Inspections from a Site perspective

Wits RHI
Shandukani Research Centre

Acknowledge contributions from our entire team

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SACRA
Conference

University of the Witwatersrand
WITS RHI

Why have we been inspected 9 times (awaiting 10th ?)

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

1

FDA (n=3)

Atazanavir (2008)

Fosamprenavir (2012)

Raltegravir (2013)

EMeA (n=3)

Darunavir (2011)

Raltegravir (2013)

Dolutegravir (2016)

2

Large number of patients

Cohort n=4

Chiang Mai

3

Etravirine (SPONSOR 2017)

and

Simulated Inspection(2018)

4

MCC

Unannounced inspection (2013)

Stressful news!

Notification of the inspections were received from FDA and the EMA

(FDA domestic unannounced but international are announced)

PREPARATION

- United States Law
- USP
- Code of Federal Regulations: Title 21

  Legal binding force

Part 11 Electronic records: electronic signatures

Part 50 Protection of Human Subjects

Part 54 Financial Disclosure by Clinical Investigators

Part 56 Institutional Review Boards

Part 58 Good laboratory Practices

Part 312 Investigational New Drug Application

Part 314 Applications for FDA Approval to market a New Drug

- ICH Guidelines

E6 Good Clinical Practices

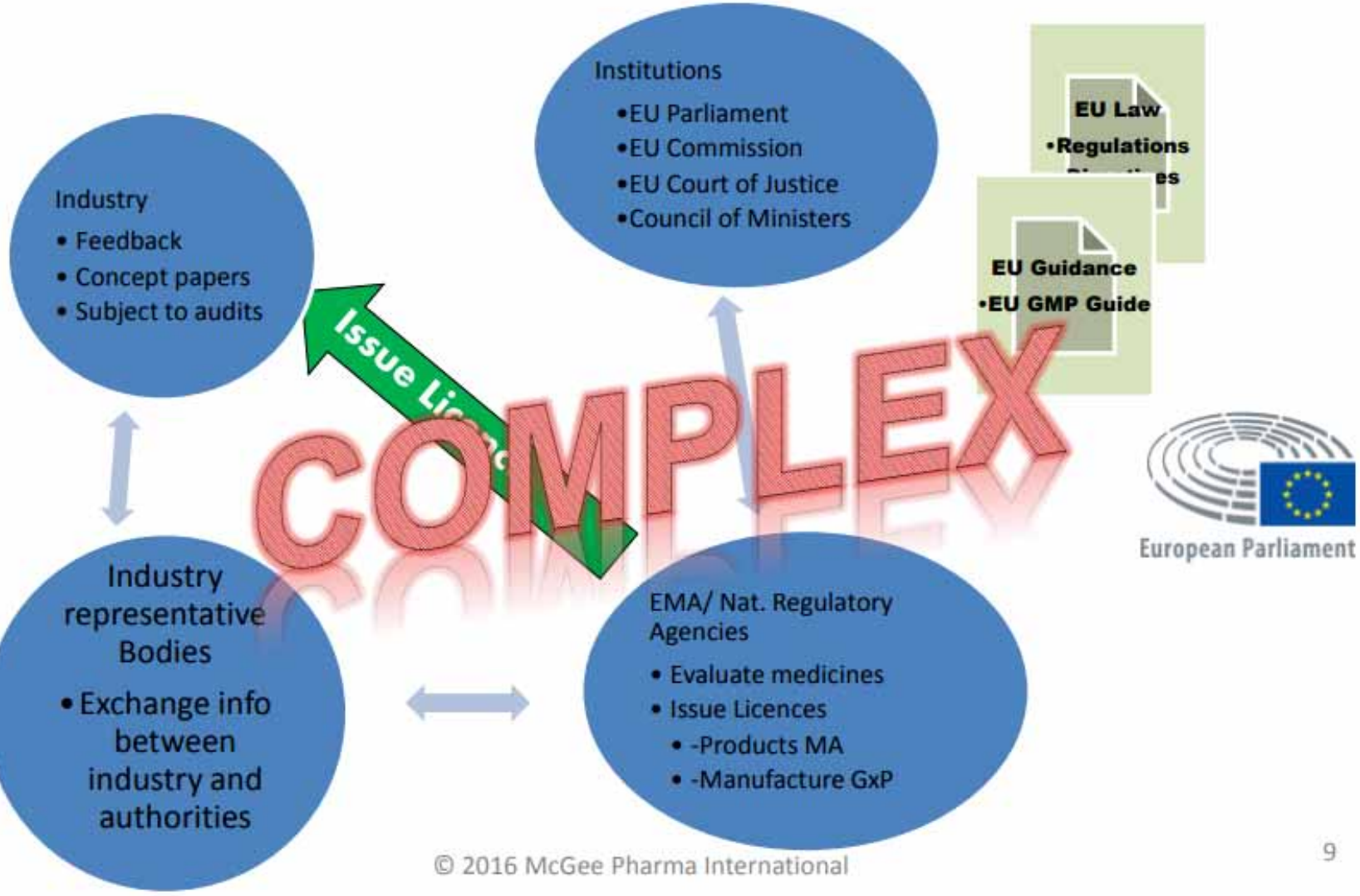
E2A Clinical Safety data management

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

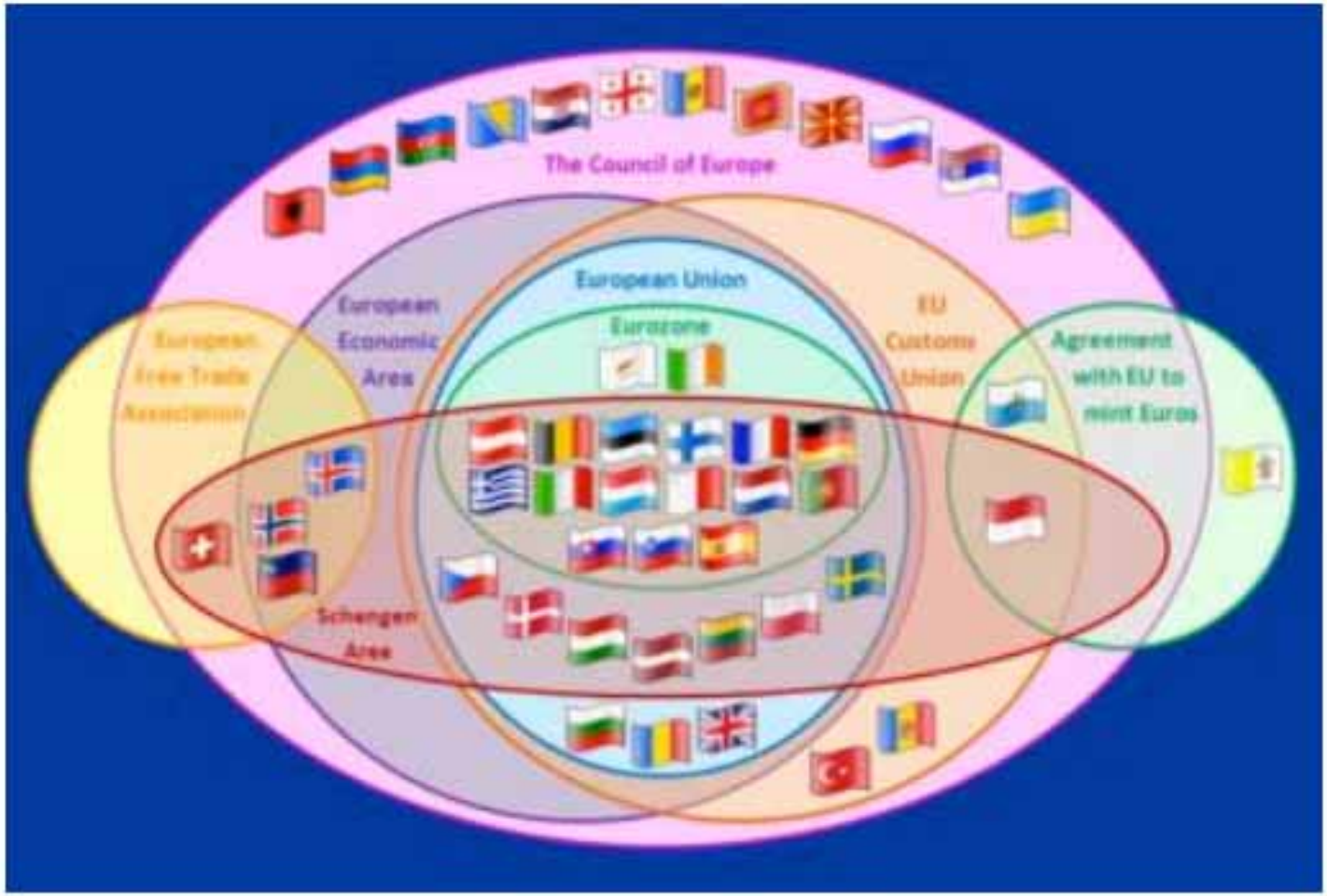
- The EMA works closely with the national competent authorities of the Member States of the European Union (EU) and the European Economic Area (EEA) responsible for human medicines

- Makes a recommendation and the European Commission authorises medicines
- Is responsible for the scientific evaluation, supervision and safety monitoring of medicines (only those managed through centralised authorisation procedure) developed by pharmaceutical companies
- Works closely with Member States and EEA countries

How Things Work in the EU/EEA



How things work in the EU



EU requirements

- **Regulations** – have binding legal force in every member state (MS) and enter into force on a set date in all

EU Clinical Trial Regulation (EU-CTR) was approved in April 2014 and published in the Official Journal of the European Union on 27 May 2014

- **Directives** – lay down outcomes that must be achieved, MS interpret when transposing into national laws

European Union Clinical Trials Directive

European Union Good Clinical Practice Directive

Determine appropriate staff members

-delegation log (appropriate qualifications and training on file?)

-involved in the trial

-available for interviews during the inspection

-provide this list to inspectors

NOT THE TIME TO SHOWCASE

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 SCs did ICF's
Study Coordinator	
Study Coordinator	
Sub-Investigator	
Project Manager CLS	

- 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 overtime! 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 neat, 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
- Prepare a study specific folder, summarize documents for specific study audited

Clinical

- Investigators reviewed protocol, inclusion and exclusion criteria met?

  Enrolment violations were identified
  All PD's reported, CAPA's done and implemented
  Immediately did root cause analysis why it happened

- Participant summaries were prepared

- PI reviewed all files

- Good to know what PD's and 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 and trial milestones
- Reviewed with dedicated staff (documentation)
- When were participants enrolled
- Reportable events reported

Informed Consent

- Informed Consent Forms (ICFs) and process:
  review all, including screen failures

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

- Participants have signed subsequent ICFs & 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 plans
- Signed off by the Principal Investigator (PI)

Special attention

- All approved ICFs (including footers/dates)
- IOR/FDA1572 forms (remember new staff)
- Ethics Committee and SAHPRA approvals
- Delegation logs (review and review, dates signatures, training)
- Log listing studies PI involved in

Training

- Attendance list and training material in the same file
- Delegated duties correspond with training
- New staff are trained before they are delegated and before they start working on the study
- Training on various systems corresponds with delegation to those tasks
- Temporary / separate file with relevant study and applicable staff

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 (when was what used)

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

- Often request an audit trail for data entry
- Verified access code security
- Correspondence with DMC re changes to database

IT

- Security of electronic records (SharePoint) & backed up regularly (off-site external server)

Maintenance

- Maintenance records up to date
- Serial numbers of specific equipment used for trial documented
  - Can it be easily identified?

Pharmacy Review

- Restricted access to pharmacy
- Storage areas, continuous temperature monitoring systems, fridges etc.
- IP stored separately, each study labelled
- Separate area/s for quarantined, expired & returned stock
- Cleaning logs
- Power back-up systems in place
- Dispensing areas vs admin workspace (in line with GPP and SAPC guidelines)

Review Pharmacy documents

- Pharmacy SOPs
- Prescriptions completed correctly, all fields
- Contact reports, issues reported to PAB or Sponsor
- Certificate of Analysis information consistent with shipping documents and stock received
- Shipping documents sorted, marked and filed chronologically
- Correlate stock received - entries drug accountability logs
- All medication dispensed to participants correlates with entries on accountability logs

Review Pharmacy documents

- Verification and documentation of electronic and manual temperature logs (labelled)
- Destruction certificates
- 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 was not version controlled

Lab kit storage area

- Temperature monitoring
- No expired lab kits
- Clearly labelled if more than one study

Sample Processing area

- Calibrations & equipment services up to date and on file for entire study period
- Information sheet - specifications for processing of samples
- Log to document PID, spinning speed, start time, stop time and time placed in freezer
- Log for freezer samples (in and out)

NB. Chain of custody log for samples sent to lab

Emergency trolley

- Easy access
- Checked routinely, equipment functioning, batteries charged
- No expired stock
- Required medication available (as per SAHPRA document)

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

- *Source document and financial agreement signed before study start*
- *Ensure responsibilities of the sponsor/s and of the site are clearly defined in the contract*
- *Contract with lab*
- *Checklist / formal process used by FHI to know the site is ready to start*
- *Laboratory Processing Chart dated correctly*
- Many questions about monitoring contract (DAIDS and PPD)

Regulatory: Investigator Site Files

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

  All sections should be present, even if documents are elsewhere
  Not to miss any required documents
- Protocols must be signed by PI on receipt
- Investigator Brochures must all be submitted to the regulatory authorities and staff must be alerted of new versions, proof of training
- Log of all protocol updates, approvals, implementation dates, informed consents used
- All documentation given to the participant must be version controlled and submitted to ethics for approval
- Staff CV's to be available on paper and also saved online.

  Staff CVs should be available from study start (including CV's of external stakeholders e.g. contracted lab personnel)

Regulatory: Investigator Site Files

- Staff qualifications: should match their delegated duties and qualification certificates should be available
- Participant screening, enrolment & screening failure logs available
- All reportable events - reported within the designated timelines (sponsor & regulatory timelines)
- Progress reports submission including acknowledgements must be on file
- ALL monitoring visit logs should state if the protocol has been reviewed at that visit

Regulatory: Investigator Site Files

- Ethics committee lists should state the validity of the committee (year)
- FDA1572/ IOR forms must be completed when new staff arrive and when they leave
- Financial Disclosures should be completed at study start and if required by the sponsor, annually thereafter.
- Insurance cover should be valid and should be reviewed to check that none of the potential participants have been excluded in the cover.
- PI to review the delegation of duties in relation to the qualifications of the study staff

Informed Consents

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

SAE's

- Timeliness of site awareness, 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

Pre-Arrival and Room Preparation

- Ensure a quiet dedicated lockable room with ample working surfaces available and bookshelf for files
- Proximity close to a bathroom (don’t want them wandering around)
- Internet connection (telephone, if requested)
- Power cords, extensions and US/Europe plugs helpful
- Copier, scanner and printer
- Put up “Please Keep Quiet, inspection in process” notices to keep noise levels at a minimum

INSPECTORS ON SITE

	FDA	EMA
Duration	5 days	3-5 days
People	1	2 or more
Approach	Formal docs form 482 with FDA signature and NOI	Informal discussion purpose and expectations No formal documents
Shandukani Research Centre site always does a welcoming meeting and Includes all relevant staff		

Arrival

- What we read about inspections made us react quite nervously to the first few inspectors. 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 never walk around the site unattended

- 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 & they communicate with staff outside, document what is asked and answered during interviews
- One staff member to remain with them at all times. NEVER leave them alone

- *Do not volunteer lots of extra information, only answer the question asked*
- Interview: “Describe how you did…” testing knowledge and adherence of SOPs
- PI interviewed extensively, as well as the sub-investigator, Regulatory Manager, Study coordinator, Data manager, PoR and QA staff
- All staff involved in ICF’s
- Do not answer questions if task was not delegated to you (even though you may know the answer)
- Compared and cross referenced “by the way” questions to the above interview answers
- Remain calm even if difficult questions are asked

- Know beforehand how to handle documents from DAIDS (sponsor) - different time zones can make it difficult to obtain an answer quickly
- Discussion between DAIDS/SAHPRA and ourselves as to what documentation we were allowed to provide to the investigators. We deferred to SAHPRA 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 a log of what is requested, time requested, and time document was provided (plus a copy for the site)*
- Each document needs to be assigned a number, entered on a log, stamped “confidential” and “certified copy of original” with signature and date, and copied for inspector and the site file
- Keep an electronic pdf version of the documents, same numbering system (watermark “confidential” if not stamped)
- Electronic copies (on a memory stick) vs hard copies

- Do not answer a question if you are not certain of the answer. You may request to refer to the protocol, participants files etc. and get back to them later
- Always refer to the participants file before answering a clinical question
- 24 hour emergency numbers are sometimes tested (who answers, how the call is handled and escalated)

- Data processes: they will choose one CRF with many corrections, and verify all entries: who made the changes, reasons for these changes, in order to confirm site and DMC processes
- All entries should be attributable
- 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 guaranteed
- Proof of the PIs involvement throughout the study
- Workload of PI
- Weekly meeting minutes supporting
- Daily debriefing calls with DAIDS

- Refreshments and assistance with transport sometimes “tricky”

CLOSE OUT MEETING & REPORT

Summarized findings

FDA x 3 inspections

•No Form 483 for any inspections for our site

3 classifications

- NAI – no action indicated
- VAI – voluntary action indicated
- OAI – Official action indicated (Issued at the conclusion if violations are found)

Summarized findings

EMA x 3 inspections

- Verbally discuss shortcomings, problems etc at the close-out meeting
- Divide findings in critical (0), major (9) and minor (10) findings
- Report within days, except in 2016 – 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

SAHPRA x 1 inspection

- No findings

Summarized findings

Sponsor x 1

We were asked via DAIDS to respond to certain issues

Simulated x 1 inspection

Awaiting report - This was by far the most “INTENSE” audit

CONCLUSION

Focus

FDA

Data collection and integrity

EMA

SOPs and Processes

Consistent Quality Control
Changes to improve

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FDA and EMA

Participant safety, regulatory , equipment, pharmacy and laboratory issues

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Previous inspections findings addressed

Learning experience
Improved our skills
to pick up errors,
Identify issues,
ensure good documentation,
ensure processes are followed at all times

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QA processes started on P1020a (our 1st clinical trial) have been improved and applied to all trials. Future inspections will be easier

Continuous learning and training

Do things right the first time!

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