ISO14155: 2011

Clinical investigation of medical devices for human subjects
- Good Clinical Practice -

ISO TC194 WG4

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What is GCP?

- Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

- Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

(ICH-GCP)

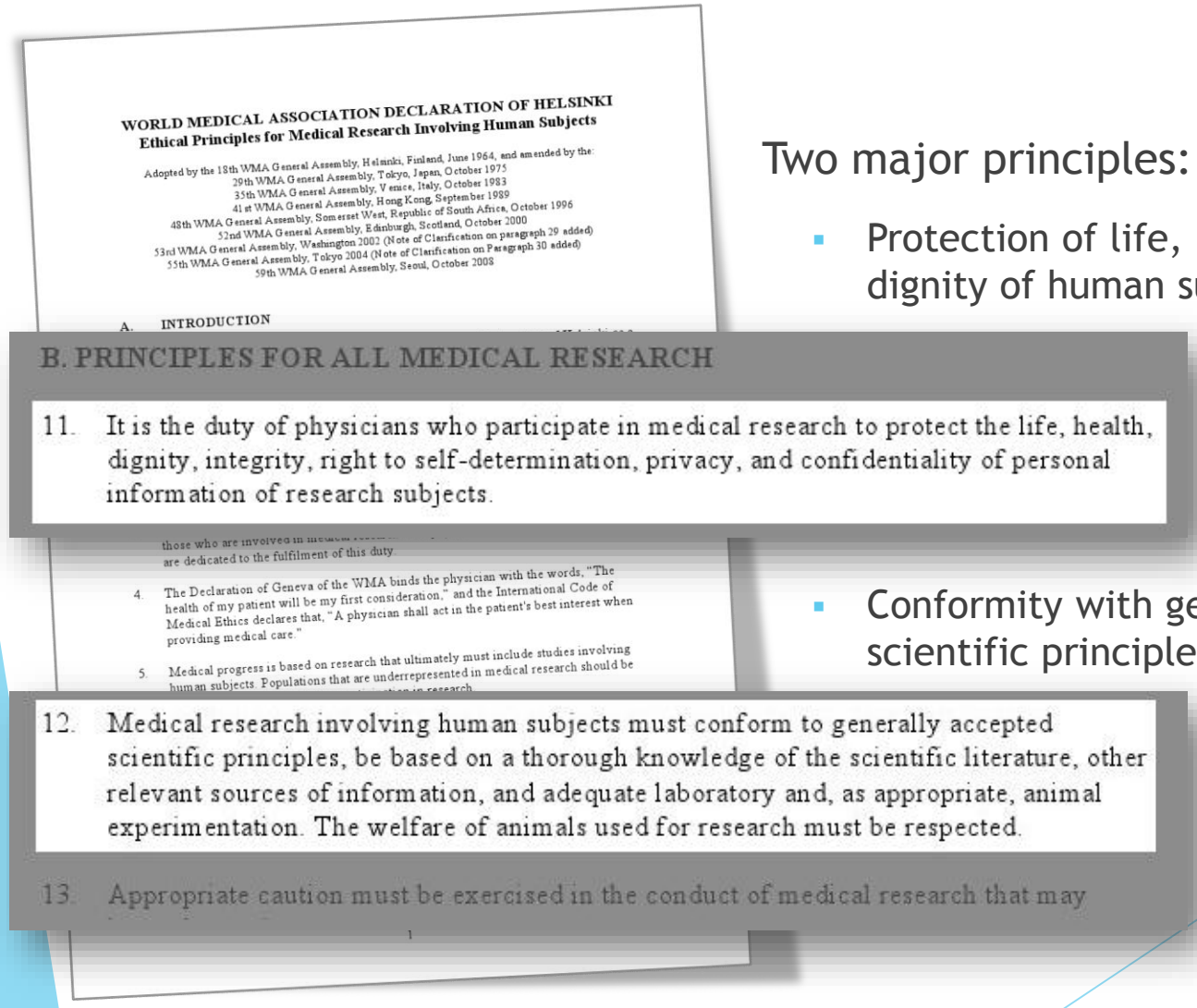
Three important foundations

- Nuremberg Code (1947)
- Declaration of Helsinki (1964)
- Belmont Report (1979)

10 points of Nuremberg Code

1. Required is the voluntary, well-informed, understanding consent of the human subject in a full legal capacity.
2. The experiment should aim at positive results for society that cannot be procured in some other way.
3. It should be based on previous knowledge (like, an expectation derived from animal experiments) that justifies the experiment.
4. The experiment should be set up in a way that avoids unnecessary physical and mental suffering and injuries.
5. It should not be conducted when there is any reason to believe that it implies a risk of death or disabling injury.
6. The risks of the experiment should be in proportion to (that is, not exceed) the expected humanitarian benefits.
7. Preparations and facilities must be provided that adequately protect the subjects against the experiment's risks.
8. The staff who conduct or take part in the experiment must be fully trained and scientifically qualified.
9. The human subjects must be free to immediately quit the experiment at any point when they feel physically or mentally unable to go on.
10. Likewise, the medical staff must stop the experiment at any point when they observe that continuation would be dangerous.

Basic Concept of Declaration of Helsinki



WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may

Two major principles:

- Protection of life, health, privacy, and dignity of human subjects
- Conformity with generally accepted scientific principles

Basic Ethical Principles of Belmont Report

- Respect for Persons

  Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, second, that persons with diminished autonomy are entitled to protection.

- Beneficence

  Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being.

- Justice

  Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved."

History of ISO 14155

- ISO14155: 1996
- ISO14155: 2003 - Part1, - Part2
- ISO14155: 2009 (Revision only to annex)
- ISO14155: 2011 (harmonized with ICH GCP and other global guidelines)
- ISO14155: 201X

Structure of ISO14155: 2011

1. Scope
2. Normative references (ISO14971: 2007)
3. Terms and definitions
4. Ethical considerations
5. Clinical investigation planning
6. Clinical investigation conduct
7. Suspension, termination and close-out of the clinical investigation
8. Responsibilities of the sponsor
9. Responsibilities of the principal investigator

Structure of ISO14155: 2011 Annexes

- Annex A Clinical investigation plan (CIP) (normative)
- Annex B Investigator's brochure (IB) (normative)
- Annex C Case report form (CRFs) (informative)
- Annex D Clinical investigation report (informative)
- Annex E Essential clinical investigation documents (informative)
- Annex F Adverse event categorization (informative)

1. Scope

- This International Standard addresses good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purpose.

- This International Standard specifies general requirements intended to

  - Protect the rights, safety and well-being of human subjects,

  - ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results,

  - define the responsibilities of the sponsor and principal investigator,

  - assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices

4. Ethical considerations

4.1 General

Clinical investigations shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. These principles protect the rights, safety and well-being of human subjects, which are the most important considerations and shall prevail over interests of science and society. These principles shall be understood, observed, and applied at every step in the clinical investigation.

4.2 Improper influence or inducement

4.3 Compensation and additional health care

4.4 Responsibilities

4.5 Communication with the ethics committee

4.6 Vulnerable populations

4.7 Informed consent

5. Clinical investigation planning

5.1 General

All parties participating in the conduct of the clinical investigation shall be qualifies by education, training or experience to perform their tasks and this shall be documented appropriately.

5.2 Risk evaluation

5.3 Justification for the design of the clinical investigation

5.4 Clinical investigation plan (CIP)

5.5 Investigator's brochure (IB)

5.6 Case report forms (CRFs)

5.7 Monitoring plan

5.8 Investigation site selection

5.9 Agreement(s)

5.10 Labelling

5. 11 Data monitoring committee

6. Clinical investigation conduct

6.1 General

The clinical investigation shall be conducted in accordance with the CIP. The clinical investigation shall not commence until written approval/favourable opinion from the EC and, if required, the relevant regulatory authorities of the countries where the clinical investigation is taking place has been received.

6.2 Investigation site initiation

6.3 Investigation site monitoring

6.4 Adverse events and device deficiencies

6.5 Clinical investigation documents and documentation

6.6 Additional members of the investigation site team

6.7 Subject privacy and confidentiality of data

6.8 Document and data control

6.9 Investigational device accountability

6.10 Accounting for subjects

6.11 Auditing

7. Suspension, termination and close-out of the clinical investigation

7.1 Suspension or premature termination of the clinical investigation

7.2 Routine close-put

7.3 Clinical investigation report

7.4 Document retention

8. Responsibilities of the sponsor

8.1 Clinical Quality assurance and quality control

8.2 Clinical investigation planning and conduct

8.3 Outsourcing of duties and functions

8.4 Communication with regulatory authorities

9. Responsibilities of the principal investigator

9.1 General

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation. If the sponsor contracts and institution to conduct the clinical investigation, the institution shall appoint an appropriately qualified person to be the principal investigator.

9.2 Qualification of the principal investigator

9.3 Qualification of investigation site

9.4 Communication with the EC

9.5 Informed consent process

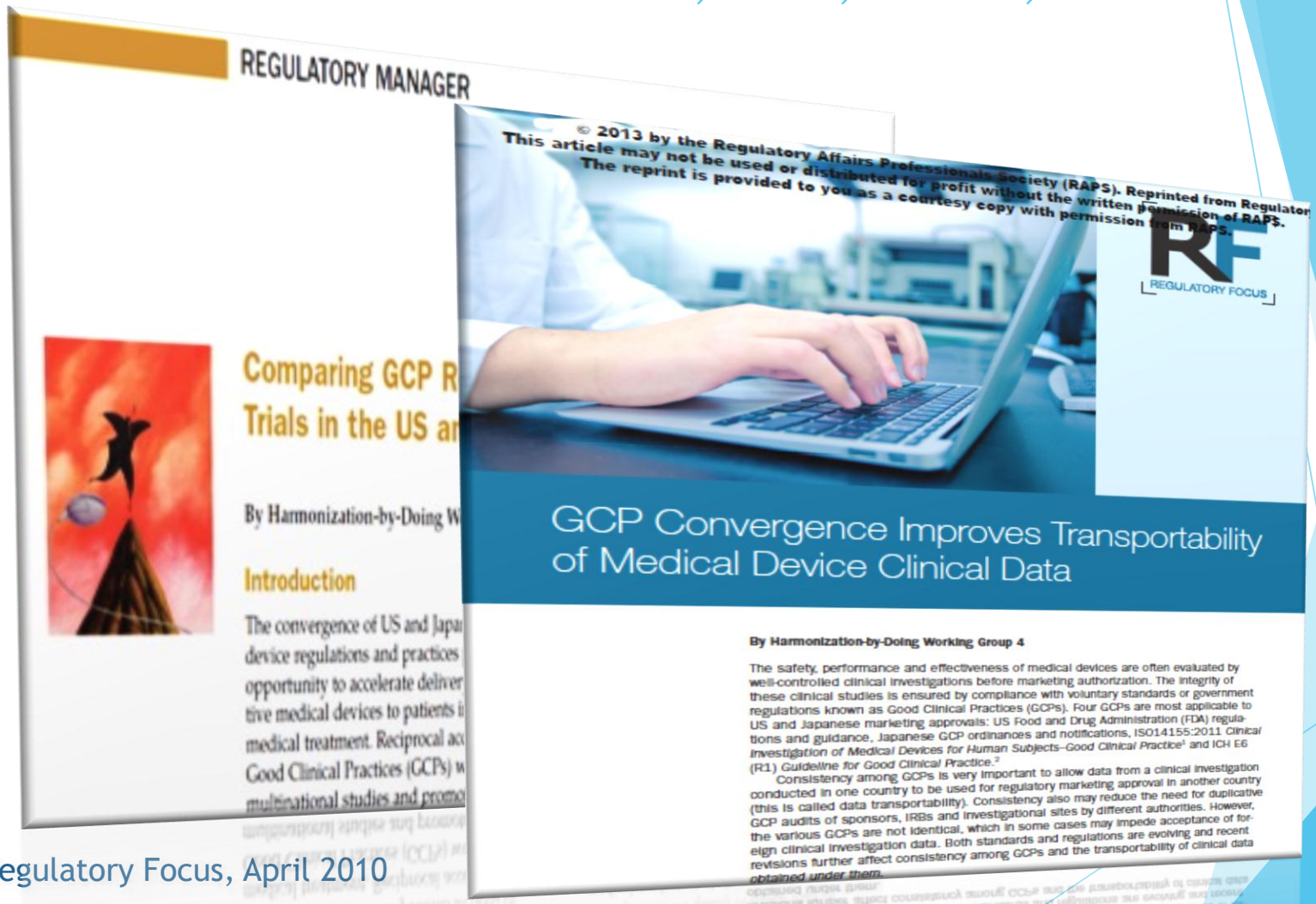
9.6 compliance with the CIP

9.7 Medical care of subjects

9.8 Safety reporting

Comparison among GCPs

US GCP, J-GCP, ISO GCP, ICH GCP



Regulatory Focus, April 2010

Regulatory Focus, January 2013

Revision of ISO14155: 2011

Objectives of current review

Outstanding actions of rev 2011

- Include guidance on study design
- Continued increased guidance on risk management applicable to clinical investigations

Revision of ISO14155: 2011

Objectives of current review

Update/align with regulations

- New MDR in Europe
- Update GCP regulations under US – FDA
- Continuous alignment with guidance documents
  - EU MEDDEV 2.7.1, 2.7.2 and 2.7.3
  - RDC ANVISA 10/15
  - US risk based monitoring
- Connect to other horizontal standards
  - ISO 14971
  - ISO 13485

Revision of ISO14155: 2011

Objectives of current review

GCP for medical device clinical investigations

- Connection to ICH E6 – Rev 2
  - Focused on medical devices while
  - keeping language close to ICH E6–Rev 2 where possible

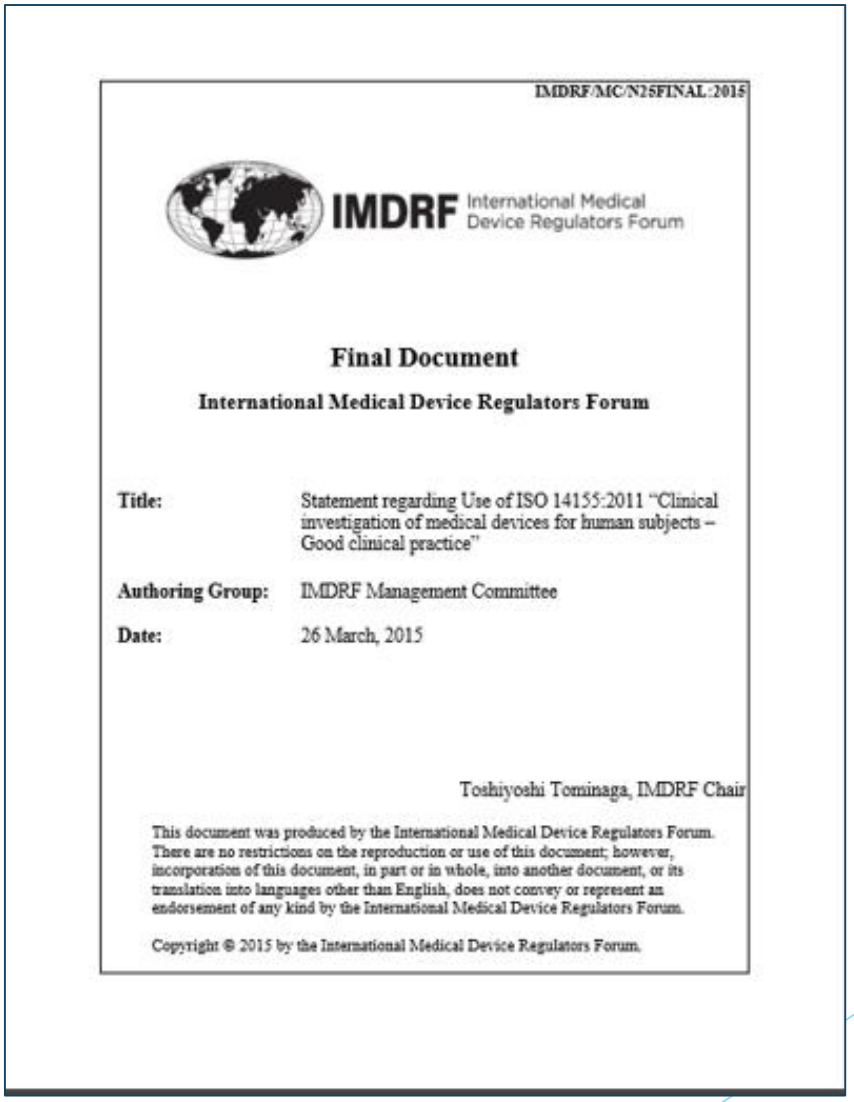
Wider international collaboration

Revision of ISO14155: 2011

Work in progress

- ✓ Scope – effectiveness
- ✓ Public data base
- ✓ Study Design
- ✓ electronic data systems and data protection
- ✓ Subject follow up compliance
- ✓ Gap analysis with ISO 13485 and US - QSR
- ✓ Monitoring plan – risk based monitoring
- ✓ New Annex with guidance for EC/IRB
- ✓ New Annex application of risk management (ISO 14971) to clinical investigations
- ✓ New Annex guidance on audits

Use of ISO14155: 2011



IMDRF/MC/N25FINAL:2015

IMDRF International Medical Device Regulators Forum

Final Document

International Medical Device Regulators Forum

Title:	Statement regarding Use of ISO 14155:2011 "Clinical investigation of medical devices for human subjects – Good clinical practice"
Authoring Group:	IMDRF Management Committee
Date:	26 March, 2015

Toshiyoshi Tominaga, IMDRF Chair

Thank you!