EMA & FDA Inspections: Site perspective

Shandukani Research Centre

Why were we inspected?

- Pharmaceutical company applied for registration of the study drug (Phase I/II dosing studies in paediatrics)
- Large number of participants enrolled

- Part of FDA's biosafety monitoring program
- Inspection designed to evaluate the conduct of research and to ensure that the rights, safety and welfare of the human subjects of the study have been protected

Preparation

Stressful news

"**FDA** only announces GCP inspection not specifying which study will be audited"

Shandukani Research, Wits RHI site has been involved in clinical trials for 10 years

Preparation

- Plan of action was prepared. Internet searches were helpful in compiling a plan of action
- Roles and responsibilities were assigned
- Regulatory Bodies and Laboratory were informed as well as research and clinic staff
- Remember to inform DAIDS and the Sponsor!
- One (very organized) person coordinating preparation
- MS Project was used by the Programme Manager to make sure all issues were reviewed and addressed in time

Preparation

- Plenty of extra hours are needed for review since normal research activities continued
- During regular PPD visits 10% of IND files are monitored, thus the role of internal Quality Control (QC) and Quality Assurance (QA) is very important
- PPD reviewed relevant files during their quarterly visit
- Regular telephone conferences with sponsors and DAIDS

Preparation

Filing

- Ensure that all documents are easy to find and consistent across all studies
- Make it as easy as possible for the inspector to find what he/she needs to review
- Everyone should know where everything can be found in his/her files
- This applies to the laboratory as well!

Preparation

- Regulatory Review undertaken by independent CRA
- Informed Consent process extremely important
- Good to have Informed Consent Forms (ICFs) QA'ed and in separate files
- Ensure that all reportable events have been reported to the relevant regulatory bodies

- **Note to files**
  - Important to clarify issues, but do not have too many notes to files
  - Signed off by the Principal Investigator (PI)

- **Special attention:**
  - All approved ICFs
  - IOR/FDA1572 forms
  - Ethics Committee and MCC approvals
  - Delegation logs
  - Studies that PI is currently involved in must be listed in a log

Preparation

- **Training**
  - Training logs are up to date in a file
  - Attendance list and training material in the same file
  - Staff delegation duties should correspond with the training
  - New staff are trained before they start working on the study (mention how they are trained, self training was not acceptable)

- **Maintenance**
  - All maintenance records are up to date
  - Serial numbers of equipment used for this trial are documented
  - Specific equipment used are noted

- **Standard Operating Procedures (SOPs)**
  - Ensure that they are up to date and followed. The staff are interviewed (separately) to confirm if they are familiar with these and are following them
  - If there was a change in SOP, all staff need to know about it
  - Staff training on SOP training is documented
  - Signed off by Principal Investigator

Preparation

- **Review Pharmacy documents**
  - Prescriptions all completed correctly, all areas filled in
  - Contact reports, all issues reported to Pharmaceutical Affair Branch (PAB) or Sponsor
  - Shipping documents sorted, marked and filed logically
  - Correlate stock received with all entries into drug accountability logs
  - All participants entries correlate with entries on accountability logs
  - Temperature logs (electronic and manual)
    - all in sequence
    - no dates missing
    - temperature excursions well documented and appropriately reported

Preparation

- **Lab kit area** on site (not a formal lab)
  - All equipment service records available
  - Temperature monitoring for all lab kits
  - Logs kept for centrifuge
- Dummy runs were held with the team to ensure what we say we do is exactly what is happening and that the team confirms the process
- Black bag days (clean-up day) were scheduled, no unnecessary items/paper work lying around

Problems Identified and Important points

Important points

- Regulatory Site Investigator Files
- **Informed Consents**
  - Correct version
  - Procedure
  - All elements mentioned in the ICF (Ethics, SA GCP, ICH GCP, DAIDS)

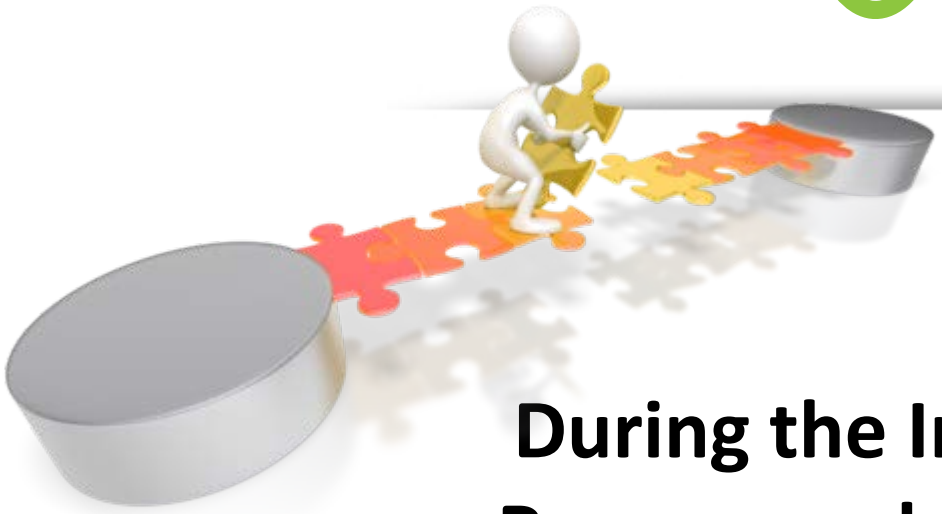
  For example: 'Your records may be reviewed by the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), National Institutes of Health (NIH), the Medicines Control Council (MCC), the National Health Research Ethics Council (NHREC), the University of the Witwatersrand, Human Research Ethics Committee (Wits HREC - Medical), study staff, study monitors, your personal doctor, **other local and international regulatory authorities**, and drug companies supporting this study.'
- **SAE's**
  - Timeliness of reporting
  - Management
  - Follow up on resolution
  - Reporting plan

Important points

- **Schedule of evaluations:**
  - Toxicity
  - Efficacy points
- **Investigational drug related issues:**
  - How was correct dosing ensured?
  - Pharmacokinetic (PK) samples collection and PK procedures
  - Site awareness and reaction to PK results

Challenges

- Large number of unmonitored files by PPD
- Impossible to do a 100% monitoring in such a short time
- Select a number of unmonitored files to pick up trends
- The point is to be aware of what the problems are rather than correct all problems
- Data verification on the database



During the Inspection: Process and Challenges

Process while EMA & FDA Inspector is Present

- What we read made us react quite nervously to the inspector. We could not make the visitor feel at home with us in South Africa!
- They may arrive early - 45 minutes before the planned time
- Visitor cards and Sign-in log were prepared with a dedicated person at reception

Process while EMA & FDA Inspector is Present

- Quiet dedicated boardroom with ample working surface for the period of inspection
- One person (who knew most aspects of the study well) was dedicated to assist with requests for electronic documents, photocopying and to answer basic questions
- Interviewed different people that worked on the study to ensure all staff know and adhered to SOPs
- Look at processes according to SOP and when SOP changed did the team process the change
- Keep photocopies of all documents requested with a log

Process while EMA & FDA Inspector is Present

- Do not answer a question you are not certain of just tell the FDA/EMA investigator you will look it up and provide the information later = Open communication with the inspectors.
- Always look at the participant file before answering a clinical question. Remember, you can't remember every participant!
- Ensure participant identifiers on copies of source documents requested are blacked out (e.g. Lab reports)
- **Principal Investigator Responsibilites:**
  - Daily meetings between the PI and inspector
  - Interviews with the PI
  - Questions and proof of the PIs involvement throughout the study
- Refreshments and assistance with transport was requested
- The inspector clarified this is not the case when inspecting US sites!

Closure

- **FDA x 3 inspections**
  - No Form 483: Notice of Inspectional Observations, may be issued at the conclusion of the inspection if violations are found
- **EMA x 2 inspections**

  Divide findings in major and minor findings
  - Need to address within certain time frame after inspection
- **MCC x 1 inspection**
  - No findings

Closure

- Learning experience which improved our skills
  - to pick up transcription errors
  - identify missed tests
  - ensure a good paper trail
- QA processes started later on P1020a (our 1st clinical trial) have been improved and applied to all trials– will make future inspections easier
- Alerted us to the need for continuing training required