Case Examples Highlighting Multi-Centre Clinical Trial Issues

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Introduction

- Survey presentation from Bernd highlighted the following issues when working in support of clinical trials :
  - Communication
  - Early Involvement
  - Detailed Direction/Instruction

- Objective of this presentation is to look at a number of examples provided by TT-12 team members which demonstrate the problems

Storage Temperature Examples

- Description
  - Clinics often have limited or zero sample storage capacity at -80ºC
    - You can all probably recall being asked the question – “is it really necessary to store the plasma samples at -80ºC?”
  - 3 cases, plasma samples were stored at -20ºC instead of - 80ºC

- Potential Consequences
  - Sample instability at -20ºC but not at -80ºC
  - Could result in errors in PK calculations with serious implications for future volunteers/patients

- Resolution/Outcomes for the 3 cases
  - Short term -20ºC storage stability experiment to cover period until shipment to central lab
  - Additional assay validation at -20ºC
  - **Repeat of clinical study as analyte instability demonstrated at -20ºC** (an expensive error)

Sample Collection Examples

- Description
  - 2 studies planned : samples were collected but not planned to be measured and sent to laboratory for freezer storage
  - Approximately 5000 samples were delivered in plastic bags, with an electronic file
- Potential Consequences
  - Impossible to find specific samples easily and efficiently
- Resolution/Outcome
  - Developed Excel Macro to find a tube in the e-file list and also generated a box number with box position for each sample
  - Entered box numbers in Watson so they appeared on work list
  - A lot of time and effort would have been saved by delivery of the samples in organised boxes in the first place!

Sample Collection Examples

- Description
  - Concentrations of biomarker to be determined in washed erythrocytes, i.e. intracellular, by LC-MS/MS
  - Clinical site tasks : Collect blood, pellet erythrocytes, wash 3x with PBS with intermittent centrifugation (as explained in manual)
  - Bioanalytical lab delivered a supply of concentrated 10xPBS (clearly labelled) to clinical site
  - Clinical site washed cells not with diluted 1xPBS, but with concentrated 10xPBS
- Potential Consequences
  - Did this error have an effect on the results…..?
    - Evaluation currently ongoing
- Resolution
  - Clarification of Communication Process

Sample Collection Examples

- Description
  - Alternative vacutainer used in a planned clinical study – documented in protocol deviation
  - Unfortunately, the bioanalytical lab was only notified after shipment of the samples
- Potential Consequences
  - Delay in sample analysis due to additional anti-coagulant testing required
  - Instability of samples in alternative vacutainer would have invalidated the study
- Resolution
  - Further validation work performed to demonstrate no impact on sample stability

Anti-Coagulant Example

- Description
  - Some clinical study plasma samples were prepared in Li-heparin tubes instead of EDTA, the method having been validated using EDTA plasma
- Potential Consequences
  - Errors in quantitation of the Li-heparin samples
- Resolution
  - Additional QCs prepared in Li-heparin and quantitated vs the EDTA calibration curve
  - The QCs met the 15% acceptance criteria, demonstrating acceptability
  - Study later inspected by FDA, no issues

Sample Handling/Instability Example

- Description
  - Extremely unstable compound in plasma, urine, whole blood but stable in organic solvent
  - Phase 1 study well controlled
  - Multi-centre study : sampling kits and instructional video sent to sites
  - Kits contained :
    - Tube with IS
    - Tube with 10x concentrated IS for over-curve samples (to be diluted 10x)
- Outcome
  - 3 out of 5 sites showed anomalous results
    - No or unacceptably low IS responses observed : IS tubes used were older than 2 months
    - CRA noticed that IS solution placed outside the refrigerator on a central heating element
- Conclusion
  - BA not involved in recruitment/enrolment program, feedback regarding analytical reagent stability not given/foreseen as an issue
  - Even if your instructions seem very detailed to you, clinical personnel may not interpret as you expect. For difficult compounds, it will be very difficult to provide instructions that are 100% fool-proof.

Sample Instability/Pipetting Example

- Description
  - Acid stabiliser required to be added to sample at time of urine collection at specific %
- Issues
  - Do the clinic have the required accurate pipettes?
  - Are the clinical staff trained in pipetting?
- Outcome
  - Detailed instruction required in Lab Manual

Sample Labeling Example

- Description
  - Clinical site collected plasma samples into pre-labeled tubes
  - The samples were shipped to a Central Lab and the Central Lab added their own label – unfortunately on top of the original label
- Consequences
  - In many cases, not possible to read both labels
  - In some cases, the information on the duplicate labels was not the same
  - Multiple labelling resulted in difficulty for the bioanalytical lab to fit the tubes into the robotic sample handling racks
- Outcome
  - Uncertainty around sample id : those samples could not be analysed
  - Problems in handling samples : slowed down the analysis

Randomisation List Example

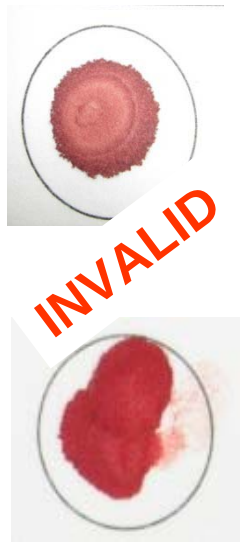
- Description
  - Samples arrived and once randomisation list received there was nothing to match the two together

- Issues
  - Receiving the right information before the samples arrive
  - In large multi centre studies the randomisation list is not always the only thing you need to identify samples
  - Elaborate procedure to retrieve the list (via IT company, monthly phone call to obtain password, file retrieval)

- Outcome
  - Involvement in early discussions between Clinic, Sponsor and CRO

DBS Example

- Description
  - Multi-site global clinical study
  - DBS cards received from clinical sites with incorrect spotting observed eg.
    - different volume spotted
    - multiple spots on the one circle
    - spotting outside of the sample circle
    - barcode label obscuring the spot
- Consequences
  - Cards with irregular spotting could not be analysed
- Outcome
  - Feedback and training material provided to clinical trial team to improve sample spotting



Multi-site Example (1)

- Description
  - 3 different studies, same project
  - No barcodes on tubes received from Australia and Japan sites
  - Tubes agreed previously with Central Lab not used at clinical sites
  - Incompliant 10mL tubes received from US site
  - No notification of sample shipment date in advance
  - Samples delivered to wrong address
  - ……apart from this, everything was fine!

- Consequences
  - Samples without barcodes re-shipped to Central Lab for re-labeling
  - 10 mL tubes not compatible with Tecan robot
  - Additional F/T work and additional aliquoting step required
  - Unexpected sample arrival

- Resolution
  - Improve interaction with clinical and central lab colleagues

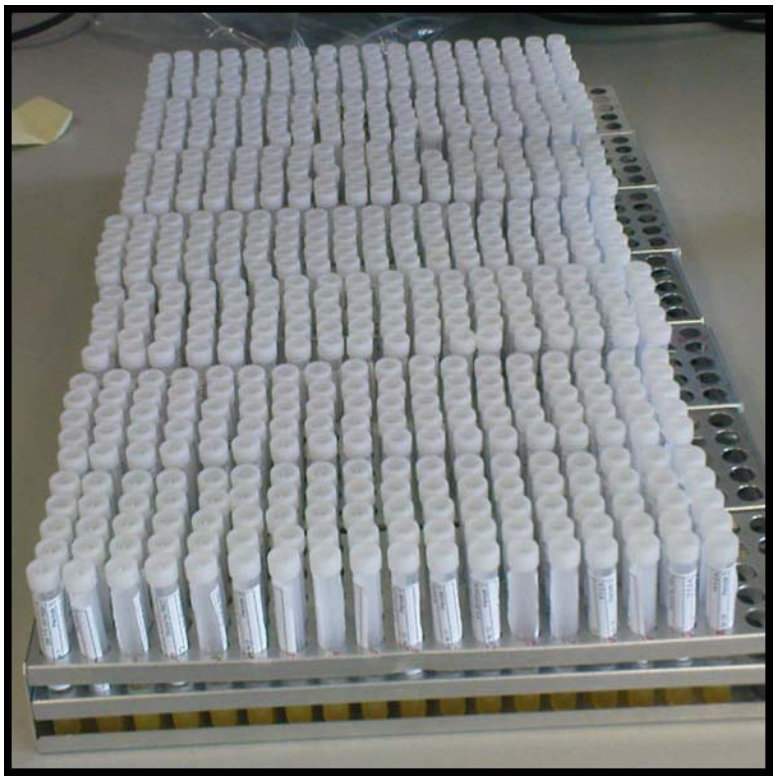
Multi-site Example (2)

- Description
  - No sample shipment list received from the clinical site
  - Several handwritten labels
  - Discrepancy between information on sample list and tube label (discovered during ‘Data Cleaning’)
  - Biomarker and plasma PK samples mixed in one bag
  - Delivery of ‘forgotten’ samples after finalisation of bioanalysis and data transfer
- Potential Consequences
  - Not possible to verify complete sample shipment
  - Difficult to read hand written labels
  - Additional time and effort required to sort out frozen biomarker and PK samples and repackage.
  - Delay in ‘final’ data as additional analysis and PK evaluation required to include the ‘forgotten’ samples
- Resolution
  - Suggest more direct interaction between the bioanalytical lab and the clinical site

Summary

- Multiple examples shown
- Some examples require more effort to ‘fix’ than others
- However, none should prove impossible
- Remember to consider the clinical perspective as well as our own

EBF Recommendation



- Take the initiative to open communication early during protocol drafting
- Ensure understanding of the needs of both parties (clinical and bioanalysis)
- Assume nothing – ensure that the protocol / lab manual are as detailed as they need to be
- Provide training if necessary and consider being present at the clinical study initiation meeting
- Keep communicating

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