SAAPI CONFERENCE

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04 October 2018

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The Impact of Local and Global Regulations and Guidelines on the South African Clinical Trials Industry

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Disclaimer

This presentation is intended to draw attention to specific points of interest and should not be considered as regulatory advice.

Any errors or opinions are those of the presenter.

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Local Stakeholders

- Study participant
- Trial sponsor (pharma company, university or individual)
  - Monitor: employed by sponsor to monitor conduct of study at site(s)
- Investigators and site staff (nurses, study coordinators, pharmacists)
- Ethics Committees
- Regulatory bodies (SAHPRA, NDoH)
- Provincial / district authorities and hospital review boards

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Many Requirements to Satisfy

- Clinical trial data need to be acceptable to many international regulators
- Data is collected in many countries – differing local regulations
- Data may be reviewed, processed and analysed in countries where it was not collected (cross-border transfer)
- Uses healthcare data which often require special protections

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International Guidelines

- Provide some level of harmonization
  - Recognised by regulators at different times
  - Hold different status in different regions
  - May be superseded by local laws
- Alignment with these may lead to unintended problems
- Different focus of regulators during pre-marketing authorisation clinical trial inspections

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Applicable International Guidelines

- International Conference on Harmonisation Guidelines:
  - E2A: Clinical Safety Data Management
  - E3: Clinical Study Reporting
  - E6: Good Clinical Practice
  - E7: Geriatric Populations
  - E8: General Considerations for Clinical Trials
  - E9: Statistical Principles
  - E11: Pediatric Populations
- PIC/S GMP
- Other regional regulations / guidelines may apply
  - General Data Protection Regulations (EU)
  - e.g.: site appended to IND makes 21 CRF applicable

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Unintended Problems

SA GMP v5 Annex 13
(Section 13.6.7.3)

Particulars should appear in at least one of the official languages.

The particulars listed in item 13.6.7.1 should appear on the immediate container and on the outer packaging (except for immediate containers in the cases described in items 13.6.7.4 & 13.6.7.5).

The requirements with respect to the contents of the label on the immediate container and outer packaging are summarised in table 1.

PIC/S 1 January 2017 Annex 13
(Article 28)

Particulars should appear in the official language(s) of the country in which the investigational medicinal product is to be used.

The particulars listed in Article 26 should appear on the primary packaging and on the secondary packaging (except for the cases described in Articles 29 and 30).

The requirements with respect to the contents of the label on the primary and secondary packaging are summarised in table 1. Other languages may be included.

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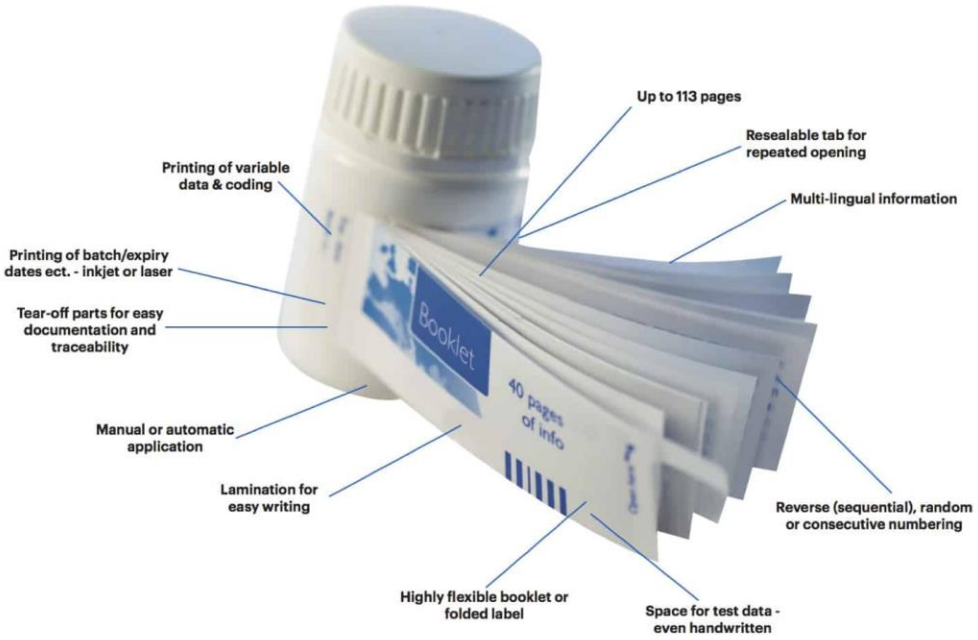
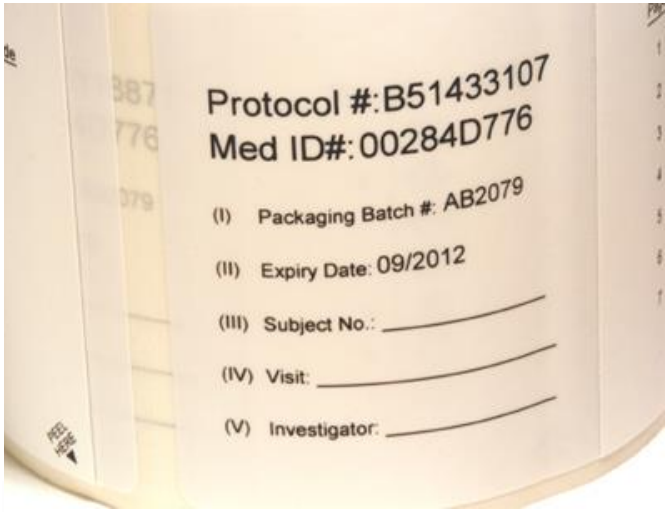
Booklet Labels





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Regulatory Inspection Focus

FDA	EMA	MCC/SAHPRA
Usually triggered by marketing application – high enrolling sites	Usually triggered by marketing application – high enrolling sites	May be routine or for-cause (issues in progress reports or complaint received)
Strong focus on data integrity – large volumes of source document verification, trace all changes from start for a data point that has been revised a number of times List of disbarred investigators	Strong focus on processes, examination of SOPs, training records, trial logs etc., lots of interviews to verify familiarity with processes	General assessment or targeted at identified issue Significant focus on data integrity Have identified problem investigators and closed sites but no list available

Based on WHRI presentation at SACRA Conference 2018

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International Guidelines
Recent GCP Revisions

- ICH E6 Good Clinical Practice Step 4 Nov 2016
  - Risk proportionate monitoring based in ICH Q9 principles (focus on data and processes key to participant safety and study endpoints, centralized data analysis for trends)
  - Pre-planned steps, thresholds and escalation plans
  - Review of signals and adjustment of plans where indicated
  - Thorough documentation of rationale for plan and revisions to plan

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Selected Local Regulation

- Medicines Act (101 of 1965 as amended)
  - Medical Device Regulations 09 Dec 2017
  - General Regulations 25 Aug 2017
- National Health Act (61 of 2003)
  - Export (and import) of biological samples
  - NHRC (and PHRCs) and NHREC
  - Ministerial consent for non-therapeutic research in minors
  - SA Good Clinical Practice Guidelines
- Children's Act (38 of 2005)
- Genetically Modified Organisms Act (15 of 1997)
- Hazardous Substances Act (15 of 1973)
- (Protection of Personal Information Act)

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Other Selected Local Guidelines

- Good Pharmacy Practice Guidelines
- HPCSA General Ethical Guidelines on Health Research
- Clinical Trials Committee (SAHPRA)
  - Post clinical trial access / continued access
  - Emergency procedures for clinical trial sites
  - Clinical trial investigators (co-principal investigators)
  - Oversight and Monitoring in Clinical Trials
  - Participant time, inconvenience and expenses compensation
  - Adverse event reporting (update pending)
  - (Capacity building and transformation)

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Challenges

- Discrepancies between Acts – which one governs?
- Unwritten requirements – completing clinical trial applications guideline last updated in 2003
- Bodies who try to take on responsibilities already undertaken by others
  - Hospital boards wanting to change ICFs (ethics committee responsibility)
  - PHRCs wanting to act as ethics committees (start- up delays, trial potentially never started)
- Documents published for implementation without previous draft for comment
  - Materials Transfer Agreement
- Forms do not always align with regulation

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Clinical Trials in Sub-Saharan Africa

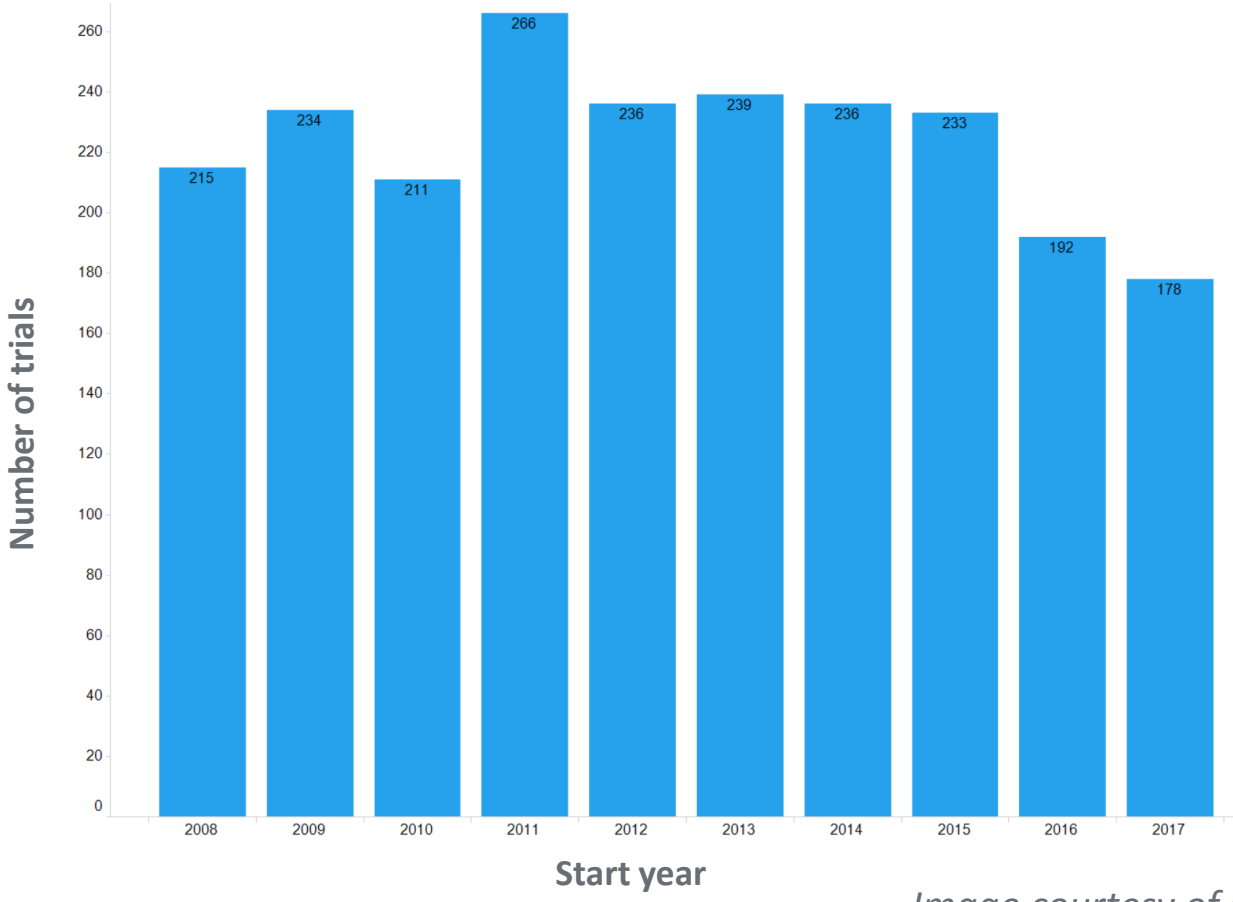

Image courtesy of Clarivate Analytics

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Number of Trials Reviewed by CTC

	1A	1B	2A	2B	3	4	5	6	Total
2016	0	1	16	93	28	0	4	10	152
2015	0	4	13	111	34	0	3	3	168
2014	0	2	11	151	29	2	1	10	206

Could uncertainty regarding some of the draft regulations have impacted Sponsors' decisions to use South African sites?

Images courtesy of Clinical Trials Committee – Nov 2017

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Hope!

- New review and approval processes should reduce timelines once fully operational
- Clinical Trials Committee (& SAHPRA) engagement with industry significantly improved
  - Regular clinical trial stakeholder meetings
  - Regular updates by email regarding issues
  - Responsiveness to industry comments, revisions to guidelines and forms
  - Plans to create and update guidelines (unwritten requirements will be documented), updates on status of guidelines being provided at stakeholder meetings

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Questions

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