempting to supply IMP – knowing that there was IMP in the pharmacy – the IRT system stated that there was no stock to resupply

- In an incidence where the research nurse is made aware that all current packs in pharmacy are of the opposite allocation to the participant they are attempting to resupply, this risks the potential breaking of the blind for several active participants when that one participant is unblinded

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Example – IRT User Access

- Double blind, randomized large cardiac outcomes study (active versus placebo)
- Vendor provided IRT system
- Emergency unblinding permitted at clinical investigator site level via IRT interaction
- Global unblinding access granted to > 100 clinical investigators and multiple contract research organization study team members

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Examples - Emergency Unblinding Gone Wrong

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Example – Back-up Failure

- Usual Process is to unblind in an emergency via IRT system
- Not all PIs in the trial had activated the ability to unblind – this had not been checked on monitoring or at site initiation
- In circumstances where the IRT is not working, or the PI is unable to unblind, the back-up is a call centre that can also unblind if needed
- In order for the call center to un-blind they need to receive from the calling physician the patient ID number and the patient randomization number. Sites did not have the randomization numbers of subjects, therefore it was not possible to unblind quickly

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Example – Significant Delay

- Paediatric study - Subject experienced an SAE leading to the decision by the Investigator to withdraw the patient from the double-blind study to give a protocol-prohibited medication. The Medical Monitor provided the Investigator with the telephone number for the Help Desk, whose responsibility includes provision of the treatment allocation upon request
- The Investigator received an automatic response email from the helpdesk, with the treatment allocation of the patient in the format of a sequenced number (without a code break), hence the blinding was maintained
- Patient had to be manually unblinded
- Approximately 5 hours later, the Investigator received the information required to treat the patient

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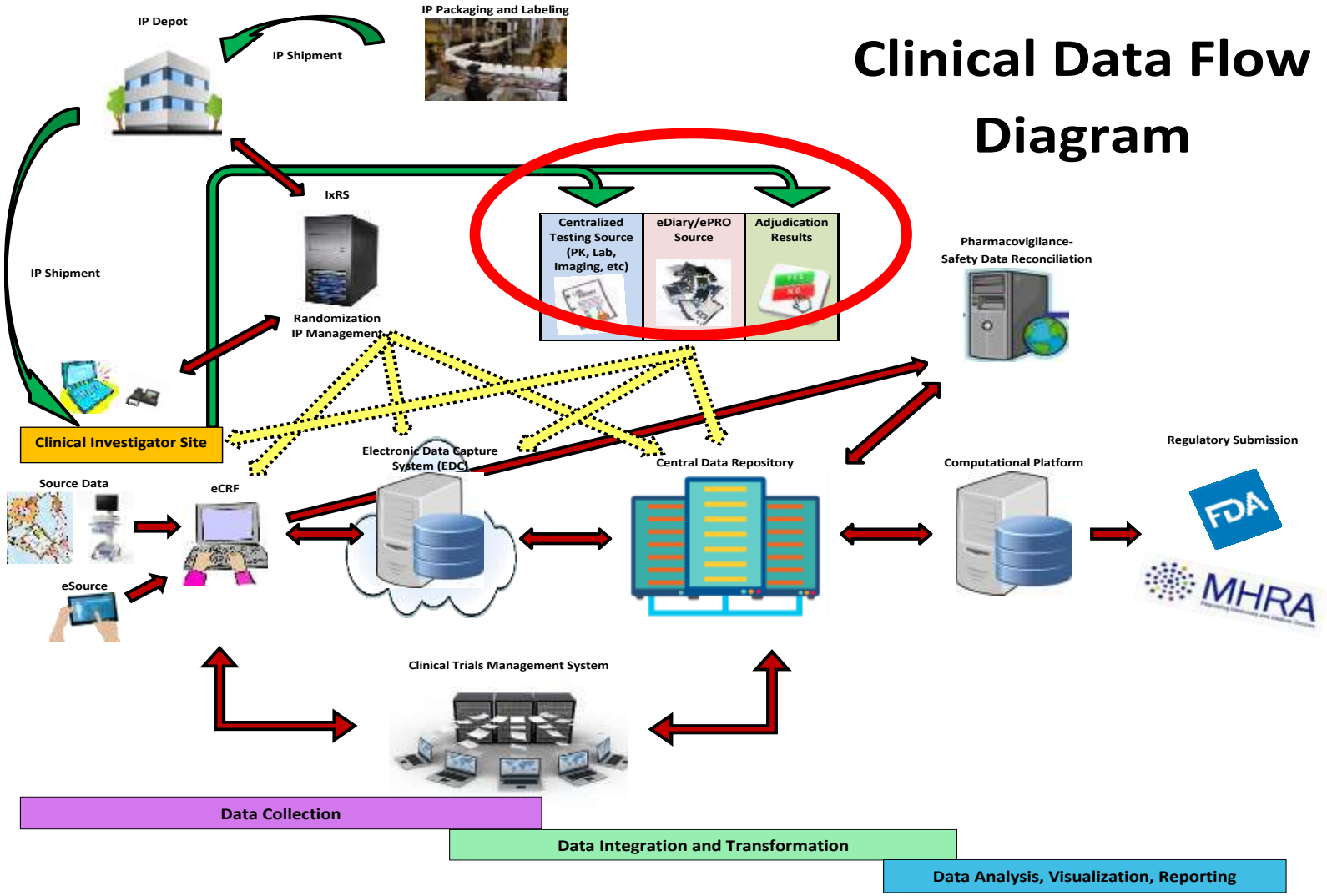
Items Sent from Investigator Sites



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Example – Adjudication Packages

- Unblinded, randomized oncology study
- Blinded Adjudication Committee used for primary endpoint assessment
- Site sends source documentation that includes actual treatment received
- Vendor staff responsible for assembly of adjudication packages (source documentation and eCRF data) fails to recognize and transfers packages that reveal treatment to Adjudication Committee

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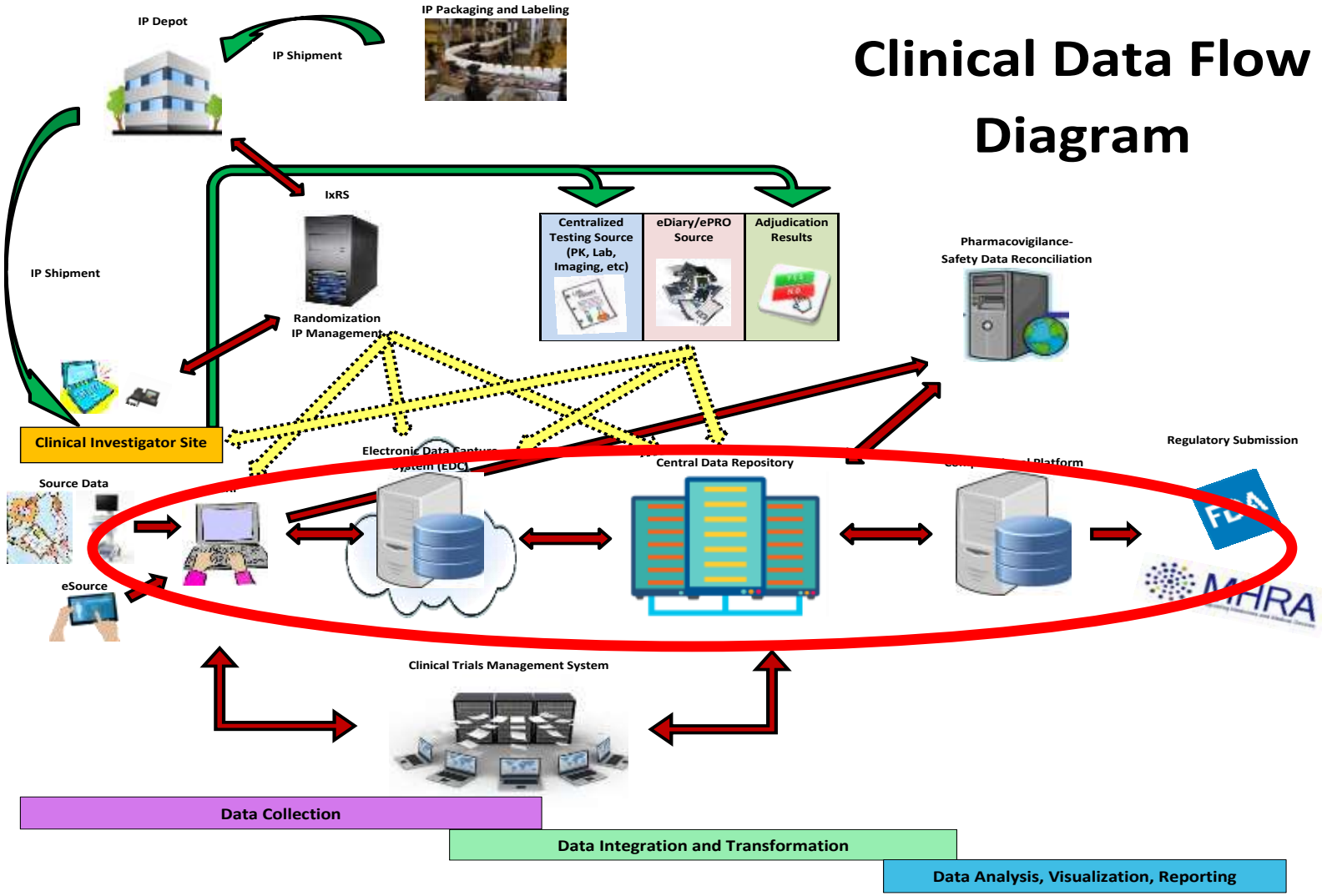
EDC Data Masking Issues



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Example – CRF Design

- As per protocol, patients are randomised into 2 arms: standard of care arm and an imaging (ultrasound) arm
- The protocol states that the sonographers who are performing the assessment of US images and scoring, must be blinded to clinical data and randomisation allocation (i.e. assigned study arm) of the patients.
- The clinical team (following the patients and making treatment decisions) and the patients are not blinded to the allocation arm.
- The database and electronic case report form (eCRF) have been built by the Sponsor, the imaging part of the eCRF and randomization part were programmed by eCRF provider.

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Example – CRF Design (cont.)

- During a site audit, it was noticed that the US pages of the eCRF for sonography entries disclose the allocation arm of the patients.
- This allocation to the study arm appears in the eCRF page name on those pages to which the sonographers have access to. Therefore, any sonographer entering data into these eCRF pages can see the header of the eCRF pages and thus would be un-blinded to the applicable study arm.

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Example – Multiple Unmasking Events in Single Trial

- Unblinded, randomized study
- Test product versus approved comparator
- Oral versus IV dosing (different dosage and frequency administration)
- Per protocol differing procedures for treatment arms, Test arm:
  - Pharmacokinetic consent and assessment
  - Pharmacogenomic consent and assessment
- Data Management Plan calls for masking data prior to transfer to statistical group to prevent unblinded aggregate analyses

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Example – Multiple Unmasking Events in Single Trial

- Review of study specific folders on statistical server found SDTM and raw data files with:
  - Treatment arm unmasked
  - Dosing amount and frequency unmasked
  - Disposition datasets that showed date of pharmacokinetic and pharmacogenomic consents (only obtained for subjects on Test arm)
  - Pharmacokinetic results datasets with subject numbers (only present for subjects on Test arm)
- Review of data management folder access (raw unblinded data) found Statistical Team members with administrator privileges

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Data Variables – Unblinding Risks

- Treatment code or arm variables
- Dosage (including dosage adjustment related)
- Frequency
- Route of administration
- Laboratory values when specific abnormalities associated with one of treatment arms
- Therapeutic drug level monitoring
- Physical sign or symptom recorded that is specific side effect one treatment arm
- **ANY** variables associated with testing being performed in only select treatment arms

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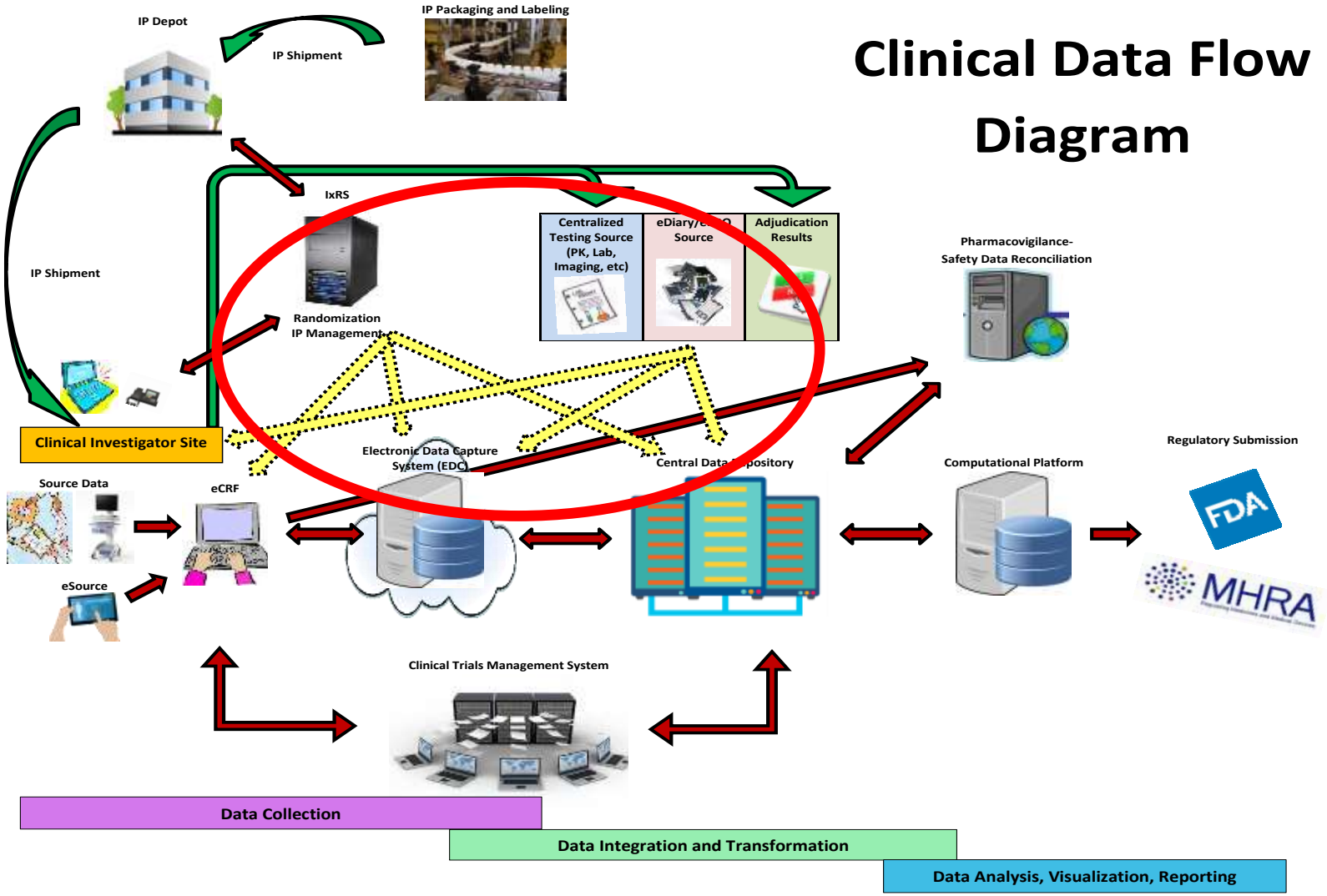
Other Data Masking Issues



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Example – Laboratory Reports

- Bioanalytical file provided by the contract laboratory to the sponsor via email
- File included sample analysis dates, which identified them as those on active as the placebo subjects were excluded from the file
- Study data transfer specification was in place but not followed
- Affected 48 subjects
- Root cause analysis revealed this had happened with 3 other sponsors previously

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Example – Safety Listings

- 6 monthly safety line listings were sent to the study mailbox for onward distribution to Regulatory Authorities and investigators (blinded and unblinded reports were sent)
- Unblinded attachments were then submitted via a safety web-based portal to all the study teams – including investigators, study co-ordinators, CRAs and study managers from the sponsor and CRO
- Affected a number of trials with the same IMP and a large number of study staff and subjects
- Audit trails were useful in determining who had accessed and opened the files

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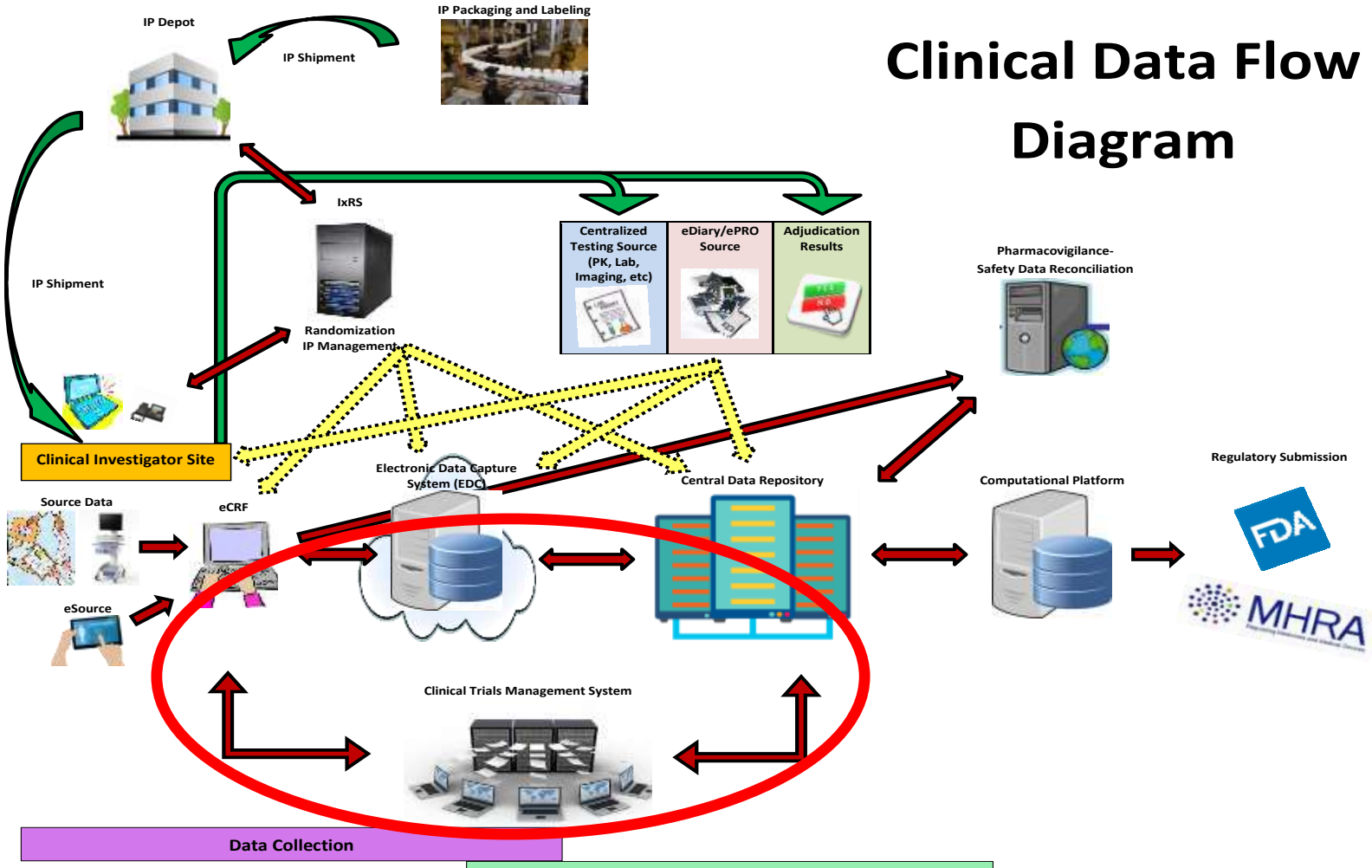
Clinical Trial Management Systems Issues



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Examples – General Filing

- Unblinded monitor continued to use the same password which was provided by the outgoing monitor for the protection of visit reports. The password was very generic (i.e. trial ID code). Knowledge of one password could potentially lead to unblinding of many reports and potentially, the use of a password across trials and monitors in different roles
- A large number of unblinding issues identified in the TMF; including provision of randomisation allocation reports, emails that could unblind, filing of unblinded DMC data, file notes that unblind, emailing of randomisation codes, safety listings that contained only confirmed SUSARs (not SAEs) plus subject numbers

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Examples – General Filing

- The accountability log for the IMP which clearly stated which patient received which drug was held within the site master file and no attempt to limit access to this documentation had been made
- There were a number of unsealed randomization envelopes filed with the respective case report form (CRF). Each envelope revealed which study drug each patient had been assigned

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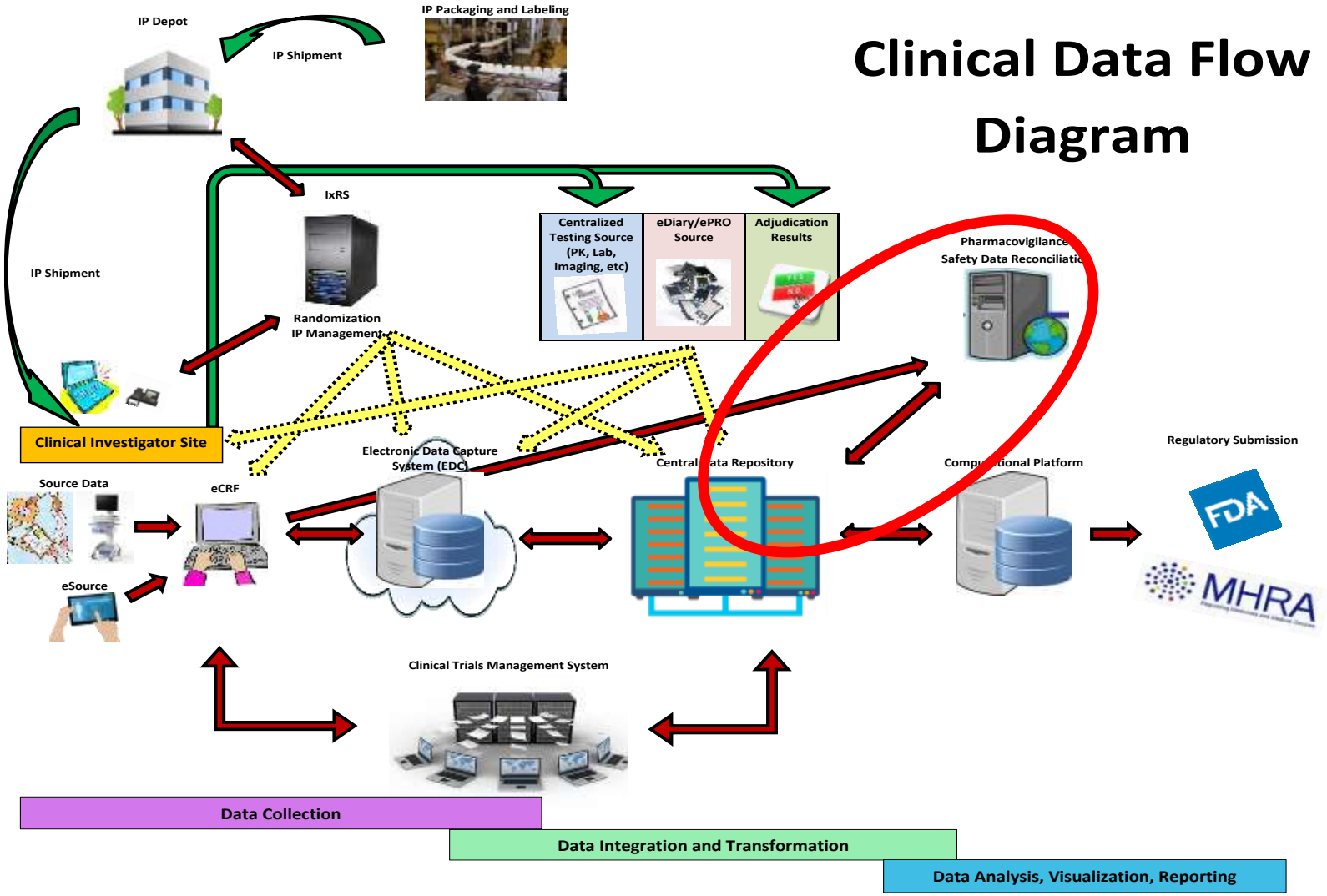
Safety Data Reconciliation Issues



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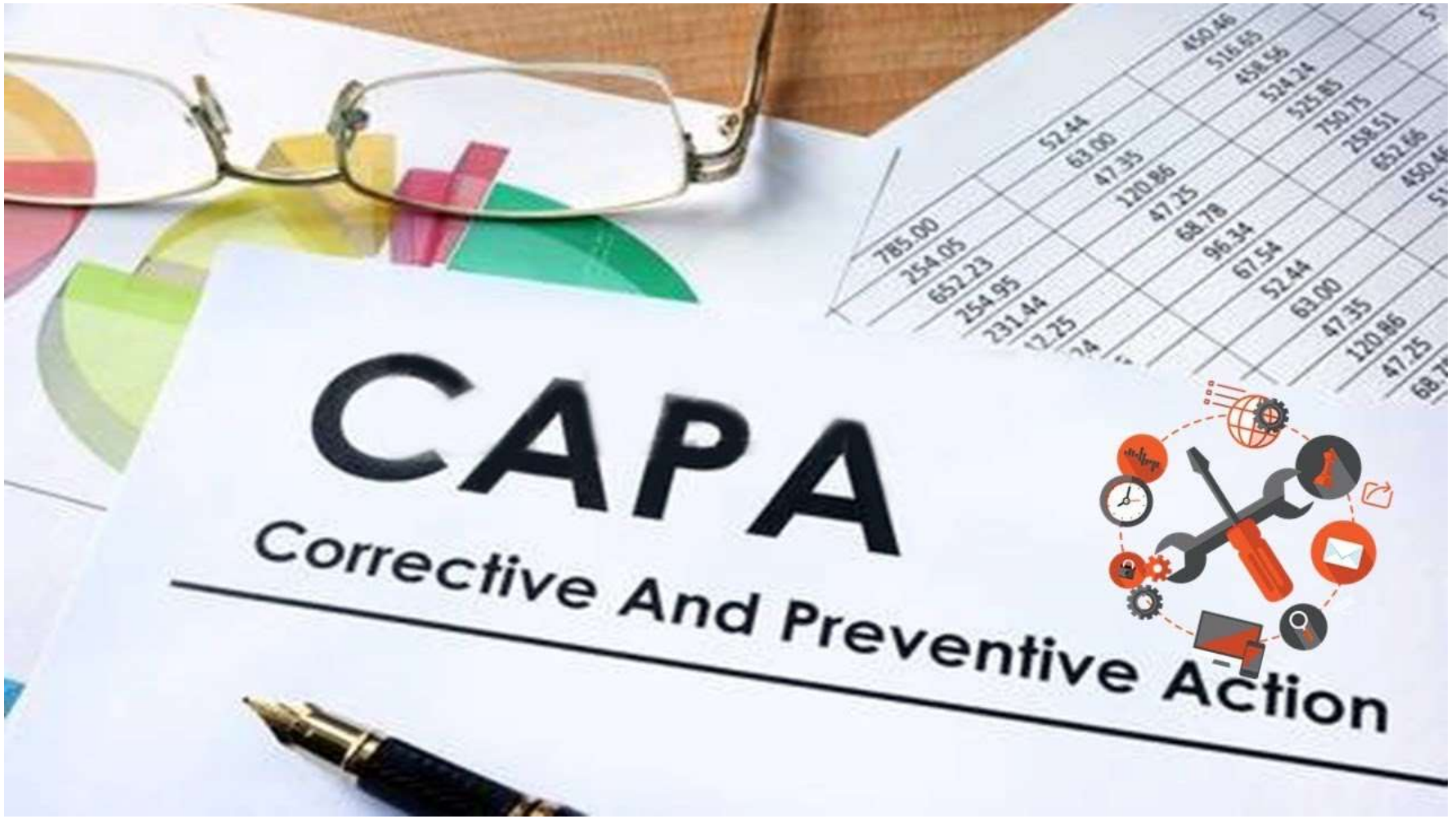
CAPA Lessons



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An Example

Analgesic trial in Caesarean section, comparative, double blind, placebo controlled. Single centre approx. 200 patients. Primary outcome is a pain score by the patient

- First MHRA Inspection revealed there were no accountability records – IMP preparation was checked by 2 non-trial staff, but this was not documented
- The study design utilized a set of randomization envelopes which were opened by the investigators making up the IMP and then re-sealed and signed. This made monitoring difficult as the envelopes needed re-opening and re-sealing and also did not provide for a robust un-blinding procedure.

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An Example (continued)

CAPA

- Accountability records instigated, monthly ward rounds by pharmacy
- An un-blind randomisation list was produced to be held securely in the new pharmacy file on the ward for the team drawing up the IMP

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CAPA

- Serious Breach – in order to make up the IMP the randomization list was held in the pharmacy file on the ward. This was accessed by the (blinded) CI to prepare allocated treatment for the patient – therefore accessing the entire list
- Review of this practice revealed that staff shortages led to blinded investigators accessing blind break envelopes to make up the IMP

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CAPA continued

Second MHRA Inspection:

- Randomization envelopes (when used initially) should have been stored in the CRF to evidence what the patient should have received – for the majority of CRFs this was not the case
- The randomization list was created by a statistician, but then given to the CI, who then generated the randomization envelopes, therefore negating the blind
- A number of CRFs included the randomization allocation (A, B, C or D) therefore unblinding anyone who accessed the CRF and inputs the data into the database

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Training…….a step too far

- Training in relation to maintaining the blind is important – but must be in the context of GCP documentation requirements
- Inspection of a trial where the protocol required that half the subjects receive eye drops alone and the other half receive eye drops plus lignocaine.
- The medical notes contained an entry on the date of the IMP administration; however each entry, for all subjects (131), stated that they received both drops and lignocaine
- This was because the physician's understanding was that they could not document what was actually given as this would unblind – however this meant that there was NO documentation to demonstrate what the subject received
- Data was invalidated

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It’s not all bad news……..

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Example of Getting it Right!

- In a Phase I Unit pharmacy where a study requires unblinded preparation/dispensation, an unblinded box is prepared
- This box has a numerical key code, only available to the delegated unblinded team. Code is held in restricted access pharmacy only electronic folder and is updated every 6 months. The box is kept in a locked cupboard, the key to this is stored in a numerical coded key box which has restricted access. The code to this is updated every 6 months.

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Example of Getting it Right!

- When IMP is received that needs to remain blinded it is stored in a non-see through bag and locked with a padlock.
- The key to this is kept in the unblinded box along with any other documentation that needs to remain blinded.

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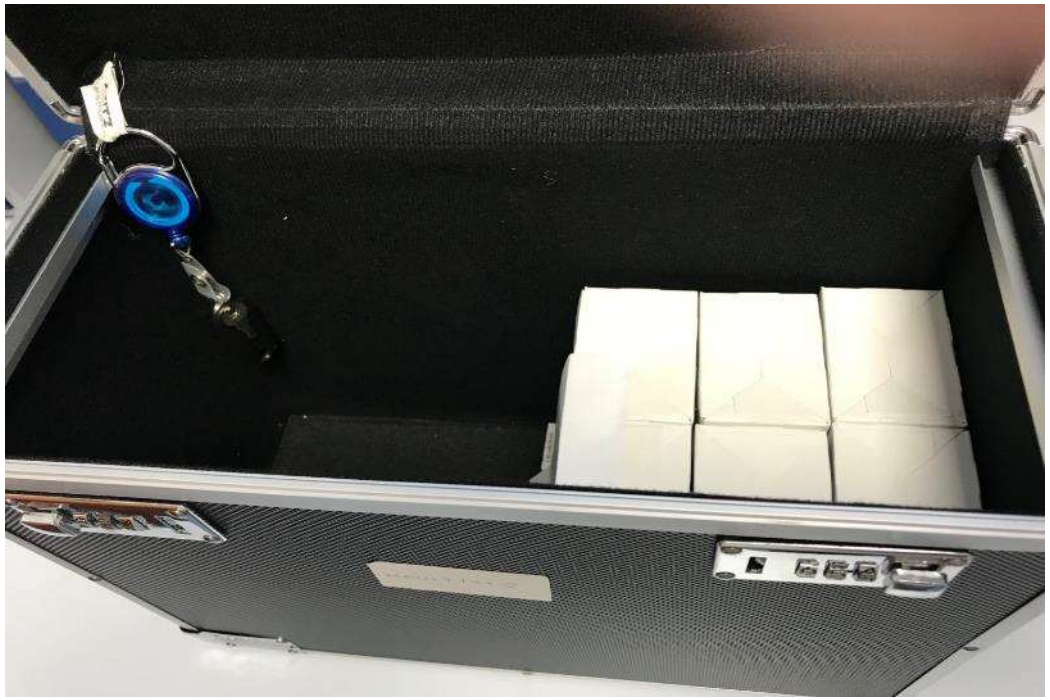
Example of Getting it Right!

- Returned IMP including empty boxes required for monitoring if small can be stored in the locked box or if larger stored in another opaque locked bag (key again stored in unblinded box).



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Summary

- Let me count the ways…….22 examples – but many more exist!
- Issues in unblinding may lead to rejection of data submitted for a marketing authorization
- Understand your data flow, perform a risk assessment, develop mitigation and risk control strategies
- Good CAPA – poor CAPA

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Summary

- Inspectors may (and do) request a list of unblinding incidents on inspection
- MHRA Serious breaches – common issue
- FDA –common issue picked up on inspection
- Being transparent about any issues is helpful and can reduce delays in authorisation/approvals process

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Challenge Questions

1. True or False? Premature unblinding of subjects' treatment allocation is never appropriate in ongoing study.

   ANSWER: False

2. Premature unblinding of subjects' treatment allocation may result from which of the following?

   a) Failure to mask dosage and administration variables
   b) Mismanagement of IRT access privileges
   c) IMP labeling and shipping documentation
   d) All of the above

   ANSWER: d)

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