Ethics review committee function, with special reference to GCP and clinical trials

FERCSL workshop on GCP and clinical trials, November 2016

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What I hope to cover…

- A brief history of ‘GCP’
- The ‘ethics’ background to GCP
- What are the various ‘GCP’ guidelines?
- What do they ***say*** specifically about how research ethics committees should function?
- How should committees ***approach*** such guidelines?
  - What are the pitfalls?

History

A brief history

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Late-1990s	These are later adopted by Canada, Australia, Switzerland, etc.

A brief ***future***

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Late-1990s	These are later adopted by Canada, Australia, Switzerland, etc.
The future	The Industry's goal: "A '**single dossier**' for the whole world." The Industry's dream: "Registration in US/EU/Japan leads to **automatic registration** in the whole world."

The background

The bedrock of research ethics

- The World Medical Association (WMA) Declaration of Helsinki (DoH)
  - Latest edition: 2013
  - Published in *Journal of the American Medical Association (JAMA),* November 27, 2013
    - 2013; 310(20): 2191

The ‘work’ of ethics: balancing benefits and risks

Benefits	Risks
The importance of scientific validity to ensure that the conclusions are generalizable	Study subjects
The need to ensure the reliability of data	Healthcare sector
The importance of wide dissemination of the findings and conclusions	Research and scientific community
	The wider community
	Environment

The DoH, the FDA and the Industry

- The FDA referred to the DoH as the basis for research ethics, until 2004
- Between 2000 and 2004, the DoH added two paragraphs and footnotes
  - Para 29: Limiting the use of placebo in clinical trials
  - Para 30: The responsibility of trials sponsors towards participants
- The FDA thereafter stopped referring to the DoH

‘Ethics’ and ‘justice’

“What I think has happened to some extent is that the Declaration has moved from a purely ethical document to a document that is increasingly interested in social justice…For example, [the WMA] clearly are very upset that people in poor countries don’t have really good medical care. And I am upset by that too. But I don’t think that determines the ethics of a trial.”

Robert Temple

Director of the Office of Medical Policy, FDA

Quoted in *EMBO Reports* 2006; 7: 7.

If not DoH, then what?

- Instead, in 2008 they referred to the ICH-GCP for ethical guidance
  - but ***only*** for clinical trials that are conducted ***outside*** the US where the data are used for registration with the FDA!
  - "…Merely **harmonizing** its regulations with a global standard.."

The world of clinical trials

Markets

Regulators

Sponsors/Industry

Investigators

Study subjects/participants

The world of clinical trials

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GCP guidelines

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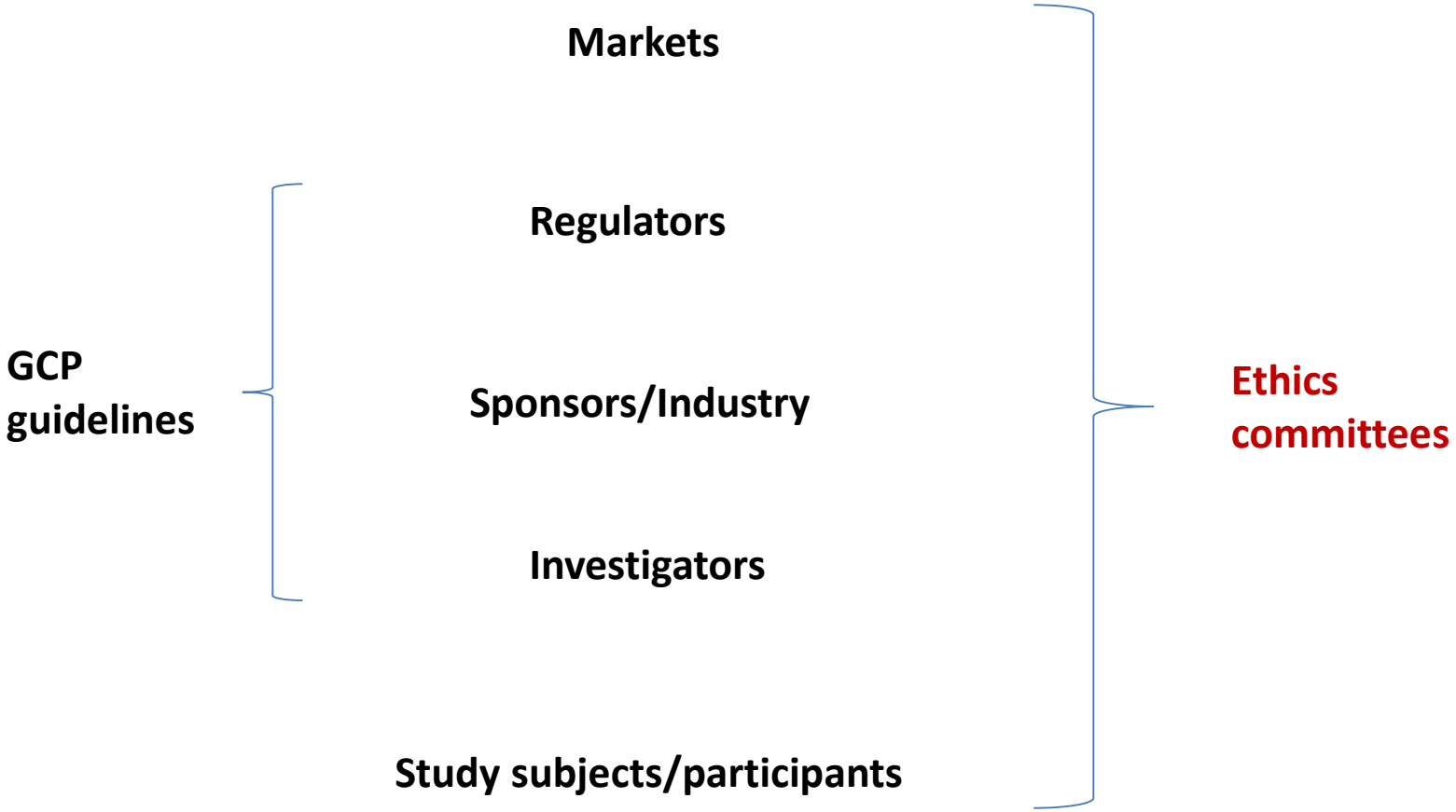

Other documents and what they say

Other documents

Year	Organization	Document
2000	World Health Organization (WHO)	*Operational Guidelines for Ethics Review Committees that Review Biomedical Research*
2002	Council for International Organizations of Medical Sciences (CIOMS)	*International Ethical Guidelines for Biomedical Research Involving Human Subjects*
2005	WHO	*Handbook for Good Clinical Research Practice (GCP)*
2006	Indian Council of Medical Research (ICMR)	*Ethical Guidelines for Biomedical Research on Human Participants*
2016	The next edition of the ICH-GCP is expected…	

The best guide…

- The WHO Handbook (2005)
  - Combines the contents of these different guidelines
  - Fragments the whole research ‘process’ into 15 ‘activities’
  - States research ethics into 14 ‘principles’
  - Re-arranges the contents of the other guidelines under these principles, and provides references to the relevant sections in them

The 14 'WHO Principles of GCP'

1. Ethical conduct
2. Protocol
3. Risk identification
4. Benefit-risk assessment
5. Review by Independent Ethics Committee/Independent Review Board
6. Protocol compliance
7. Informed consent
8. Continuing review/on-going benefit-risk assessment
9. Investigator qualifications
10. Staff qualifications
11. Records
12. Confidentiality/privacy
13. Good manufacturing practice
14. Quality systems

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Principle 5: Review by IEC/IRB

- Principle:
  - Research involving humans should receive IEC/IRB approval/favourable opinion prior to initiation.
- Application:
  - Composition of committee
  - Review of protocol
  - Necessity for prior approval
  - Types of decision
- Implementation
  - A to-do list
- References
  - ICH E6, sections 3.1, 3.2, 3.3, 3.4
  - WHO Op Guidelines for ERCs, sections 4, 6, 7, 8, 9, 10
  - CIOMS, guidelines 2, 3

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ICH E6 (3.1)

- Responsibilities:
  - Safeguarding the rights, safety and wellbeing of trial subjects
  - Documents that should be obtained, how to give its views
  - Qualifications of the investigator
  - Continuing review (at least once a year)
  - Requesting more information
  - Special situations
    - Non-therapeutic trial with guardian's consent, prior consent not possible
  - Payments

ICH E6, cont. (3.2)

- Composition, functions and operation
  - Number of members and their areas of expertise
    - Non-scientific, non-institutional
  - SOPs, minutes, compliance with guidelines and regulations
  - Quorum, which members can vote
  - Investigator can provide information, but cannot take part in deliberations or vote
  - Inviting non-members with expertise

ICH E6, cont. (3.3)

- Procedures
  - Composition, authority
  - Conduct of meetings
  - Conducting initial/continuing review and determining frequency of review
  - Expedited review and minor amendments
  - Specify that only prior approval is given
  - Specify that there should be no deviation, except when necessary to eliminate immediate hazards to subjects or when changes are only logistical/organizational
  - Reporting of deviations, changing risk, serious and unexpected ADRs, new information on risk
  - Notifying decisions

ICH E6, cont. (3.4)

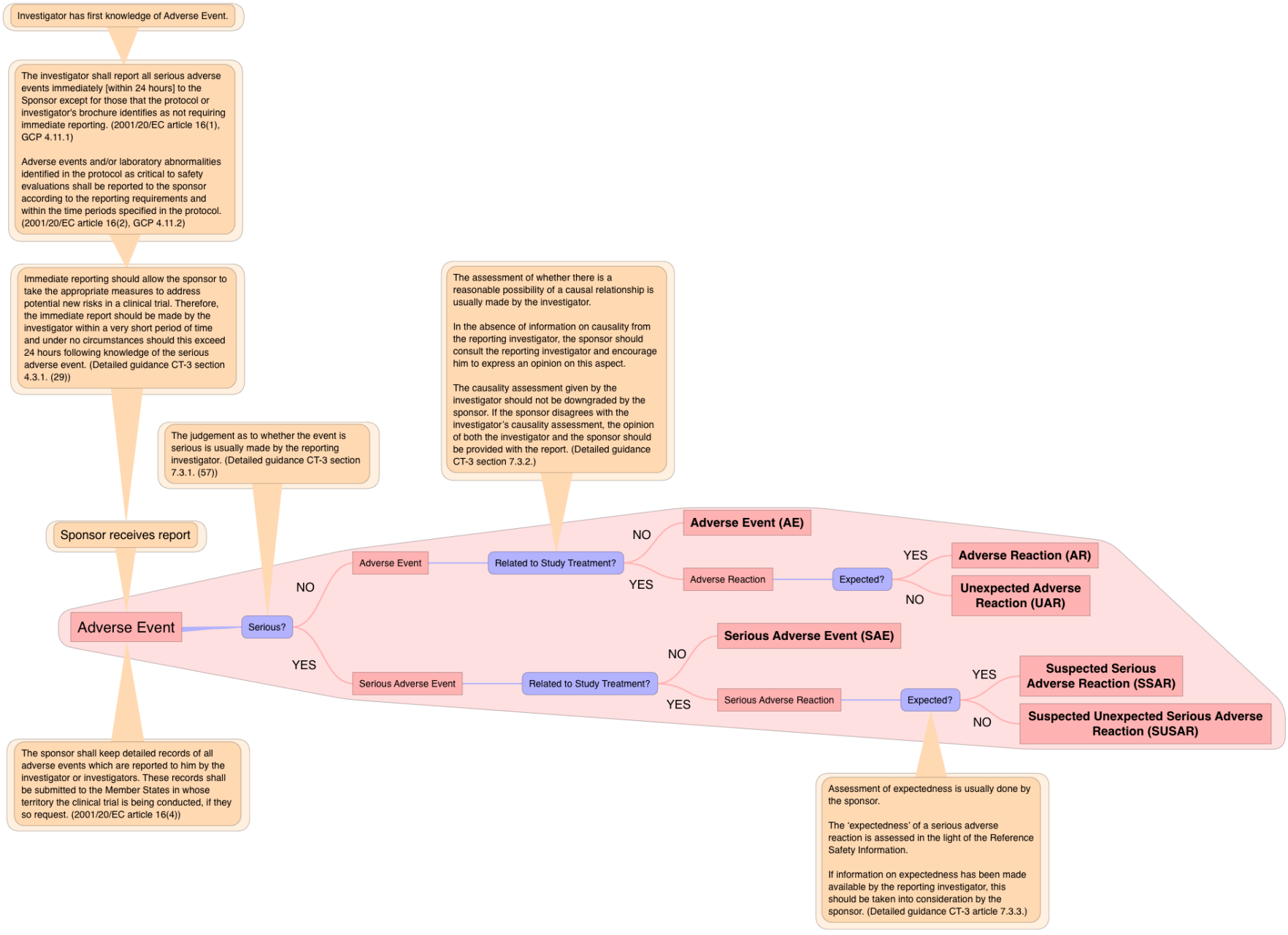
- Records
  - What records to keep and for how long (minimum 3 years)
  - "The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists."

Points to ponder…

- Qualifications are only of the investigator, not other staff
  - Only qualification, not time commitment etc. considered
- Deviations without prior approval allowed in 2 situations
  - To eliminate immediate hazards to subjects
  - Minor logistical changes (eg, telephone numbers)
- Only *serious + unexpected ADRs* need to be reported to the committee

ICH E6 and the future of clinical trials

- The duration of subject follow up for trials testing long-term, non-essential drugs in chronic illness
  - The risk of long-term side effects due to non-essential drugs
- Reporting adverse events
  - Only SUSARs need to be reported
  - The evidence base for adverse drug reactions is being shifted from regulators and the medical profession to the Industry
- Animal carcinogenicity testing for long-term drugs
  - A case of de-harmonization!


Investigator has first knowledge of Adverse Event.
The investigator shall report all serious adverse events immediately [within 24 hours] to the Sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. (2001/20/EC article 16(1), GCP 4.11.1)
Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol. (2001/20/EC article 16(2), GCP 4.11.2)
Immediate reporting should allow the sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made by the investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event. (Detailed guidance CT-3 section 4.3.1. (29))
The judgement as to whether the event is serious is usually made by the reporting investigator. (Detailed guidance CT-3 section 7.3.1. (57))
The assessment of whether there is a reasonable possibility of a causal relationship is usually made by the investigator.
In the absence of information on causality from the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express an opinion on this aspect.
The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided with the report. (Detailed guidance CT-3 section 7.3.2.)
Sponsor receives report
Adverse Event
Serious?
NO
YES
Adverse Event
Related to Study Treatment?
NO
YES
Adverse Event (AE)
Adverse Reaction
Expected?
YES
NO
Adverse Reaction (AR)
Unexpected Adverse Reaction (UAR)
Serious Adverse Event
Related to Study Treatment?
NO
YES
Serious Adverse Event (SAE)
Serious Adverse Reaction
Expected?
YES
NO
Suspected Serious Adverse Reaction (SSAR)
Suspected Unexpected Serious Adverse Reaction (SUSAR)
The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the Member States in whose territory the clinical trial is being conducted, if they so request. (2001/20/EC article 16(4))
Assessment of expectedness is usually done by the sponsor.
The 'expectedness' of a serious adverse reaction is assessed in the light of the Reference Safety Information.
If information on expectedness has been made available by the reporting investigator, this should be taken into consideration by the sponsor. (Detailed guidance CT-3 article 7.3.3.)

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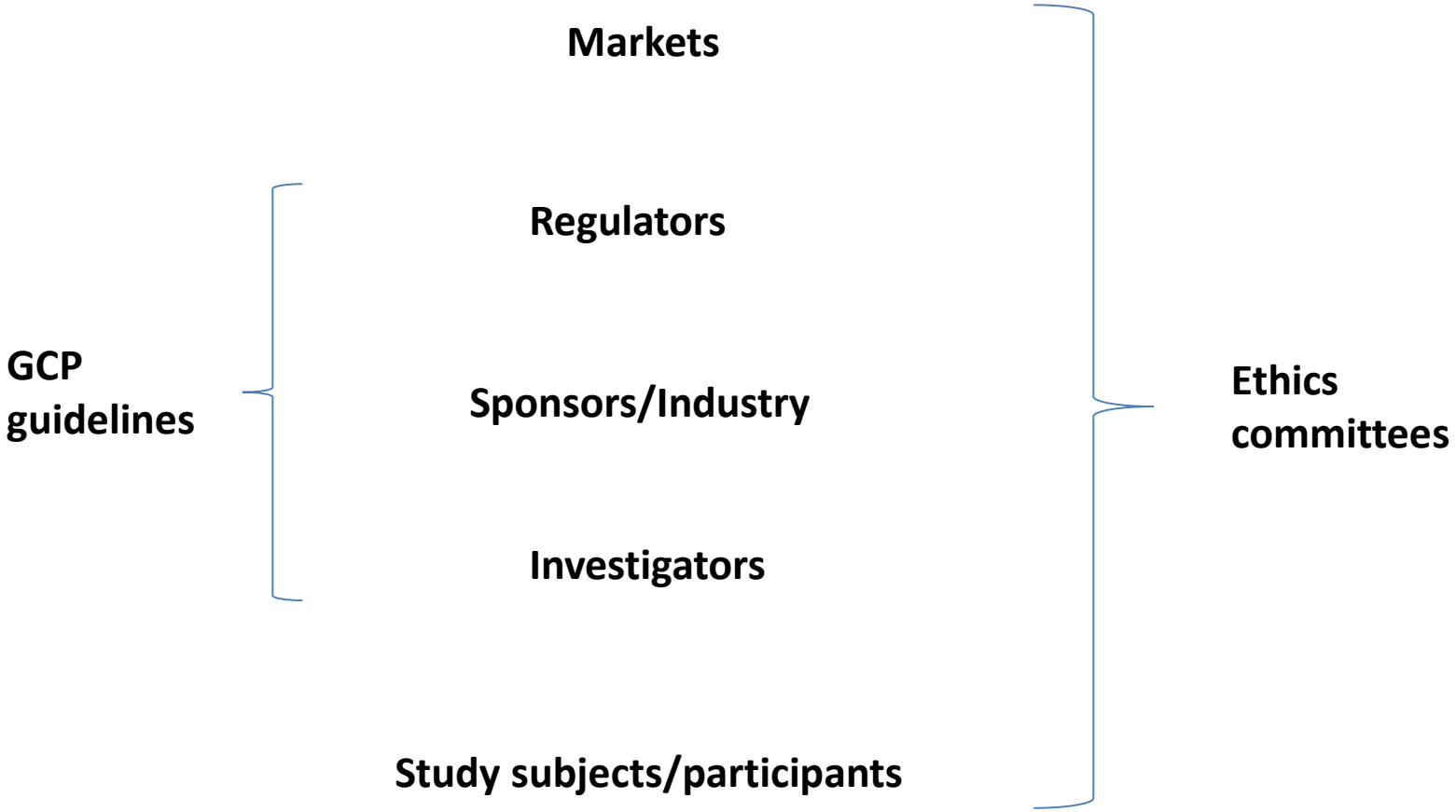

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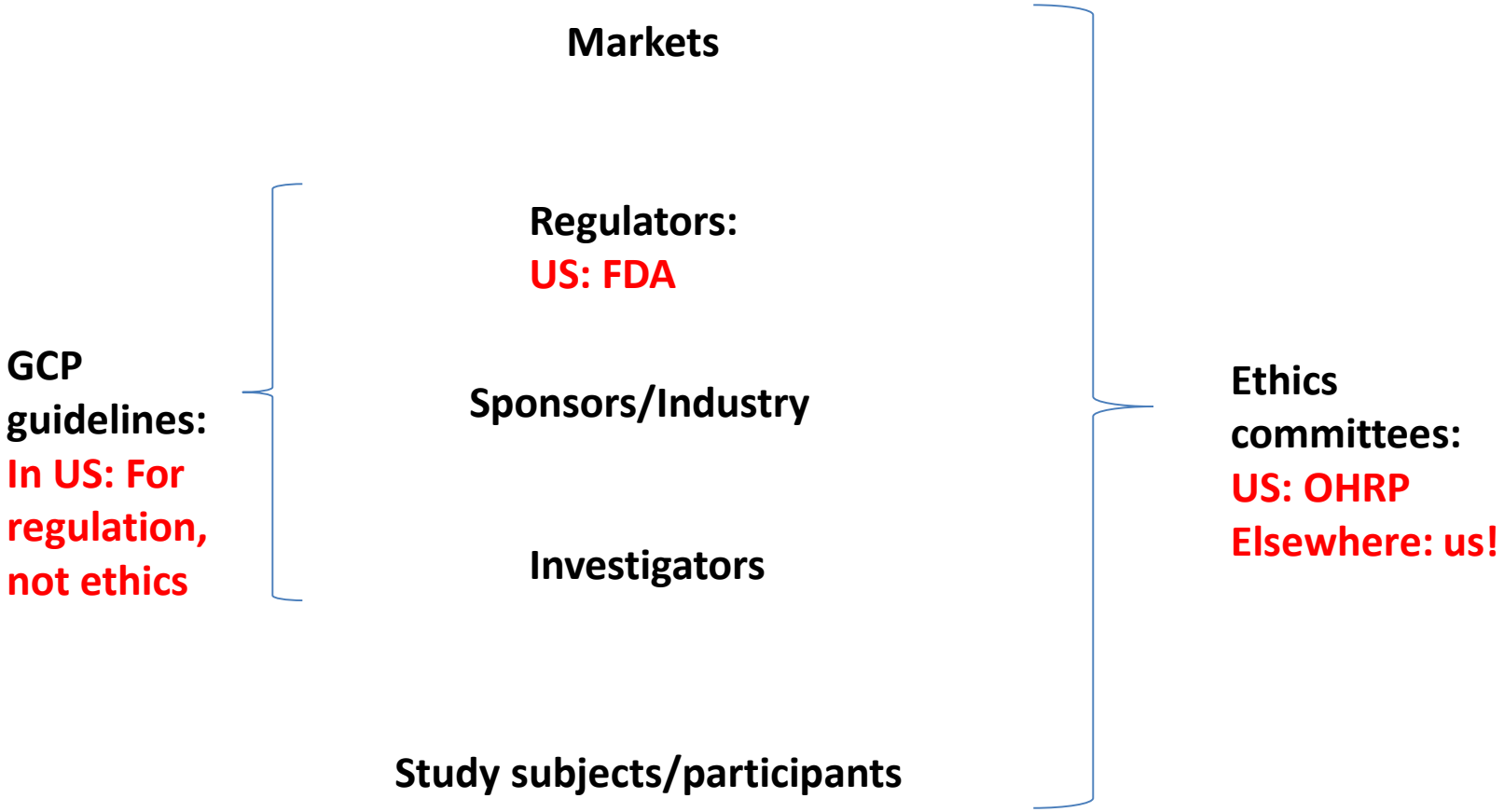

CIOMS (guideline 2)

- Ethical review committees
  - The need for scientific review
  - The nature and composition of committees
  - The need for prior approval
  - Further review, including, if necessary, monitoring

CIOMS (guideline 3)

- Ethical review of externally sponsored research
  - Ethical standards and double standards
  - The research must be “responsive” to national or local “health needs and priorities” in the host country

Points to ponder (1)

- Scientific review vis-à-vis ethical review
- Emergency compassionate use
- Special issues relating to multi-center research using one protocol
- Sanctions
- The roles of sponsors vis-à-vis investigators
- The allusion to double standards

Points to ponder, cont. (2)

- Externally sponsored research in low-resource settings
  - It must be “responsive”
  - “Any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.”
    - Pre-trial discussions should consider the needed healthcare infrastructure, royalties, subsidies, IPR, drug distribution
    - If drug is found to be beneficial, it should be provided to subjects until it is registered in that country

Points to ponder, cont. (3)

- The use of placebo
- Equitable distribution of benefit and risk
- The non-use of special groups
  - Children, the elderly, the pregnant, vulnerable groups
- The over-use of some groups
  - Poor-resource settings, settings with little access to rights

Take home messages

- There are ***several*** 'GCP' guidelines, with subtle differences between them
- Investigators are required to ***adhere*** to these guidelines strictly – but ethics committees ***can (and should)*** think beyond them, if they are to maximize the benefit-risk balance
- The ***WHO Handbook*** is a good compendium to navigate this complex field
- The **CIOMS guidelines** probably provides the current best guide to ethics committees in underdeveloped countries

Thank you!