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A New horizon of medical research ethics : viewed from the basis of radiological protection

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Self-introduction

- Expertise: medical research ethics
- Vice chair of ethics committee, NIRS

  Ethics committee members of other institutes
- Quality assurance (monitoring & audit) of medical research
- Medical journal editor “Clinical Evaluation”
- Member of
  - ICRP TG94 (Pub. 138: Ethical foundations of the system of radiological protection);
  - ICRP TG 109 (Ethics in Radiological Protection for Medical Diagnosis and Treatment)

Contents

- Evolution of medical research ethics
- Evolution of radiological protection ethics
- Examples: view from procedural values
- Conclusion

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Evolution of medical research ethics

Theoretical framework

- Traditional: Man to man model
  - Expert's responsibility
    to protect individual's rights
    in deterministic circumstances
    "paternalistic"

- Emerging: Population/ecosystem model
  - Corporate's social responsibility
    to protect population/ecosystem
    in uncertain, probabilistic circumstances
    "patient/citizen-centeredness"

Evolution of medical research ethics

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Evolution of medical research ethics

Dominant Principles

◆ Traditional: Beachamp&Chiledress/Belmont Report
- Respect for autonomy
- Non-maleficence
- Beneficence
- Justice

→ Combined in Belmont Report

additional

◆ Emerging: CIOMS 2016/WMA's activities/ (Emmanuel)
- Social value (never override individual's rights)
- Community engagement/(collaborative partnership)

- 2016 revision of CIOMS guidelines, in collaboration with WHO;
- World Medical Association (WMA) since its 50th anniversary of the Declaration of Helsinki
- Emanuel EJ, et al., eds. The Oxford Textbook of Clinical Research Ethics. 2008.

Evolution of medical research ethics

Procedural requirements

◆ Traditional:

- informed consent
- privacy protection
- safety assurance

← Risk benefit assessment & Oversight By Ethics committee

＊Scientific validity: requirement of ethical justification

◆ Emerging:

- Achieve public health, global health
- Avoid harm to human, including future generations; animals; ecosystem

← Institutional governance & Citizen's oversight

＊Not only scientific validity, but also availability of result: additional requirement of ethical justification =social value

Evolution of medical research ethics

Tactics to achieve justification

◆ Traditional:

- Informed consent: information; conception, voluntariness
- Privacy protection/safety assurance & compensation
- Multiplicity of ethics committee members
- Education, training

◆ Emerging:

- Early involvement of participants/community
- Logistics and politics for availability of research results
- Study registration in publicly accessible database
- Sharing of individual personal data

Evolution of medical research ethics

Topics of interests

◆ Traditional:

- Dilemmas: individuals; individual vs society
  e.g., abortion; end-of-life care; placebo-controlled trial
- Protection of “categorized” vulnerable populations
  e.g., child; incapable adult; woman; prisoner; poverty

◆ Emerging:

- Disaster situations: natural; man-made; war conflict
- “Big data”; whole genome sequence
  Biobank and health database; online/digital tool
- Protection of context-dependent vulnerability

Evolution of medical research ethics

Protection of vulnerability

◆ Traditional:

- Basically you should not involve vulnerable subjects into risky research.
- Inclusion of vulnerable subjects must be justified.
  "Paternalistic"

◆ Emerging:

- Basically you should involve vulnerable subjects into research, to generate knowledge for health needs of them.
- Exclusion of vulnerable subjects must be justified.
  Achieve "Respect individual's rights and social value"

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Evolution of ethical bases of RP in ICRP recommendations 1928-2007

ICRP Publication 109

Table 3.1. The historical development of ICRP recommendations.

Factor analysed	Early recommendations	Intermediate recommendations	Present recommendations
Circumstances of exposure considered	Occupational exposure in medicine	All occupational exposure, then all exposure of mankind	All exposure of all species
Who/what is being protected	Protection of man alone	Environment assumed protected because man is protected	Demonstration that environment is protected
Known effects of radiation exposure, aims of radiological protection	Prevent deterministic effects...	... and avoid stochastic effects...	... and recognise the possibility of non-targeted effects
The ethical basis of protection	'Respect for life' virtue ethics	Focus on utilitarian ethics	Increasing emphasis on deontological ethics
Protection methods	Advice on practical protection methods	Application of dose limits, then application of optimisation	Optimisation of protection under dose and risk constraints

Sub categories of normative ethics

"**3.2.4 Ethical bases of radiological protection**" described in Clarke, R.H., Valentin, J., 2009, The history of ICRP and the Evolution of its Policies. In ICRP Publication 109. Ann. ICRP 39(1), pp. 75-105.

Challenges of ICRP: To the next step

Western theories of ethics (Annex A. of Pub. 138)

Meta-ethics: discussing the general meaning of ideas such as “virtue”, “good” of “right”.

Normative ethics: discussing how one should act, and which values and norms should be followed.

Virtue ethics: discussing virtuous life based on a certain concept of human nature.

consequentialist ethics (teleological ethics; utilitarianism): discussing the preferability of certain actions on the bases of their outcomes. (Well know example: “the greatest happiness of the greatest number”)

Deontological ethics: discussing a set of obligations or rules for human society.

Applied ethics: discussing specific issues based on ethical theories or principles, e.g., bioethics, medical ethics (Annex B. of Pub. 138) , research ethics, environmental ethics, business ethics, neuro ethics, nuclear ethics..

Challenges of ICRP: To the next step

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Ethical basis of RP system, Clarke & Valentin, 2009, Pub 109

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Core ethical values, Pub. 138 ➡ **Bases of radiological protection ethics**

JJHP, in press. Courtesy of Prof. Yasuhito Sasaki, a former president of NIRS

Basis of “radiological protection ethics”

Principles: research ethics

ICRP’s core ethical values

- Traditional:
  - Respect for autonomy
  - Non-maleficence
  - Beneficence
  - Justice

Beneficence/Non-maleficence
Prudence ★
Justice
Dignity ★

ICRP’s procedural values ★

- Emerging:
  - Social value
  - Community engagement

Accountability
Transparency
Inclusiveness
(stakeholder participation)

Core values of "radiological protection ethics"

- Beneficence/non-maleficence: doing good, not to harm
- Prudence★: ability to make informed and carefully considered choices without full knowledge of the scope and consequences of actions.

  Original: practical wisdom

  LNT model/precautional principle

  self governance=reason of human dignity
- Justice: distributive justice of risk and benefit;

  procedural justice of decision making
- Dignity★: every individual deserves unconditional respect, irrespective of personal attributes or circumstances such as age, sex, health, disability, social condition, ethnic origin, religion, etc.

  higher level than "respect for autonomy"

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Procedural values of “radiological protection ethics”

- Accountability:
  Organizational responsibility to account their action and decision to all the affected people:
  present generation; future generation.
- Transparency:
  Traditional model: informed consent
  Emerging model: citizen’s choice
- Inclusiveness (stakeholder participation)
  Explicit guidelines for
  efficient stakeholders participation

Great potential to analyze actual issues in medical research, based on RP new core/procedural values

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Examples

Emerging topics in research ethics (extraction from CIOMS 2016)	**RP related topics View from procedural values**
Social value*	**Diagnostic research**** Pub 62 social benefit vs >10mSv, repeated dose **Radiation therapy research** involving woman in low-resource settings
Community engagement	
Disaster situations	**Research in radiation disaster** **Radiation epidemiology**

* Scientific and social value and respect for rights

**IAEA Safety Standards requirement (2014): CIOMS; Declaration of Helsinki; ICRP Pub 62.

Extractions from CIOMS 2016 (summary)

Guideline 1: Social value*

Traditional: scientific validity, generating new knowledge, is an essential requirement of ethical justifiability.

Emerging: Social value, contributing individual/public health is additional requirement.

Guideline 7: Community engagement

Researchers, …should engage potential participants and communities in an early and sustained manner in the design, development, implementation of

informed consent;

monitoring of research; and

dissemination of its results.

Including logistics and politics for availability of the results.

Necessary factors to assure "social value".

* Scientific and social value and respect for rights

Example 1: Diagnostic research

- There are many PET/CT studies involving healthy subjects, >10mSv, repeating 2 or3 times in a year.
- ICRP Pub 62 (1992) on "Radiological protection in biomedical research" provides good textbook for these types of research, suggesting >10mSv study should generate "substantial social benefit" = directly related to saving of life; prevention or mitigation of serious diseases ("Social value").

Actual situation:

- No explicit discussion about "substantial social benefit";
- No control of annual/accumulated dose of each subject.

ICRP publication 62:

Adopted 1992, published 1993

Radiological protection in Biomedical Research

Categories of risk and corresponding levels of benefit

Level of risk	Risk category*	Corresponding effective dose (adults, mSv)	Level of social benefit
trivial	Ⅰ（～10^{-6}）	＜0.1	minor
Minor to intermediate	Ⅱa（～10^{-5}）	0.1–1	intermediate to moderate
	Ⅱb（～10^{-4}）	1–10	
moderate	Ⅲ（～10^{-3}以上）	＞10**	substantial

*total detriment from the exposure; sum of the probability of fatal cancers, weighted probability of non-fatal cancers and the probability over all succeeding generations of serious hereditary disease

*To be kept below deterministic thresholds except for therapeutic experiments.

Social benefit：”usually directly related to the saving of life or the prevention or mitigation of serious disease.”

・Repeated participation should be avoided

・Expert(s) should be included in research group, ethics committee

Proposal to Example 1

- More stakeholder participation and transparency is needed not only ethics committee.

Necessary items:

- Clinical trial registration (transparency)
- Procedures of record of accumulated dose of each research subjects (accountability)
- Patient involvement (e.g. cognitive disorders) from the time of protocol design, to achieve social value.

ICRP Pub 62 can be revised to new, innovative textbook based on their core/procedural values.

Courtesy of Prof. Tomio Inoue, Chair of Ethics Committee, NIRS;
The former President, Japanese Society of Nuclear Medicine

Example 2: radiation therapy research involving woman/in low-resource setting

- In radiation therapy research for women of (a) pregnant (b) who may/will be pregnant; (c) childbearing age (Well discussed in Pub. 84, just a few missing point about the region of higher than 100-500mGy, e.g., 60Gy), there is no standardized guidelines for informed consent.
- Some researchers are planning international research in low-resource settings where hospital does not have an ethics committee.

Proposal to Example 2

- Standardized guidelines of IC are needed to provide appropriate information up to the planed/assumed radiation dose and its risk to woman/fetus/ovarium.
- Patient involvement (e.g. woman with cancer) is necessary in this process of guideline development.
- In case of low-resource settings, capacity development is needed to establish ethics committee to review the study protocol from view of the community.

These topics can be added to revised ICRP Pub 62.

Extractions from CIOMS 2016 (summary)

Guideline 20: Research in disaster

- Disasters (earthquakes, tsunamis or military conflicts, and disease outbreaks…) have a sudden and devastating impact on the health of large affected populations.
- Research should form an integral part of disaster response.
- Research can be met with great scepticism or even hostility; researchers must be equipped to negotiate these pressures in fragile political and social situations.
- An acute situation may *require* accelerated ethical review to ensure that necessary studies can begin as soon as possible without compromising ethical requirements.

Example 3: research in radiation disaster

- In the case of radiation disaster, rapid starting of survey/research is needed just after the event, e.g., radiation measurement and behavioral record of citizens; in case of emergency radiation workers, urine sampling may be additionally needed.
- Hiroshima, Nagasaki, Fukushima experiences of "guinea pig claim" caused researchers' compromised activities to pretend they are providing "support" not conducting "survey", which compromises "scientific value", therefore, "social value" (essential component of ethical justifiability).

Proposal to Example 3

- CIOMS recommends “generic protocol approval”, which can be prepared at the disaster vulnerable areas (earthquake, tsunami, as well as nuclear plant areas), in advance to event, to make possible “accelerated ethical review” at the time of event.

  (including the case: waiver of IC is justified)

- Participation of stakeholders in community is essential to facilitate “preparedness” to agree with which kind of research is necessary to generate “social value” of the damaged community.

Guidelines for ethics of research in radiation disaster situation is needed , based on “core/procedural ethical values”.

Example 4: radiation epidemiology

- In long term epidemiological survey of radiation effects, some times question arises whether incidental (unsolicited) findings/research results should be informed to research participants, sometimes to relatives; in rare situations, to relatives without consent of the person concerned.

Proposal to Example 4

- Conditions of meaningfulness of returning incidental findings/research results:
  - analytical validity
  - clinical significance
  - actionability
- Both of “right to know” and “right not to know” should be assured.
- Community engagement, information dissemination, taking measures to prevent discrimination against the person in the population.

Guidelines for ethics of radiation epidemiology research is needed, based on “core/procedural ethical values”.

Conclusion

- Evolution of medical research ethics: shifting from man to man model to population/ecosystem model.
- ICRP established a bases of ethics of radiological protection as “applied ethics” beyond “normative ethics”, identifying core/procedural values.
- A set of traditional and emerging principles of medical research ethics is similar to core and procedural ethical values identified by ICRP.
- Great potential to develop/update textbook for ethics of radiation-related research, new horizon of medical research ethics, based on radiological protection ethics.