EMA Inspection
Site perspective

Wits RHI
Shandukani Research Centre

Hermien Gous

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Cape Town

University of the Witwatersrand
WITS RHI

Why were we inspected 7 times?

Pharmaceutical company applied for registration of the study drug in a specific age group
(Phase I/II dosing studies in paediatrics)

1

FDA

Atazanavir (2008)

Fosamprenavir (2012)

Raltegravir (2013)

2

EMA

Darunavir (2011)

Raltegravir (2013)

Dolutegravir (2016)

DTG (2016)

Large number of patients

Cohort n=4

Chiang Mai

3

MCC

Unannounced inspection (2013)

PREPARATION

Determine appropriate staff members

- on delegation log
- involved in the trial
- available for interviews during the inspection
- provide this list to inspectors

Job title	
CRS leader	PI on site
Data Manager	
Programme Manager	
Regulatory Compliance Manager	
QA Manager and Pharmacist	
Internal QA monitor and associate pharmacist	
Associate Pharmacist	PoR was on Mat Leave
Study Coordinator	All 3 SCs did ICF's
Study Coordinator	
Study Coordinator	
Sub-Investigator	
Project Manager CLS	

NOT THE TIME TO SHOWCASE

- Plan of action & SOP
  Internet searches, tables, checklists & MS Project
- Notify Regulatory Bodies, Laboratory, DAIDS & Sponsor
- Roles and responsibilities were assigned
- Very organized person coordinating preparation
- Programme Manager responsible
  issues reviewed & addressed in time

- Plenty of extra hours - MUST review all documents

- Site

  Routine PPD visits 10% of IND files are monitored
  QC & QA 100% SDV by the site
  Don't assume monitors pick up all problems, more trends

- PPD reviewed relevant files during quarterly visit

  Special assignment was conducted
  Training files, 1572, reg file review
  PPD mock inspection was set-up

- Regular telephone conferences with sponsors / DAIDS

Commented on hosting: Advised that due to the location of the site, inspectors should be advised regarding transport and safety

Filing

- All documents are easy to find
  chronological & consistent
- Staff familiar with files
- All pages must have an identifier
- Information readily available in organised manner
  including off-site approved laboratory

Clinical

- Investigators reviewed protocol, inclusion and exclusion criteria met?

  Enrolment violations were identified
  Immediately did root cause analysis why it happened

- Patient summaries were prepared

- PI reviewed all files

- Good to know what AE's occurred and if any SUSARs were experienced

  Time of awareness of AE vs
  discharge summary's date signed

Regulatory

- Timeline of all approvals
- Reviewed with dedicated staff
- When were participants enrolled
- Reportable events reported

Informed Consent

- Informed Consent Forms (ICF's) and process
  review all, including screen failure

- ICF's QA'ed
  File originals in a separate file

- Participants have signed subsequent ICF's & assents timeously

Documentation of witness relationship is important

Translation certificates should have ICF & protocol version documented

Who is this delegated to? Investigator must sign, PI must know process

Notes to file

- Site to clarify but do not have too many
- Must include root cause analysis, corrective and preventative action plan
- Signed off by the Principal Investigator (PI)

Special attention

- All approved ICFs
- IOR/FDA1572 forms
- Ethics Committee and MCC approvals
- Delegation logs (review and review, dates signatures, training)
- Log listing studies PI involved in

Training

- Training logs
- Attendance list and training material in the same file
- Delegated duties correspond with training
- New staff are trained before they start working on the study
- Temporary / separate file with relevant study and applicable staff

Who was trained on the DAIDS Adverse Experience Reporting System (DAERS) system and who had access?

Standard Operating Procedures (SOPs)

- Up to date and followed
- Familiar with changes in SOP
- Staff training well documented
- Review all versions of SOPs implemented for duration of study

Training on SOPs (wanted copy of logs to review)

Review of SOP's How often was this done?

How current are SOP's?

Signed off by Principal Investigator or CRS Leader

Data Management

- Data verification of database not routinely done

Maintenance

- Maintenance records up to date
- Reviewed
- Serial numbers of specific equipment used for trial documented

Review Pharmacy documents

- Prescriptions completed correctly, all fields
- Contact reports, issues reported to PAB or Sponsor
- Shipping documents sorted, marked and filed chronological
- Correlate stock received - entries drug accountability logs
- All medication dispensed correlate with entries on accountability logs
- Verification and documentation of electronic and manual temperature logs

Review Pharmacy documents

- Labelling of products should be according to country guidelines and regulatory bodies

- Expiration dates were not printed on the original IP container label

Dosing documentation during PK sampling days – who observes the dose being administered?

Diary card given as patient aid not version controlled

Lab kit storage area

- Temperature monitoring
- No expired lab kits

Sample Processing area

- Calibrations & services up to date
- Information sheet - specifications for processing of samples
- Log to document PID, spinning speed, time when start, stop and into freezer

Sampling chain of custody very important

Emergency trolley

- Easy access
- Checked routinely
- No expired stock
- Medication available

Dummy runs were held by the PI with the team

Black bag days

- Clean drawers and notice boards
- Information on walls must be referenced
- Ensure areas clean and nothing unnecessary is visible

Contracts and Study start-up

- ***PID log to only reflect screened participants***
- ***Source document and financial agreement signed before study start***
- ***Contract with lab***
- ***Checklist / formal process used by FHI to know the site is ready to start***
- ***Laboratory Processing Chart dated correctly***
- ***Ensure responsibilities of the sponsor/s and of the site are clearly defined in the contract***
- ***Inspectors have access to all information, preferably it needs to be related to a concern or trend picked up***
- Many questions about monitoring contract (DAIDS and PPD)

Regulatory Investigator Site Files

- Indexed numerically on outside
- Inside – each file should have index

Informed Consents

- Correct versions used, all approved
- Procedure (Ask various staff members)
- All elements mentioned in the ICF

SAE's

- Timeliness of noticing, signing, documenting & reporting
- Management
- Follow up on resolution
- Reporting plan if referred

Always important to show how site has closed the loop

Schedule of evaluations

- Toxicity
- Efficacy points

Investigational drug related issues

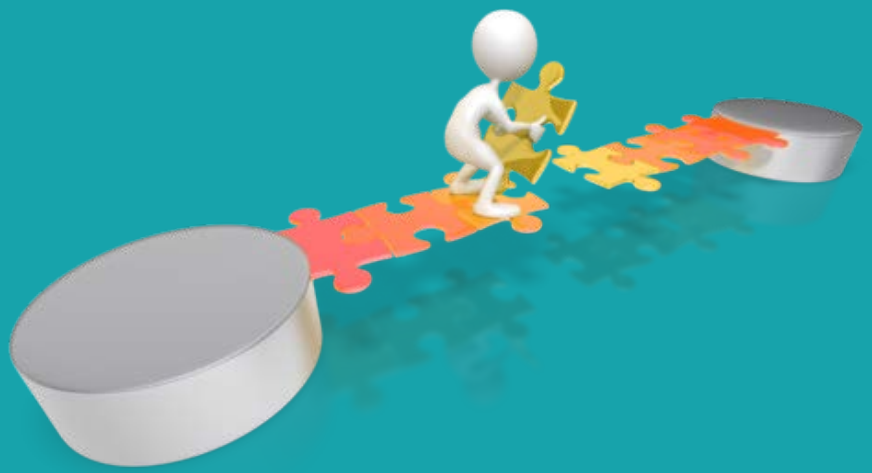
- How was correct dosing ensured?
- Adherence checked & non-adherence addressed?
- Pharmacokinetic (PK) sample collection & procedures followed as per protocol
- Medication administration in relation to meal
- Site awareness of & reaction to PK results

Remember everything cannot be PERFECT need to see processes are followed and data is accurate, quality is good and participant safety is always a priority WHILE adhering to the protocol

Arrival and Room

- Visitor cards & sign-in log with a dedicated person at reception
- Telephone & Internet connection
- Laptops
- Power cords, extensions and US/Europe plugs helpful
- Second printer
- Lock the room
- Bathroom close to the inspection room

INSPECTORS ON SITE



Arrival and room

- 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 45 minutes early

- Request copy of identification on arrival

- Issue visitor cards and remember they should not walk around the site unattended

- Quiet dedicated boardroom with ample working surfaces
- Files on a book shelf organised for the period of inspection
- Note “Please Keep Quiet, inspection in process”
- Three staff members (who knew most aspects of the study well) were dedicated to assist with requests for electronic documents, photocopying and to answer basic questions
    - Regulatory Manager
    - QA Manager
    - Study Coordinator
- Two staff members in the room provide immediate assistance & communicated with staff outside, one remained with them at all times

- Kept record of what was mentioned in opening meeting
- *Do not volunteer lots of extra information, only answer the question asked*
- Interviewed different people who worked on the study to ensure all staff know and adhered to SOPs
- PI was interviewed extensively during this inspection as well as the Study coordinator
- All staff involved in ICF's
- Compared and cross referenced "by the way" questions to the above interview answers

- Keep photocopies of all documents requested
- Know beforehand how to handle documents from DAIDS and the different time zones - difficult to obtain an answer within 1 hour
- Discussion between DAIDS/MCC and ourselves as to what documentation we were allowed to provide to the investigators. We deferred to MCC policy wherein the site is obligated to provide all requested documentation to inspectors in hard/electronic copy to avoid being seen to be obstructing the inspection
- Ensure participant identifiers on copies of source documents requested are blacked out

- *Keep list of what is requested, this helps not to forget a document*
- Each document needs to be assigned a number, entered on a log, stamped “confidential”,copied for them and the site file
- Keep an electronic version of the documents, same numbering system, in pdf format with watermark “confidential” (if not stamped)
- They requested an electronic version (on a memory stick) of all these documents to take with them when they left

- Do not answer a question if you are not certain of the answer.
- Always look at the participants file before answering a clinical question
- Don’t answer questions if not delegated to you (even though you know the answer)
- 24 hour emergency number tested, how the call is handled and escalated

- They sometimes look at one CRF, specifically one with many changes made on it, and a staff member has to verify all entries, who made the changes, and the reasons for these changes, in order to confirm site processes
- Lab had to track a specific sample through all steps, processes, and chain of custody until results were provided to site
- Should be able to “recreate the visit” with exactly the same results

Principal Investigator Responsibilities

- Know what is on the 1572
- Request daily meetings between the PI and inspectors
- Interviews with the PI almost guaranteed
- Proof of the PIs involvement throughout the study
- Weekly meeting minutes
- Daily debriefing calls with DAIDS

- Refreshments and assistance with transport "tricky"

CLOSE OUT MEETING & REPORT

Summarized findings

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 3 inspections

- Divide findings in critical (0), major (9) and minor (10) findings
- Report within days, this time – only sent report after Chiang Mai inspection
- Once report is received, site/sponsor need to address major findings within certain time frame, resolution of minor findings

MCC x 1 inspection

- No findings

CONCLUSION

Previous inspections findings addressed As mentioned in CAPA

Learning experience which improved our skills
to pick up transcription errors
identify missed tests
ensure a good paper trail
ensure processes are followed at all times

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Continuous training

Always do
it correctly

QA processes started on P1020a (our 1st clinical trial) have been improved and applied to all trials– will make future inspections easier (we have said a few times now – we are worried that we are not as stressed as before)

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