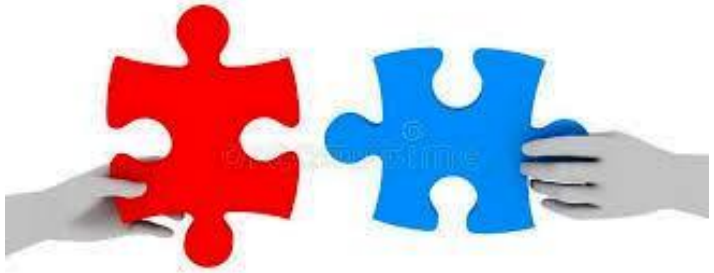
Ethical Considerations in Research



Risks & Benefits

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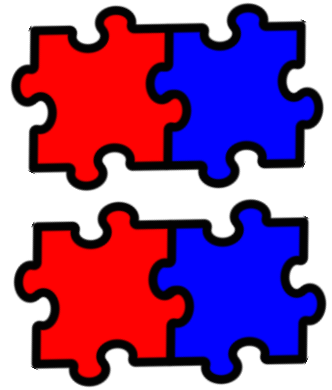
Professor and Head

Department of Forensic Medicine

University of Medicine Magway

Outline



1. **Ethical Research:** What makes Research Ethical?
2. **Ethical Considerations:** Ethical Framework
3. **Risks and Benefits:** Definition, Stratification and Assessment
4. **Guidelines on R & B:** International, Regional, National and Institutional
5. **R & B in Local Practice:** DMR, UPH and Other Medical Institutions

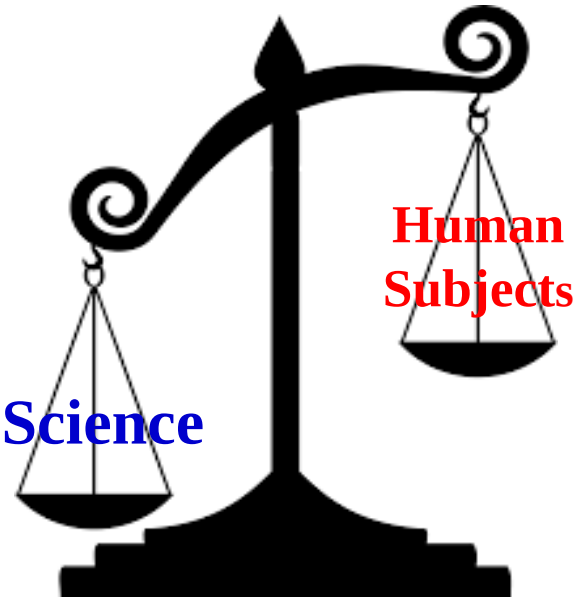
6. **Way forward:** Take Home Message

Research vs Human Research

Research: for the advancement of the science

Research involving Humans

1. For the Advancement of Science
2. For the Protection of Human Subjects

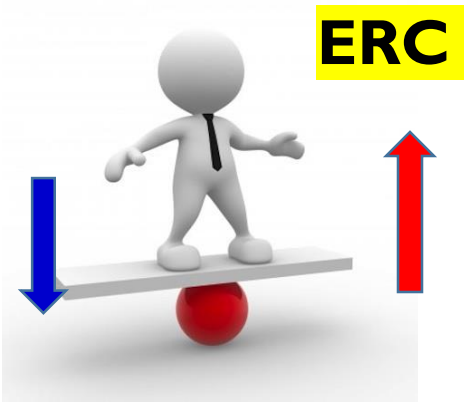


Ethical Considerations ?

for the Protection of Human Subjects

Role (Main Function) of ERC/REC/IRB

by Reviewing and Monitoring the Research



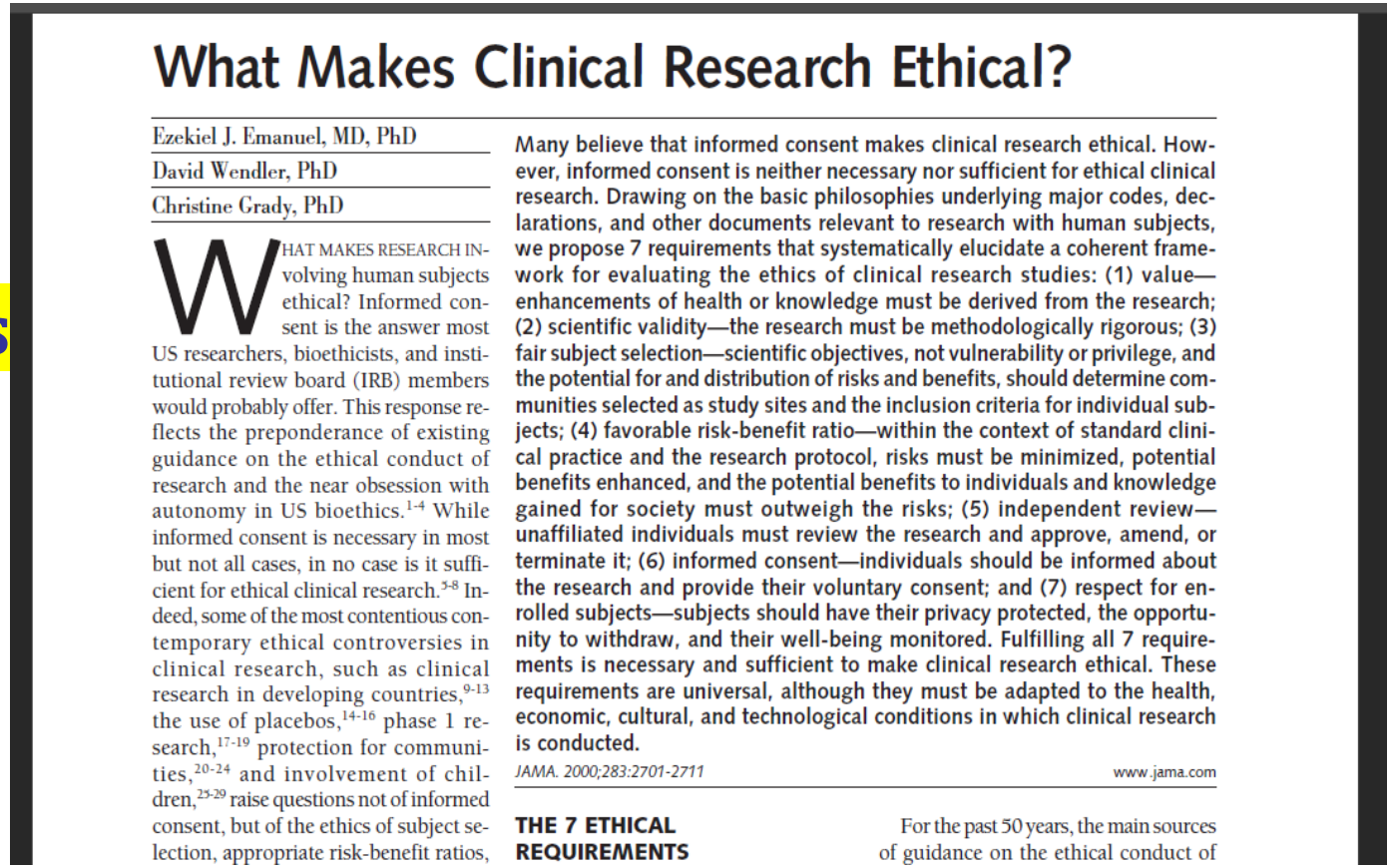
1. Ethical Research

JAMA. 2000; 283: 2701-2711

by Emanuel et al (2000)

Seven Ethical Requirements

1. Social Value
2. Scientific Validity
3. Fair Subject Selection
4. Favourable Risk-Benefit Ratio
5. Independent Review
6. Informed Consent
7. Human Subject Protection



What Makes Clinical Research Ethical?

Ezekiel J. Emanuel, MD, PhD
David Wendler, PhD
Christine Grady, PhD

Many believe that informed consent makes clinical research ethical. However, informed consent is neither necessary nor sufficient for ethical clinical research. Drawing on the basic philosophies underlying major codes, declarations, and other documents relevant to research with human subjects, we propose 7 requirements that systematically elucidate a coherent framework for evaluating the ethics of clinical research studies: (1) value—enhancements of health or knowledge must be derived from the research; (2) scientific validity—the research must be methodologically rigorous; (3) fair subject selection—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects; (4) favorable risk-benefit ratio—within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks; (5) independent review—unaffiliated individuals must review the research and approve, amend, or terminate it; (6) informed consent—individuals should be informed about the research and provide their voluntary consent; and (7) respect for enrolled subjects—subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored. Fulfilling all 7 requirements is necessary and sufficient to make clinical research ethical. These requirements are universal, although they must be adapted to the health, economic, cultural, and technological conditions in which clinical research is conducted.

JAMA. 2000;283:2701-2711 www.jama.com

WHAT MAKES RESEARCH involving human subjects ethical? Informed consent is the answer most US researchers, bioethicists, and institutional review board (IRB) members would probably offer. This response reflects the preponderance of existing guidance on the ethical conduct of research and the near obsession with autonomy in US bioethics.[1-4] While informed consent is necessary in most but not all cases, in no case is it sufficient for ethical clinical research.[5-8] Indeed, some of the most contentious contemporary ethical controversies in clinical research, such as clinical research in developing countries,[9-13] the use of placebos,[14-16] phase 1 research,[17-19] protection for communities,[20-24] and involvement of children,[25-29] raise questions not of informed consent, but of the ethics of subject selection, appropriate risk-benefit ratios,

THE 7 ETHICAL REQUIREMENTS

For the past 50 years, the main sources of guidance on the ethical conduct of

1. Ethical Research

JAMA. 2000; 283: 2701-2711

by Emanuel et al (2000)

The Journal of Infectious Diseases. 2004; 189:930-7

by Emanuel et al (2004)

What Makes Clinical Research Ethical?

What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research

Ezekiel J. Emanuel, David Wendler, Jack Killen, and Christine Grady

Department of Clinical Bioethics, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland

(See the editorial commentary by Kuritzkes, on pages 794–5.)

In recent years, there has been substantial debate about the ethics of research in developing countries [1–5]. In general, the controversies have centered on 3 issues: first, the standard of care that should be used in research in developing countries [6–13]; second, the "reasonable availability" of interventions that are proven to be useful during the course of research trials [14–19]; research-ethics committees in assessing how well the enumerated ethical principles have been fulfilled in particular cases.

MINIMIZING EXPLOITATION

An ethical framework for multinational research should minimize the possibilities of exploitation [25]. A exploits B when B may be less well established, less supported financially, and less effective in developing countries. Guidelines for ethical research should minimize the risk of exploitation under these circumstances [28].

BEYOND PRINCIPLES TO BENCHMARKS

1. Ethical Research

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by Emanuel et al (2000)

The Journal of Infectious Disease

2004; 189:930-7

by Emanuel et al (2004)

Oxford University Press.

by Emanuel et al (2008)

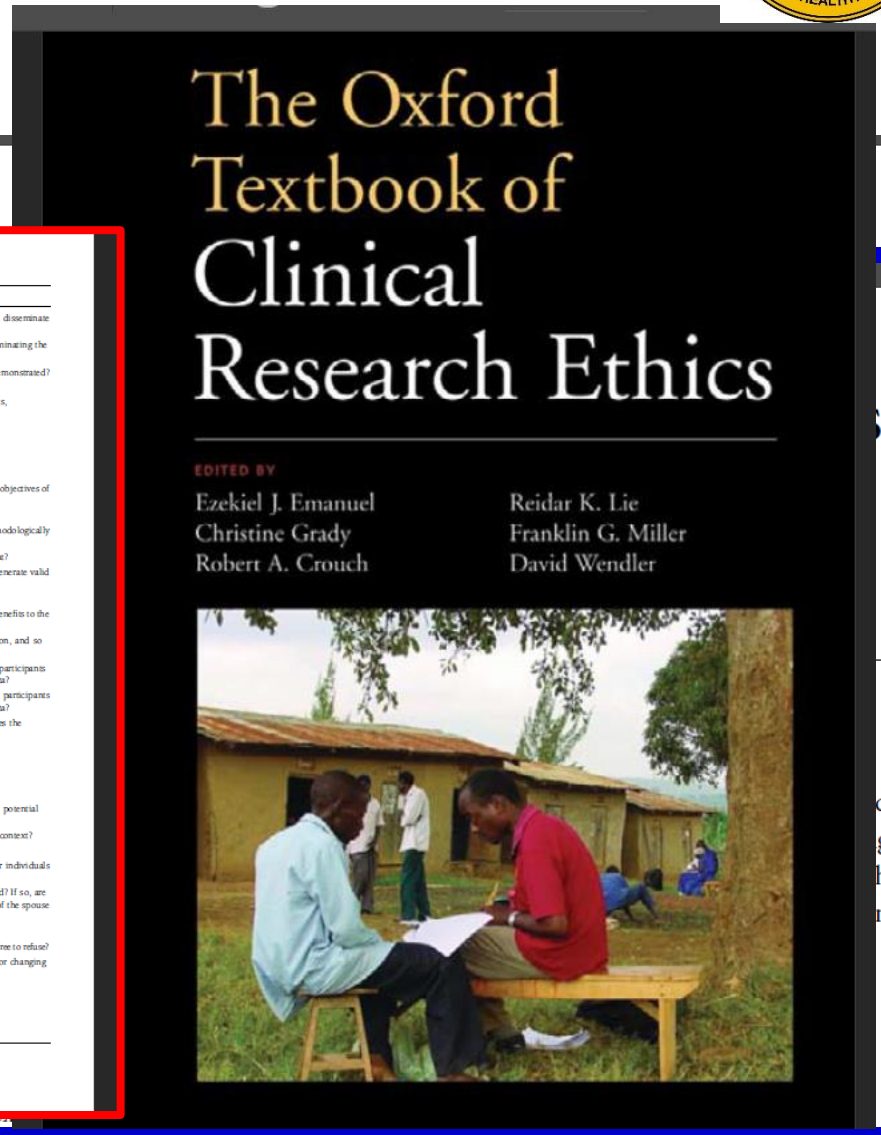
Ethical Framework

NIH adopted

Table 11.2
Principles and Benchmarks for Ethical Clinical Research

Principles	Benchmarks
Collaborative partnership	• Which community representatives will be partners, involved in helping to plan and conduct the research, disseminate the results and use the results to improve health? • How will responsibility be shared with these partners for planning and conducting the research, disseminating the results and using the results to improve health? • How will respect for the community's values, circumstances, culture, social practices, and so forth, be demonstrated? • How will fair benefits for the community from the conduct and results of the research be assured? • How will the tangible benefits of the research, such as authorship credit and intellectual property rights, be distributed to ensure fairness?
Social value	• Who will benefit from the conduct and results of research? • What is the potential value of the research for each of the prospective beneficiaries? • How will the social value of the research be enhanced? • How can adverse impacts, if any, of conducting the research be minimized?
Scientific validity	• Do the scientific and statistical design and methods satisfy generally accepted standards and achieve the objectives of the study? If not, is there clear justification for the deviations? • Will the research results be interpretable and useful in the context of the health problem? • Does the study design ensure participants health-care services they are entitled to? If not, are there methodologically compelling reasons and are participants protected from serious harm? • Is the research design practically feasible given the social, political, economic, and cultural environment?
Fair participant selection	• Is the research population selected to ensure that the research complies with scientific norms and will generate valid and reliable data? • Is the research population selected to minimize risks to the participants? • Are the individual research participants selected to maximize social value and enhance the possibility of benefits to the participants? • Are the participants vulnerable based on age, clinical status, social marginalization, economic deprivation, and so forth? If so, what safeguards are included to protect the participants?
Favorable risk-benefit ratio	• Are the potential physical, psychological, social, and economic risks of the research for the individual participants delineated and their probability and magnitude quantified to the extent possible given the available data? • Are the potential physical, psychological, social, and economic benefits of the research for the individual participants delineated and their probability and magnitude quantified to the extent possible given the available data? • When compared, do the potential benefits to the individual participants outweigh the risks? If not, does the knowledge gained from the study for society justify the net risks to the individual participants?
Independent review	• Are the procedures for independent review established by law and regulation being properly followed? • Is the review body both independent and competent? • Is the review process transparent, and are reasons given for the review committee's decisions? • Are multiple reviews minimized and reconciled if they conflict?
Informed consent	• Are recruitment procedures and incentives consistent with cultural, political and social practices of the potential participants and their community? • Are disclosure forms and verbal disclosure procedures sensitive to participants' culture, language, and context? • Is the information presented to participants complete, accurate, and not overwhelming? • Are there appropriate plans in place for obtaining permission from legally authorized representatives for individuals unable to consent for themselves? • Are supplementary consents or permissions, for example, from spouses or community leaders, obtained? If so, are there ways to ensure that the individual participant can still decide whether to participate independent of the spouse or community leader? • Are the mechanisms to symbolize consent consistent with participants' culture and context? • How will individual participants be made aware of their right to refuse to participate and are they actually be free to refuse?
Respect for participants	• How will the health and well-being of participants be monitored to minimize harms? Are the criteria for changing doses or procedures for stopping the study for the health of participants adequate? • How will the confidentiality procedures actually be implemented? • How will it be ensured that participants who want to withdraw can withdraw without penalty? • How will results of the research be disseminated? • What are the plans for care of the participants after the research is completed?

126



2. Ethical Considerations: Ethical Framework

1. **Collaborative Partnership**
2. **Social Value**
3. **Scientific Validity**
4. **Fair Subject Selection**
5. **Favourable Risk-Benefit Ratio**
6. **Independent Review**
7. **Informed Consent**
8. **Human Subject Protection**

3. Risks and Benefits: Definition, Stratification and Assessment

Risks: **The probability of harm (physical, psychological, social, legal, or ecor**

occurring as a result of participation in a research study.

All research have some risks !

So, a research should have favourable risk-benefit ratio !!

Benefits: A valued or desired outcome as a result of participation in a research study.

Stratification of Risks: Low or High ?

1. Minimal Risk: the probability and magnitude of harm or discomfort anticipated in the research which are not greater than those ordinarily encountered in daily life or during the performance of

routine physical or psychological examinations or tests.

Minor Increase above Minimal Risk (especially with Vulnerable Population)

2. Greater Than Minimal Risk

Maximal Risk ???

Ref: US DHHS OHRP (2009) Protection of Human Subjects in 45 CFR 46 which defines only Minimal Risk in Research

Types of Research-related Risks

1. **Physical**
2. **Phycological**
3. **Social**
4. **Legal**
5. **Economical**

(Ref: WHO (2011) Standards and Operational Guidance for Ethics Review)

Types of Research-related Risks

1. **Physical** — **Any form of research related physical injuries to the participants (discomfort, pain, injury, illness or disease)**
2. **Phycological** — **Any form of mental stresses (anxiety, depression, guilt, shock, loss of self-esteem & altered behaviour)**
3. **Social** — **Any changes in social standing/relationship of the participant (in the family, work, community)**
4. **Legal** — **Any liability for a violation of the law**
5. **Economical** — **Any loss of income, additional costs**

(Ref: WHO (2011) Standards and Operational Guidance for Ethics Review)

Risks: Assessment and Management

Assessment: Risks to Participants, Researchers, Sponsors and RECs, …

Risk Identification, Estimation, and Evaluation by

- ✓ **the Researchers**
- ✓ **the Sponsors**
- ✓ **the ERCs/RECs/IRBs**

Management: Risks → Protection Mechanisms

Minimizing the Risks & Maximizing the Benefits

Risks Monitoring, Reporting, Excluding and Stopping the Research !!

Benefit

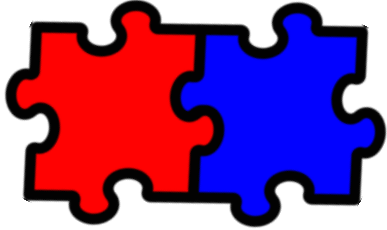
Benefits to Participants, Researchers, Sponsors and RECs, ...

1. **Direct medical benefit to subjects**
2. **Indirect benefit to subjects**
3. **Benefit to others**

Incentives should not exceed "reimbursement" for the subject's time and expenses !

According to minimum daily wage !!

Risks and Benefits



Risks and benefits must be "balanced" and in a favourable ratio.

Net Risks !

Do the potential benefits to the individual participants outweigh the risks?

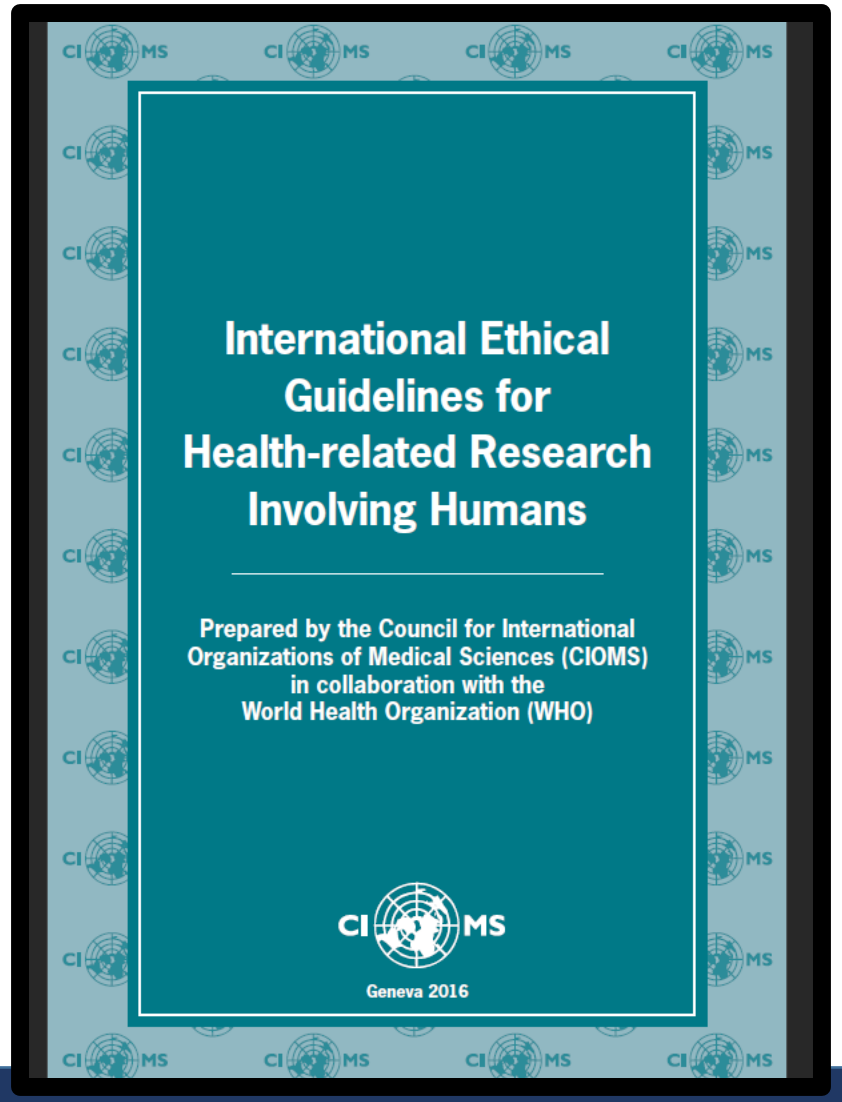
If not, does the knowledge gained from the study for society justify the net risks to the individual participants?

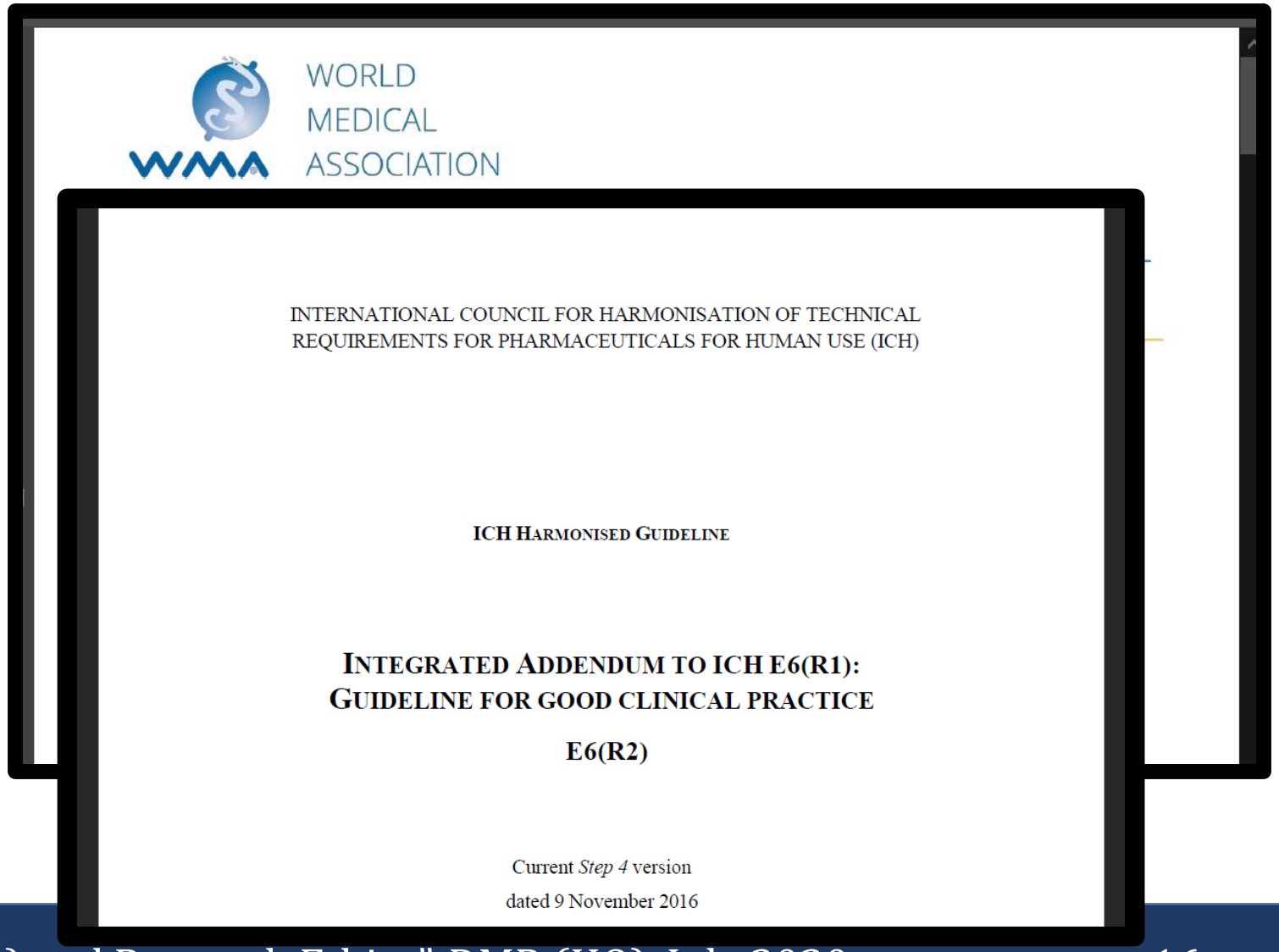
But in research with new drug, device and procedure ??

4. Guidelines on Risks and Benefits

1. International: WHO, WMA, CIOMS
2. US DHHS CFR: Research Common Rules
3. WHO SEA Region, FERCAP
4. DMR Guidelines
5. Institutional Guidelines

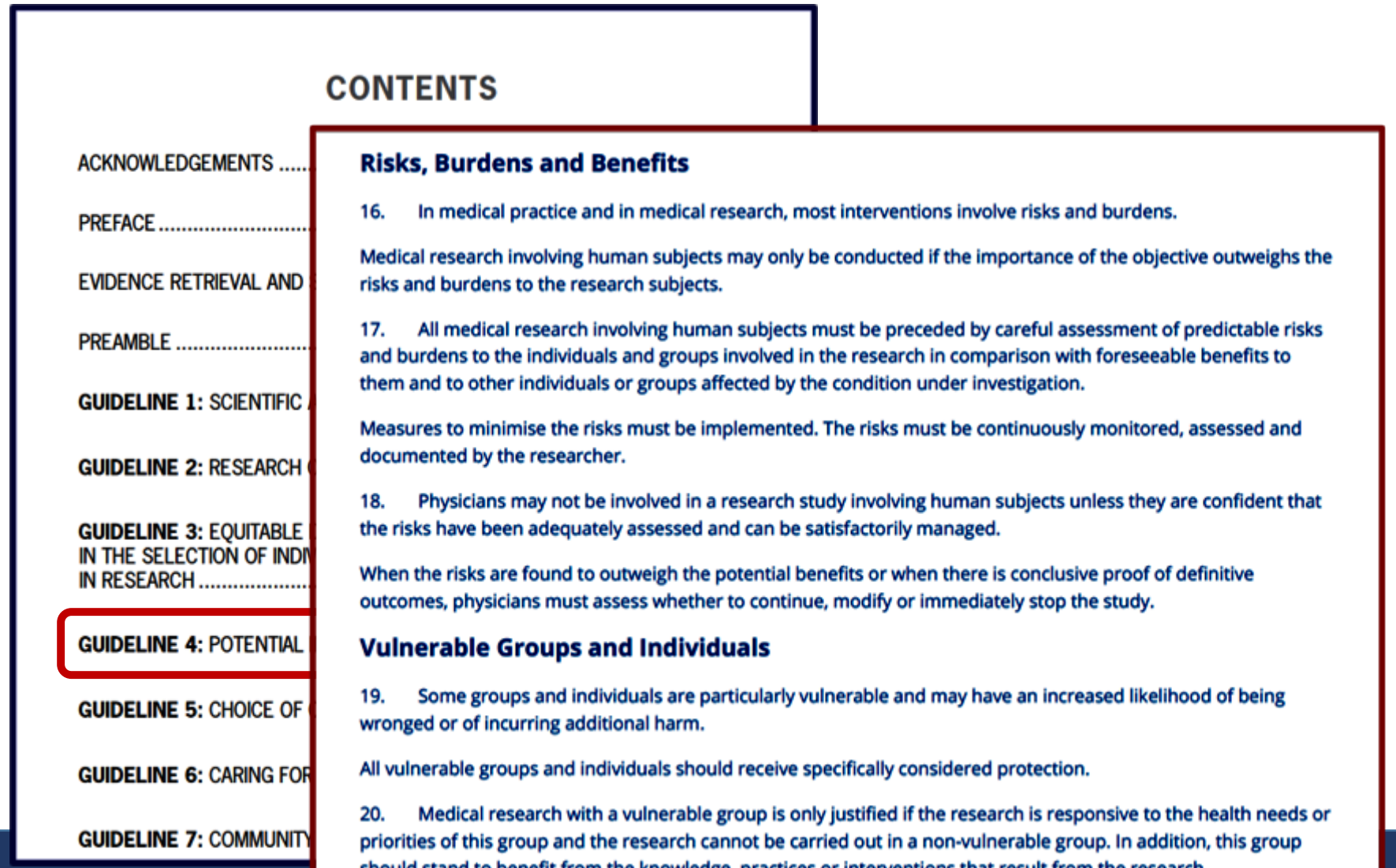
4. Guidelines on Risks and Benefits





International Ethical Guidelines on Risks & Benefits

1. **CIOMS**
2. **WMA DoH**



CONTENTS

ACKNOWLEDGEMENTS .....

PREFACE .....

EVIDENCE RETRIEVAL AND

PREAMBLE .....

GUIDELINE 1: SCIENTIFIC

GUIDELINE 2: RESEARCH

GUIDELINE 3: EQUITABLE
IN THE SELECTION OF INDI
IN RESEARCH .....

GUIDELINE 4: POTENTIAL

GUIDELINE 5: CHOICE OF

GUIDELINE 6: CARING FOR

GUIDELINE 7: COMMUNITY

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

5. R & B in Local Practice

Institu

1. DMR

Univers

2. UMB

5. RISK /BENEFIT ASSESSMENT	Yes	No	N/A	Comments
• Are the following foreseeable risks present and clearly defined?				
▪ Physical risks?				
▪ Social risks?				
▪ Psychological risks?				
▪ Legal/political risks?				
▪ Economic risks?				
• Are risks minimized as much as possible (e.g., appropriate exclusion criteria, substitution of less risky interventions, etc)?				
• Are there potential direct benefits to individuals, and if so, are they well described? (do not consider financial incentives as direct benefits)				
• Is the knowledge to be gained considered?				
• **FINAL ASSESSMENT:** Are risks to subjects reasonable when compared to anticipated direct benefits, if any, and to the knowledge to be gained?				

Do we have Risks and Benefits Assessment in our Institutions?

- ✓ **Investigators' Check-list?**
- ✓ **Reviewer's Check-list?**
- ✓ **Research Monitoring?**

6. Way Forward: Take Home Message

1. Institutional Research and Research Ethics Guidelin
2. Definition and Stratification of Risks and Benefits?
3. Risks and Benefits Assessment and Management?
4. Continuous Review and Research Monitoring?
5. Research Related Injuries and Legal Action ???

✓ **Documented, Updated and Distributed SOPs !**

✓ **Research Ethics Training of Investigators and REC/IRB Members !!**

Expert Comments or Discussions ??

Thank you very much !!