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DATA INTEGRITY IN CLINICAL RESEARCH

Singapore Clinical Research Professional (CRP) Forum

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Welcome!

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Responsibilities include
- Clinical QA
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29 years in biopharm industry

14 years in QA leadership

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Quality objectives of clinical research

HUMAN SUBJECT PROTECTION

DATA INTEGRITY

Achieved within the context of compliance with applicable laws and regulations of clinical trials of investigational products.

Data integrity – a highlight in the addendum to ICH E6 (R2) GCP

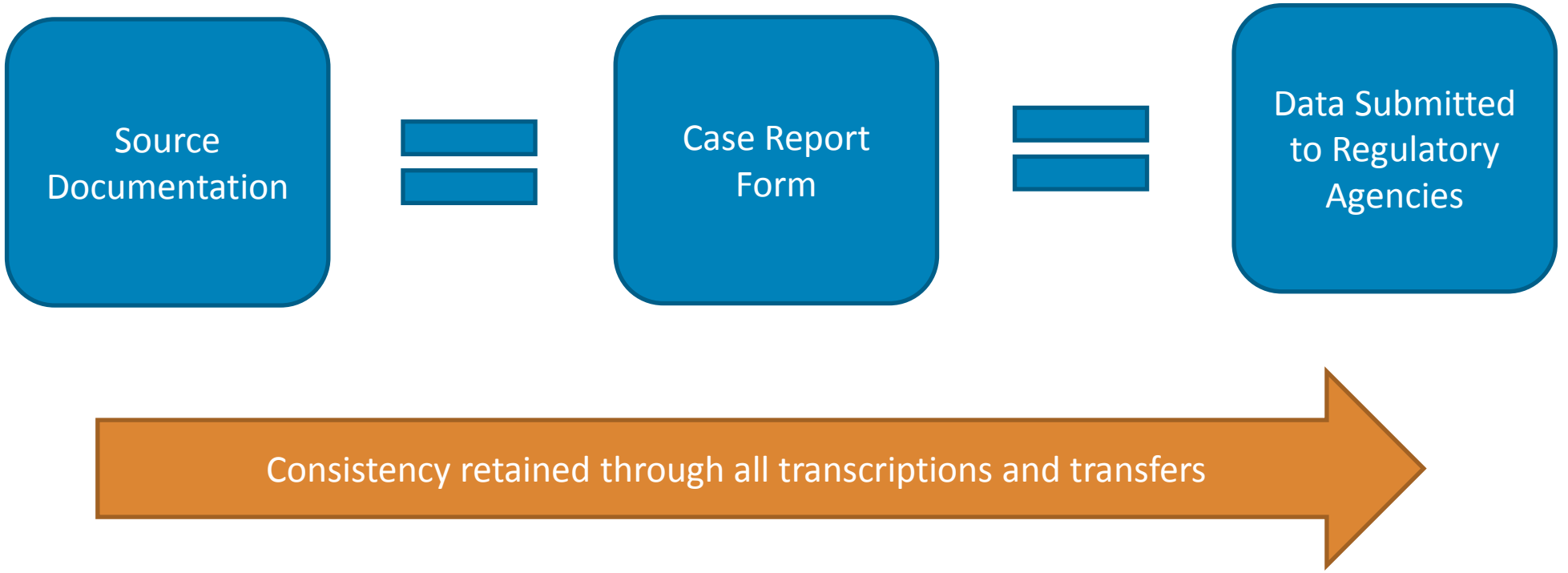
ADDENDUM

Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. This guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and data integrity. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.

Data integrity defined

The extent to which all **data are complete, consistent and accurate throughout the data lifecycle**, from initial data generation and recording through processing (including transformation and migration), use, retention, archiving and retrieval.

Maintaining integrity through the data lifecycle



Data integrity – an example in the news

GVK Biosciences: European Medicines Agency confirms recommendation to suspend medicines over flawed studies

Press release

22/05/2015

GVK Biosciences: European Medicines Agency confirms recommendation to suspend medicines over flawed studies

Medicines considered critically important for patients to remain available

The European Medicines Agency (EMA) has confirmed its recommendation to suspend a number of medicines for which authorisation in the European Union (EU) was primarily based on clinical studies conducted at GVK Biosciences in Hyderabad, India. This is the outcome of a re-examination requested by marketing authorisation holders for seven of the medicines concerned.

EMA's Committee for Medicinal Products for Human Use (CHMP) had adopted its original recommendation in January 2015 following an inspection of GVK Biosciences' site at Hyderabad by the French medicines agency (ANSM) that raised concerns about how GVK Biosciences conducted studies at the site on behalf of marketing authorisation holders.

The inspection revealed data manipulations of electrocardiograms (ECGs) during the conduct of some studies of generic medicines, which appeared to have taken place over a period of at least five years. Their systematic nature, the extended period of time during which they took place and the number of members of staff involved cast doubt on the integrity of the conduct of trials at the site generally and on the reliability of data generated.

Examples of increasing regulatory attention and new guidance

World Health Organization

2016 – Annex 5: Guidance on good data and record management practices

CFDA China Food and Drug Administration

2016 – Draft Guidance: Drug Data Management Guidance

MHRA Regulating Medicines and Medical Devices

2016 – Draft Guidance: GxP Data Integrity Definitions

Globally, emerging definitions and expectations are generally aligned

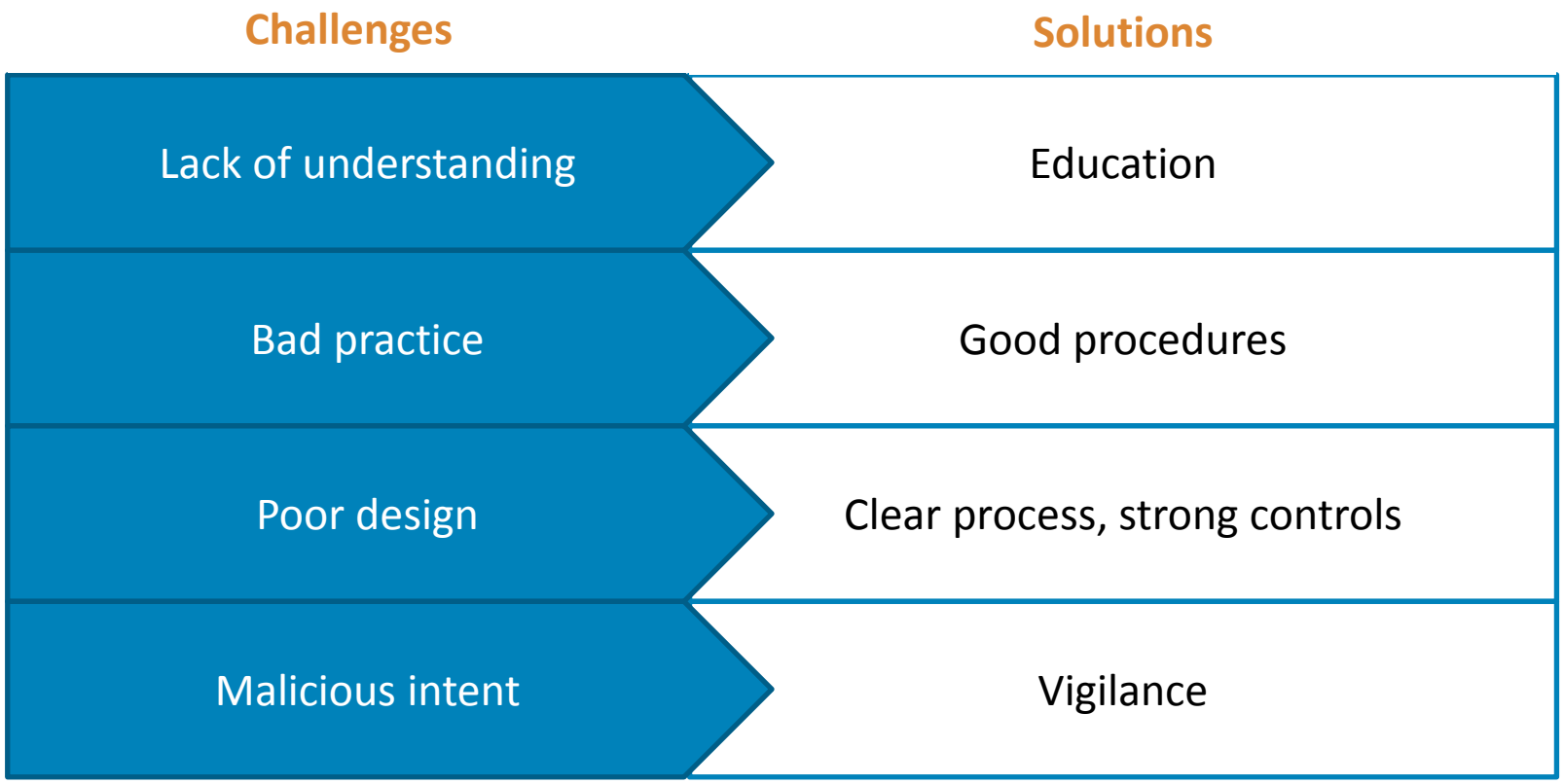
The foundation is Good Documentation Practices

- **A** Accurate
- **L** Legible
- **C** Contemporaneous
- **O** Original, or certified copy
- **A** Attributable

- **+** Complete
- **+** Consistent
- **+** Enduring
- **+** Available when needed

Applies to both PAPER RECORDS and ELECTRONIC SYSTEMS

Sources of data integrity issues



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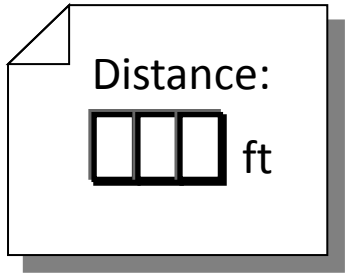
INDUSTRY CASE STUDIES

Data Integrity in Clinical Research

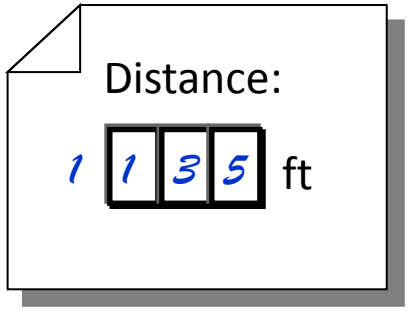
Case study – US FDA example*

1. CRF for recording the distance of a six minute walk test only allowed for 3 digits.

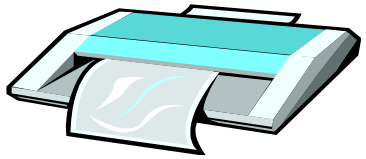


2. In some cases subjects walked
1000 ft or more.

3. In order to record the 4-digit result, the site wrote outside of the boxes.



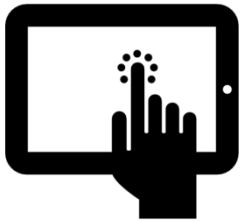
4. The sponsor used an automated scanner to process the CRFs, which missed any numbers outside the boxes.



*Donat, Adam, "Data Integrity in FDA-Regulated Clinical Trials," DIA 2017 Global Annual Meeting, 22 June 2017.

Case study – UK MHRA example*

1. Subjects reported data in electronic diary



2. Investigator sites requested changes to the subject reported data

3. The sponsor accepted the changes, with no verification

4. No source data could be provided to MHRA inspectors that supported the changes made

This example resulted in a critical observation for data integrity.

*"GCP Inspections Metrics Report," MHRA, 21 July 2017

Case study – China FDA self-audit and verification program example

No. 117 announcement by CFDA, 22 July 2017
http://www.sda.gov.cn/WS01/CL0087/124800.HTML

Goals of program:

- Ensure authenticity and reliability of clinical trial data submitted to CFDA
- Ensure subject protection

Outcome

- Applications voluntarily withdrawn: 31%
- Applications rejected after inspection: 11


CFDA 国家食品药品监督管理总局
China Food and Drug Administration

国家食品药品监督管理总局关于开展药物临床试验数据自查核查工作的公告（2015年第117号）

2015年07月22日 发布

为落实党中央、国务院用“最严谨的标准、最严格的监管、最严厉的处罚、最严肃的问责，确保广大人民群众饮食用药安全”的要求，从源头上保障药品安全、有效，国家食品药品监督管理总局决定对附件所列已申报生产或进口的待审药品注册申请开展药物临床试验数据核查，有关事宜公告如下：

Key findings of China FDA GCP inspection program

- Discrepancies between medication logs (sponsor shipping notes, hospital pharmacy logs, and patient files)
- Discrepancies between samples taken by an investigator or nurse and samples analyzed by the laboratory (e.g., there was no signed and dated sample transfer document, which is mandatory)
- Repeat analysis of samples contrary to trial protocol
- Incorrect age of trial subjects due to errors in date calculation (from the traditional Chinese calendar to the Gregorian calendar)
- Discrepancies between medical records and patient files with regards to medication not prescribed by the investigation site

Final thoughts

Educate on Good Documentation Practices – ALCOA +

Make sure source data are identified as such

Justify, document, and communicate data changes

Be vigilant

Ask questions when things don't make sense

DATA INTEGRITY

Data integrity in clinical research helps to enable regulatory success and, in turn, gets important new therapies to patients faster.

Thank you!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Abstract

Data integrity – along with human research subject protection – has long been a primary quality objective of clinical research. While the expectation for reliable data is not new, regulatory agencies around the world are renewing focus on it, as demonstrated in the proliferation of new guidance and attention in inspections. The introduction of electronic systems and new technology across the clinical research enterprise, while creating efficiencies, has introduced new data integrity challenges from access management to hackers. This presentation discusses the evolving expectations for data integrity in clinical research, example of data integrity issues, and considerations for quality control and assurance.