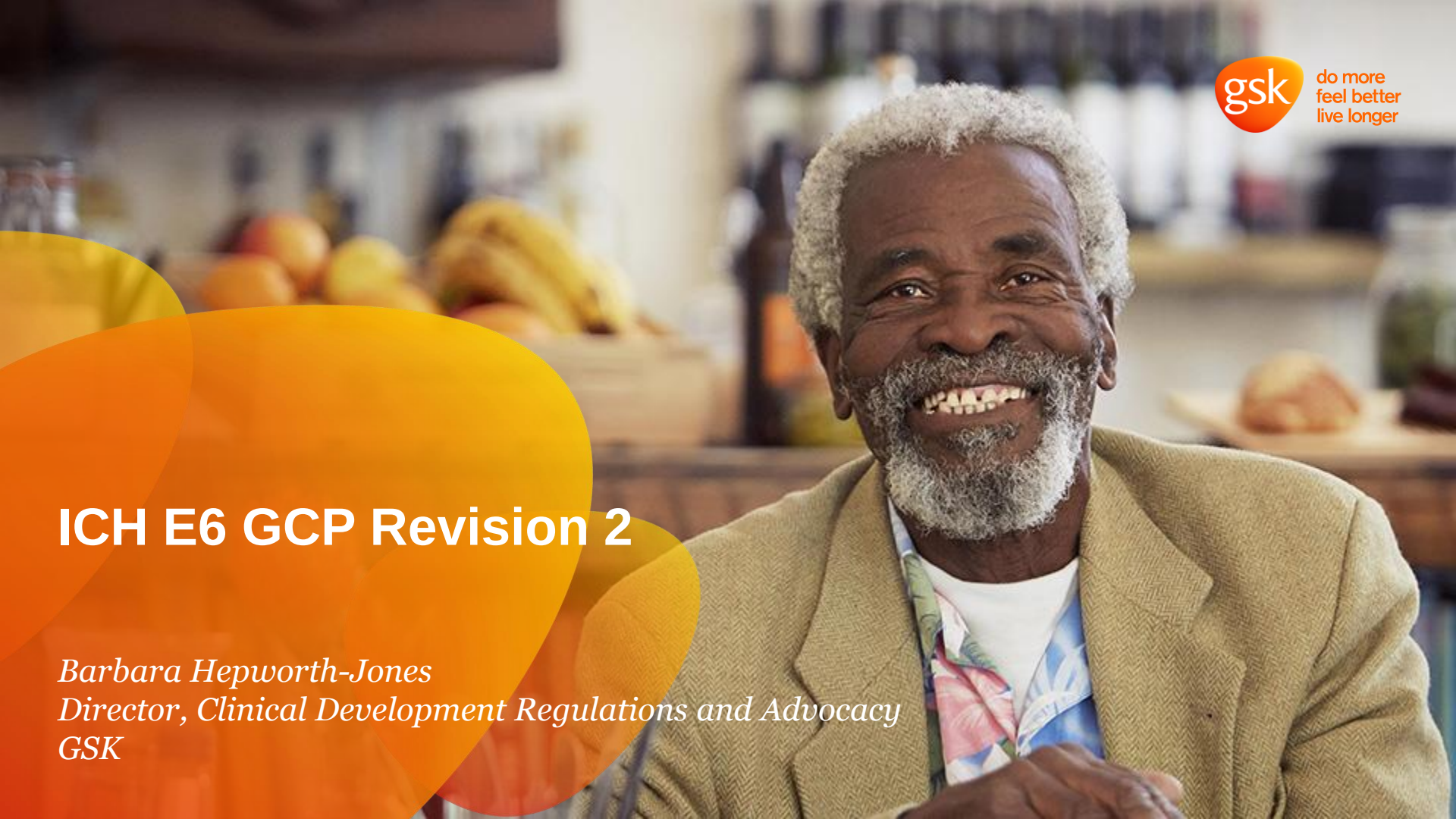


ICH E6 GCP Revision 2

Barbara Hepworth-Jones
Director, Clinical Development Regulations and Advocacy
GSK


TIME
FICTION BONUS:
"CLONE ON THE RANGE"
BY DOUGLAS COUPLAND
Will There Ever
Be Another You?


MARCH 11, 1996 $2.95
TIME
EXCLUSIVE
CASTRO: WHY WE DID IT
CAN DOLE GO ALL THE WAY?
It's
Over
Diana and Charles
are history, but a
battle royal looms
over her future

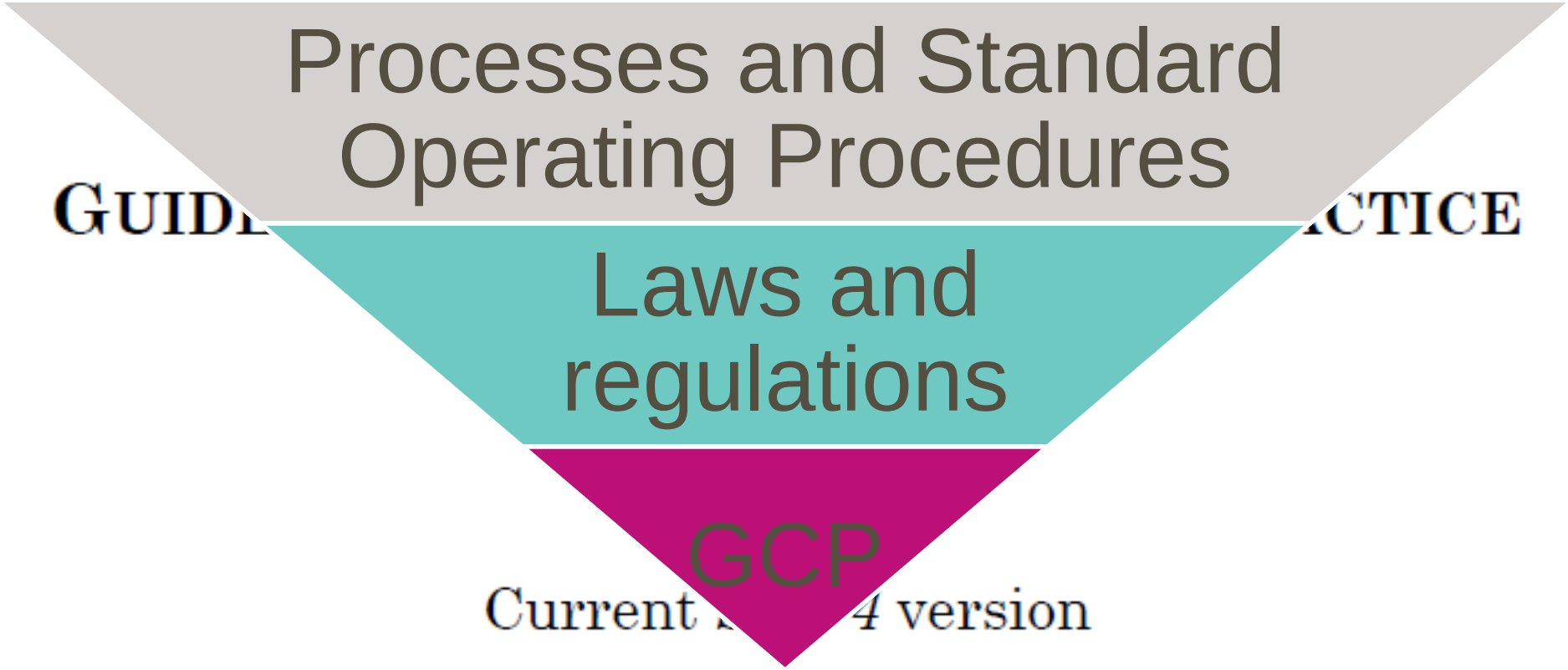
ICH HARMONISED TRIPARTITE GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE
E6(R1)

Current *Step 4* version

dated 10 June 1996

ICH HARMONISED TRIPARTITE GUIDELINE



GUIDE CTICE

Current 4 version

dated 10 June 1996

What is changing?

- Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (GCP) was formally adopted by ICH in November 2016. It now enters Step 5, implementation period
  - “ICH E6(R2) aims to encourage sponsors to implement improved oversight and management of clinical trials, while continuing to ensure protection of human subjects participating in trials and clinical trial data integrity.”
- It reflects changes over the last 20 years including increased study complexity and electronic systems
- Key themes include
  - Sponsor responsibilities/oversight
  - TMF
  - Risk assessment
  - Data integrity, handling and access

26 changes:

Current E6(R2) Addendum *Step 4* version

Code	History	Date
E6(R2)	Adoption by the Regulatory Members of the ICH Assembly under *Step 4*. Integrated Addendum to ICH E6(R1) document. Changes are integrated directly into the following sections of the parental Guideline: Introduction, 1.63, 1.64, 1.65, 2.10, 2.13, 4.2.5, 4.2.6, 4.9.0, 5.0, 5.0.1, 5.0.2, 5.0.3, 5.0.4, 5.0.5, 5.0.6, 5.0.7, 5.2.2, 5.5.3 (a), 5.5.3 (b), 5.5.3 (h), 5.18.3, 5.18.6 (e), 5.18.7, 5.20.1, 8.1	9 November 2016

Some changes are very minor e.g.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

ADDENDUM

This principle applies to all records referenced in this guideline, irrespective of the type of media used.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

New Quality Management section

5. SPONSOR

ADDENDUM

5.0 Quality Management

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

The quality management system should use a risk-based approach as described below.

5.0.1 Critical Process and Data Identification

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

5.0.2 Risk Identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

5.0.3 Risk Evaluation

The sponsor should evaluate the identified risks, against existing risk controls by considering:

(a) The likelihood of errors occurring.
(b) The extent to which such errors would be detectable.
(c) The impact of such errors on human subject protection and reliability of trial results.

5.0.4 Risk Control

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

5.0.5 Risk Communication

The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

5.0.6 Risk Review

The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

5.0.7 Risk Reporting

The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents , and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 Contract Research Organization (CRO)

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

“This amendment will now be implemented by ICH members through national and regional guidance.”

- Challenge for a global company, as dates will vary among ICH members, who include:
  - European Union
  - FDA
  - Ministry of Health, Labour and Welfare of Japan
  - Health Canada
  - Swissmedic
- So far, only the European Union has confirmed a date, **14 June 2017**
- GSK: global activities should align with R2 from 14 June 2017

http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

E6 Good Clinical Practice

Code	Document Title	Previously coded
E6(R1)	Good Clinical Practice	
E6(R2)	**Integrated Addendum to Good Clinical Practice (GCP)**	

Description : Since the finalisation of the ICH Good Clinical Practice (GCP) Guideline in 1996, 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 reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.
In this "Integrated" Addendum, changes were integrated directly into several sections of the parental Guideline.

Implementation : *Step 5*

EC	Adopted by CHMP, 15 December 2016, issued as EMA/CHMP/ICH/135/1995
MHLW/PMDA	To be notified
FDA	To be notified
Health Canada	To be notified
Swissmedic	Please refer to the press release on Swissmedic's website for information on implementation

Finalised Integrated Addendum: November 2016

- E6(R2)

- Concept Paper
- Business Plan

- E6(R2) Step 4 - Presentation

R2 won't be added to the Clinical Trials Ordinance until late 2017, but Swissmedic believe all additions are already covered by existing requirements in other guidelines so are using R2 with immediate effect

Guideline for good clinical practice E6(R2)

Step 5

Adopted by CHMP for release for consultation	23 July 2015
Start of public consultation	4 August 2015
End of consultation (deadline for comments)	3 February 2016
Final adoption by CHMP	15 December 2016
Date for coming into effect	14 June 2017

What is the Regulatory Authority perspective?

- No specific guidance from MHRA, FDA, EMA on expectations

- If written standards (SOPs, Policies, etc) state “ICH GCP” and do not specify which version, it *may* be assumed that the current version is referred to i.e. R2 after 14 June?
- GCP is so fundamental, inspectors *may* be interested in how sponsors have assessed impact and planned for change

What needed to be done at GSK?

Overview

- Ensure all areas of the business are aligned
- Assess clinical processes and associated written standards (WS; includes SOPs, guidance, policies, etc.) to identify any gaps
- Plan learning strategy so everyone impacted by GCP is up to date
- Discussions with other impacted groups who work on clinical trials but are not primarily GCP functions e.g. IT
- Get endorsement for the approach and high level plans from GSK Clinical Quality Council
  - Drive GCP quality, compliance and improvement across Clinical Development globally

Process Review

The devil is in the detail

- Authors/subject matter experts within the business have confirmed the impact on their written standard, with support from GCP specialists
- No major impact, because key changes already implemented/in progress at GSK, but this may not always be the case for other sponsors
- Detailed check to identify minor details within written standards that require alignment showed approx. 5% of written standards require minor updates/clarifications

Potential major areas of change

- Broad definition of, and standards for, the TMF
- Risk management process/SOP
- Oversight of vendors
- Risk based approach to monitoring, central monitoring activities
- Data Integrity Policy in line with R2; ALCOA CCEA

Documentation: “ALCOA”

Attributable	• Data are traceable to the originator, (person and/or a computerised system, a device, an instrument), including any changes made to data, i.e. who performed an action and when
Legible	• Data are readable and understandable
Contemporaneous	• Data are recorded at the time they are generated or observed as per regulatory requirements; or in absence of regulatory requirements, local business practices
ORIGINAL*	• Data as the file or format in which it was first generated, e.g. first paper record of manual observation, or electronic raw data file from a computerised system as per regulatory requirements; or in absence of regulatory requirements, local business practices
ACCURATE	• Data, including error corrections and edits, are correct, truthful and to the appropriate precision

***Certified / True Copy can be considered Original**

“CCEA” particularly for electronic records

Complete	•Data and records must provide the full context of the subject’s study participation
Consistent	•Data and records must be logical and contain no contradictions with other records
Enduring	•Data and records must be recorded using permanent media or, if originally recorded on temporary media, permanence is achieved through the use of certified copies
Available	•Is the source document the first place where data was recorded?

Examples of potential minor gaps

- Validation of migrated data and process for decommissioning systems
- Significant noncompliance requires root cause analysis and corrective and preventive actions. Is RCA/CAPA capability sufficient to support this?
- Ownership of CRF data
  - Sponsor should ensure investigator has control of and continuous access to CRF data
  - Sponsor should not have exclusive control of CRF data
  - Investigator/institution should have control of all essential documents/records they generate; before, during, after trial
- Investigator responsibilities: supervision of delegated tasks e.g. to other departments/physicians. Could include labs, pharmacy, eye testing, satellite sites, etc
- Sponsor oversight of sub-contractors
- More specific references to sponsor oversight and risk management

Implementation

Rolling approach to phase in and be ready by the EU implementation date

- New and revised process documents must comply with Revision 2 in order to avoid re-work
- Minor changes made for R2 compliance out of sequence and then return to the usual schedule for routine updates (less than 5% of WS)
- Alternatives that may be considered
  - Where changes are very minor, a planned process deviation as per SOP
  - Where WS are being updated routinely for release soon after 14 June, risk assessment and mitigation instead of trying to speed up the update

Approaches to learning

- Staff will be trained on revised written standards as usual, including any R2 changes
- Information campaign around R2
- Elearning module being developed for release in early April, to be completed by 14 June
- Optional webinars highlighting key changes and allowing for discussion in mid-June
- External GCP training aimed at site staff being revised. No news yet on whether Transcelerate will update their standard for GCP training to incorporate R2, but we can re-validate the revised training through the usual Transcelerate process

Questions and Discussion