1st Asian Workshop on the Ethical Dimensions of the Radiological Protection System

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Hosted by Korea Institute of Nuclear Safety (KINS)

Organised by Korean Association for Radiation Protection (KARP)

In cooperation with ICRP and IRPA

Principles of bioethics and radiological protection: What is the common ground?

Chieko Kurihara
Senior Researcher, Molecular Imaging Center (MIC)
National Institute of Radiological Sciences (NIRS)

1. Introduction: Background of this presentation

2. Inclusion of radiological protection into research ethics

3. Finding common ground of radiological protection and bioethics

4. Conclusions and future perspective

1. Introduction: Background of this presentation

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Background (1)

Graduated from the faculty of political science and economics, Waseda University;

working in the field of medical journal editing and at the bioethics research institute;

came to the Molecular Imaging Center (MIC) of the National Institute of Radiological Sciences (NIRS) (07～visiting researcher; 08～senior researcher)

Background (2)

Collaboration among Molecular Imaging Center and Research Center for Radiation Protection in NIRS, also with other research institutes
2008～2011 Voluntary survey group for "Radiological protection of human subjects"

Kurihara C, Sakai K, Akahane K, et al. Radiological protection of human subjects: the first report A comparative study of the UK, USA, and Japan regulations and domestic questionnaire survey. *Nuclear Medicine*. 2010; 47(1): 9-28. Japanese.
http://www.jsnm.org/kensa/10-08-21

Kurihara C, Yonekura Y. Radiological protection of human subject in nuclear medicine research. PET journal. 2011; (16): 39-42.Japanese

Expanded survey

Collaboration among expert committees of Japanese Society of Nuclear Medicine and Japan Radioisotope Association

RADIOISOTOPES 2010; 59: 659-673. http://www.jrias.or.jp/report/pdf/hibaku.pdf

Background (3)

“Molecular Imaging Strategic Committee” of J-SNM established a set of guidelines for clinical research using PET drugs: manufacturing (GMP), preclinical, clinical study

Not mentioned in this presentation but related activity of J-SNM

Consideration on the common ground of radiological protection and bioethics

Kurihara C. Research ethics and radiological protection: Reflecting the discussion at the Japanese Society of Radiological Technology Meeting. Japanese Journal of Radiological Technology. 2011; 67(6): 683-90.

Mentioned in the latter part of this presentation

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ICRP pub 62 (1992) : inclusion of research ethics into RP

Discussion in Japan 2008 -2011:

inclusion of RP into research ethics

ICRP: International Commission on Radiological Protection
RP: radiological protection

Research questions:

What is the international/other countries' regulations/guidelines of radiological protection of human subjects of biomedical research?

In Japan, radiological protection of human research subjects is enough or not?

Finding (1):

International/other countries' regulations/guidelines

1. International guidelines:

ICRP publication 62 (1992) → ICRP publication 103 (2007)

IAEA Basic Safety Standard 2010 Dec Agreement

ICRP recommendation should be considered;

Ethics committee should discuss about dose constraint;

Record of radiation exposure should be available for national authority

2. Regulations in US:

RDRC regulations: 21CFR361.1

Different concept of radiation risk from ICRP pub. 62

More than 70 RDRCs in US submit reports to FDA

3. Regulations in UK:

ARSAC : One national committee evaluate all the project administrating RIs to human

IAEA: International Atomic Energy Agency
RDRC: Radioactive Drug Research Committee;
ARSAC: Administration of Radioactive Substances Advisory Committee

Finding (2)

Radiation dose and risk

ICRP publication 62

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

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

・Repeated participation should be avoided

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

International Commission on Radiological Protection. ICRP Publication62：**Radiological Protection in Biomedical Research**. Adopted by the Commission in November 1992. *Annals of the ICRP Pergamon Press Ltd*. 1993.

Radiation dose limits of RDRC

Radiation dose limits under which use of radioactive drugs for research are considered and effective by the US Code of Federal Regulations (21CFR361.1)

Organ or system	Single dose	Annual and total dose
Whole body; Active blood-forming organs; Lens of the eye; Gonads	3 rem (＝30mSv)	5 rem (＝50mSv)
Other organs	5 rem (＝50mSv)	15 rem (＝150mSv)

21 CFR 361 - Prescription Drugs For Human Use Generally Recognized As Safe And Effective And Not Misbranded: Drugs Used In Research: Sec. 361.1 Radioactive drugs for certain research uses.

Allowed: investigating human physiology, pathophysiology or biochemistry

Not allowed: Safety, Efficacy, Diagnostic, Therapeutic, Clinical trials, Patient management firs-in-human, more than defined number of subjects, etc.

2009: 76 RDRCs, 628 protocols, 3297 study subjects

Fejka R. 2010 US-SNM Annual Meeting

Discussion concerning the risk of low dose radiation exposure (1)

- Reasonable evidence　an increased cancer risk
  acute doses ＞ 5 mSv.
- Good evidence　an increased cancer risk is
  acute doses ＞ 50 mSv.
- Reasonable evidence　an increased cancer risk
  protracted doses ＞ 50 mSv.
- Statistically significant evidence　an increased cancer risk
  protracted doses ＞ 100 mSv.

Brenner, et al. *PNAS* 2003.

Discussion concerning the risk of low dose radiation exposure (2)

- 50-100 mSv：no established evidence of an increase of risk for radiation less than 100 mSv
- LNT（Linear No Threshold）model

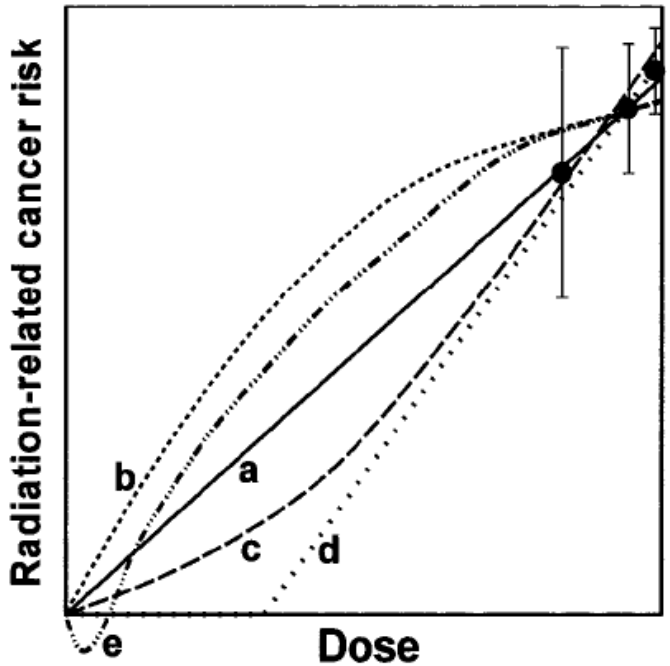
  ICRP, NCRP, ICRP, NCRP, UNSCEAR,

  the BEIR Committee

  possibility of low risk

  due to low dose

Sometimes too much sensitive.....
Sometimes too much aggressive.....



Wall, et al. BJR 2006.; Brenner, et al. *PNAS* 2003.

Finding (3)

Ethics review system

Current status and future prospect of radiation exposure to research volunteers in institutes with nuclear medicine: The report of questionnaires regarding radiation exposure to volunteers in clinical researches and clinical trials

Subcommittee on Medical Radiation Management, Medical Science and Pharmaceutical Committee, Japan Radioisotope Association

Radiation Protection Committee of the Japanese Society of Nuclear Medicine

RADIOISOTOPES 2010; 59: 659-673.

■Objectives

To depict issues on institutional radiological protection system towards establishing guidelines

■Subjects and methods

Questionnaire survey of medical institutes engaged in clinical research to administrate radionuclide during these 2 years.

■Points of analysis

1) Characteristics of research

2) Research review system concerning radiation safety

3) Selection of volunteers

4) Dose constraint or limitation in the institute

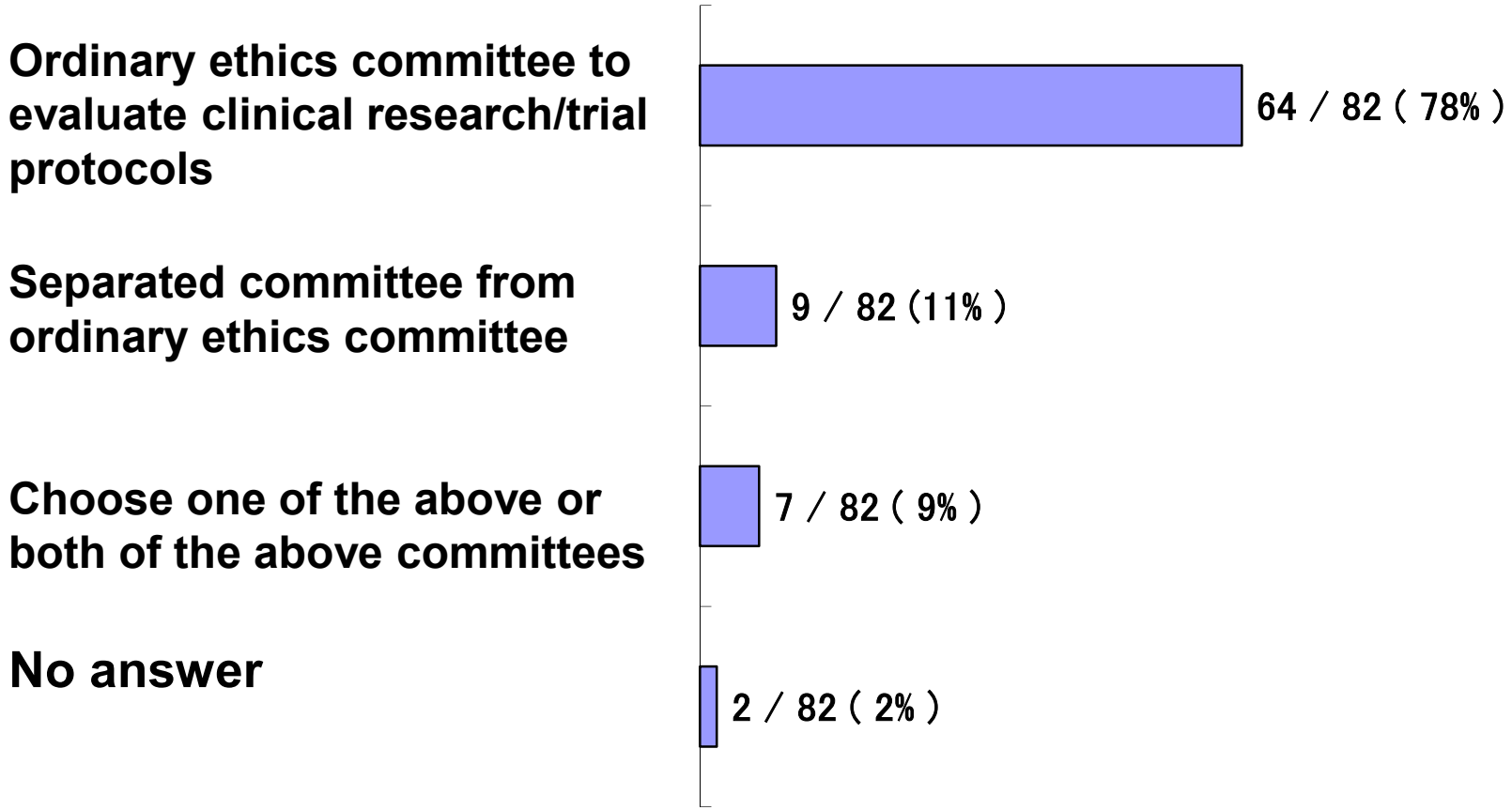
5) Informed consent process

■Obtained answers

82 institutes provided valid answers

(Questionnaire was delivered to 1287 institutes which are using RIs and 1021 responded (79%), among which 82 have been conducting research to administrate RIs to human volunteers.)

Which committee evaluates radiation safety of the research administrating RIs to human volunteers?

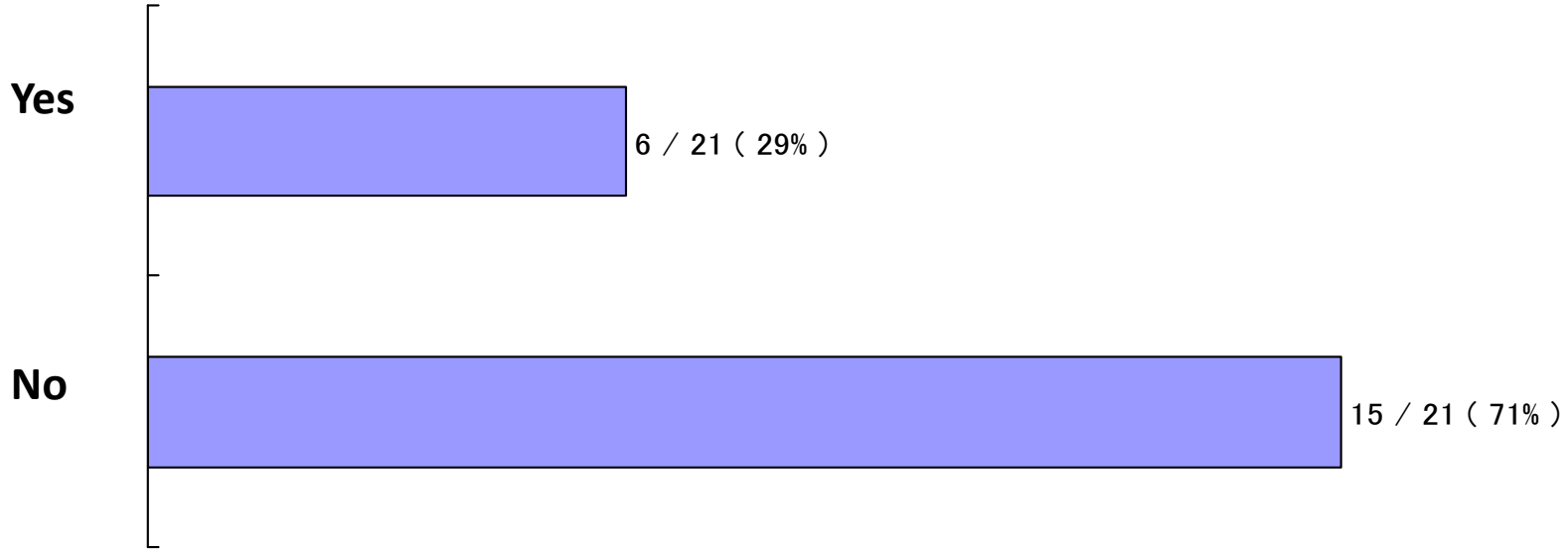


multiple answers allowed

Quoted from *RADIOISOTOPES* 2010; 59: 659-673.

At the 21/82 institutes (25%) expert of radiological science is not included in the ethics committee;

Does your ethics committee call expert when it is necessary?



Quoted from *RADIOISOTOPES* 2010; 59: 659-673.

Which standards do you refer when you evaluate radiation safety of research volunteers?

Standards for evaluation	# of the sites
Responsible researcher's evaluation	**53**
Comparing other examination and/or therapy	
Domestic laws concerning radiological protection*	**33**
Laws concerning radiation safety	
Medical Service Law	
Pharmaceutical Affairs Law	
Act on Prevention of Radiation Disease due to Radioactive Isotope, etc.	
Laws of other countries**	**0**
International recommendations (ICRP, IAEA, etc.)**	**19**
Others	**8**
Do not evaluate specifically	**8**

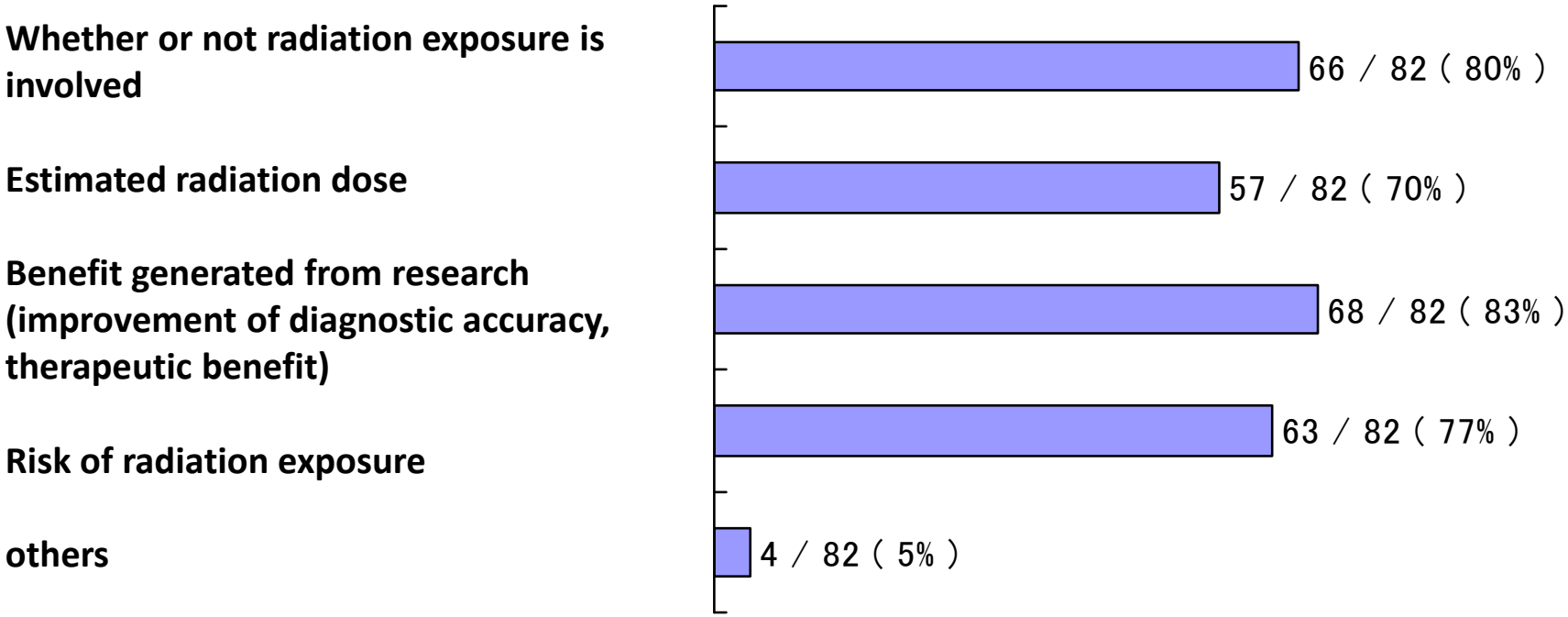
multiple answers allowed

*not including standards specific to research volunteers

** including standards specific to research volunteers

Quoted from *RADIOISOTOPES* 2010; 59: 659-673., modified by Kurihara C for this presentation

Which kind of information is explained at the time of obtaining informed consent?

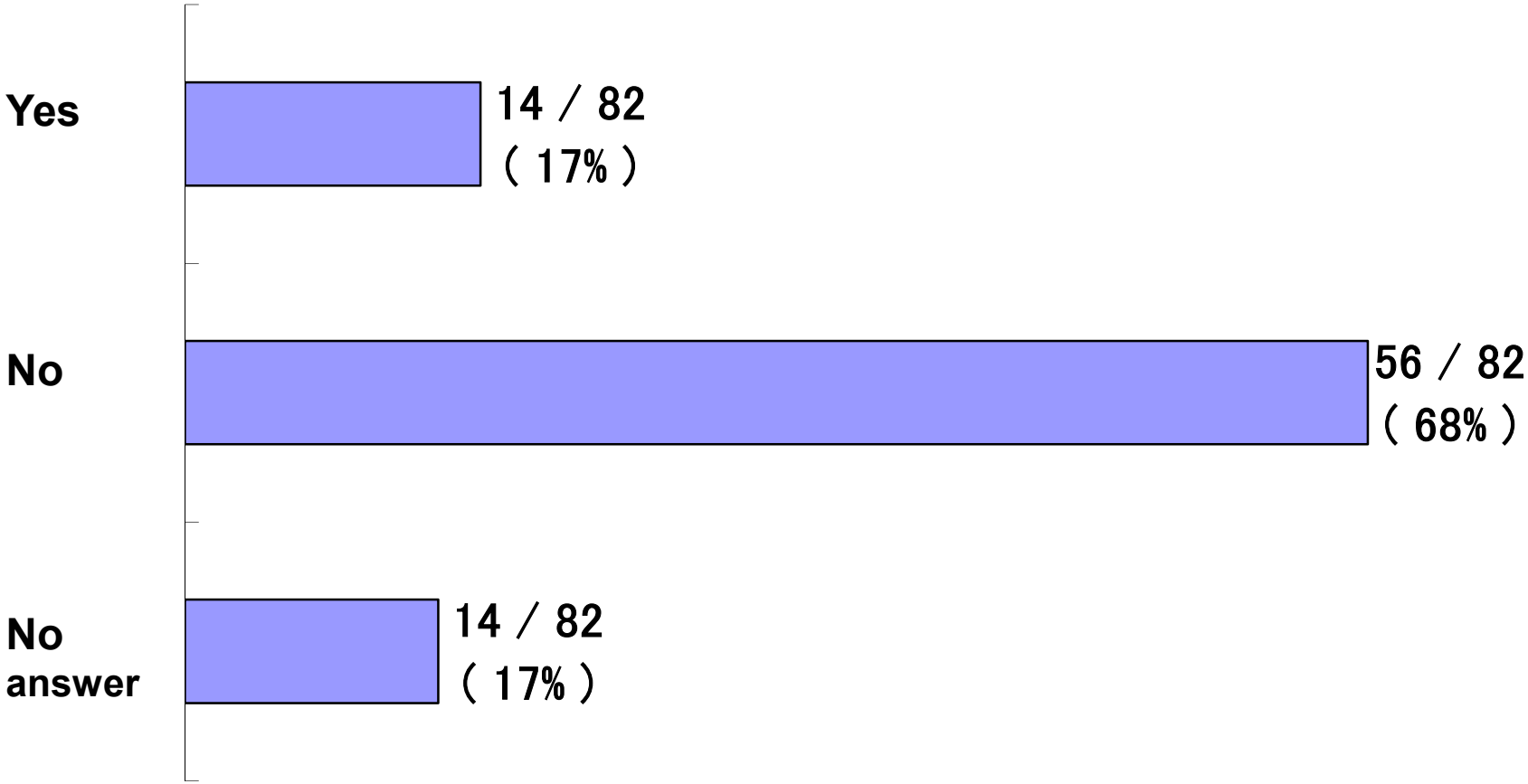


Others:
Adverse reactions of drugs; risk of procedure of examination; objectives and methods of research, etc.

multiple answers allowed

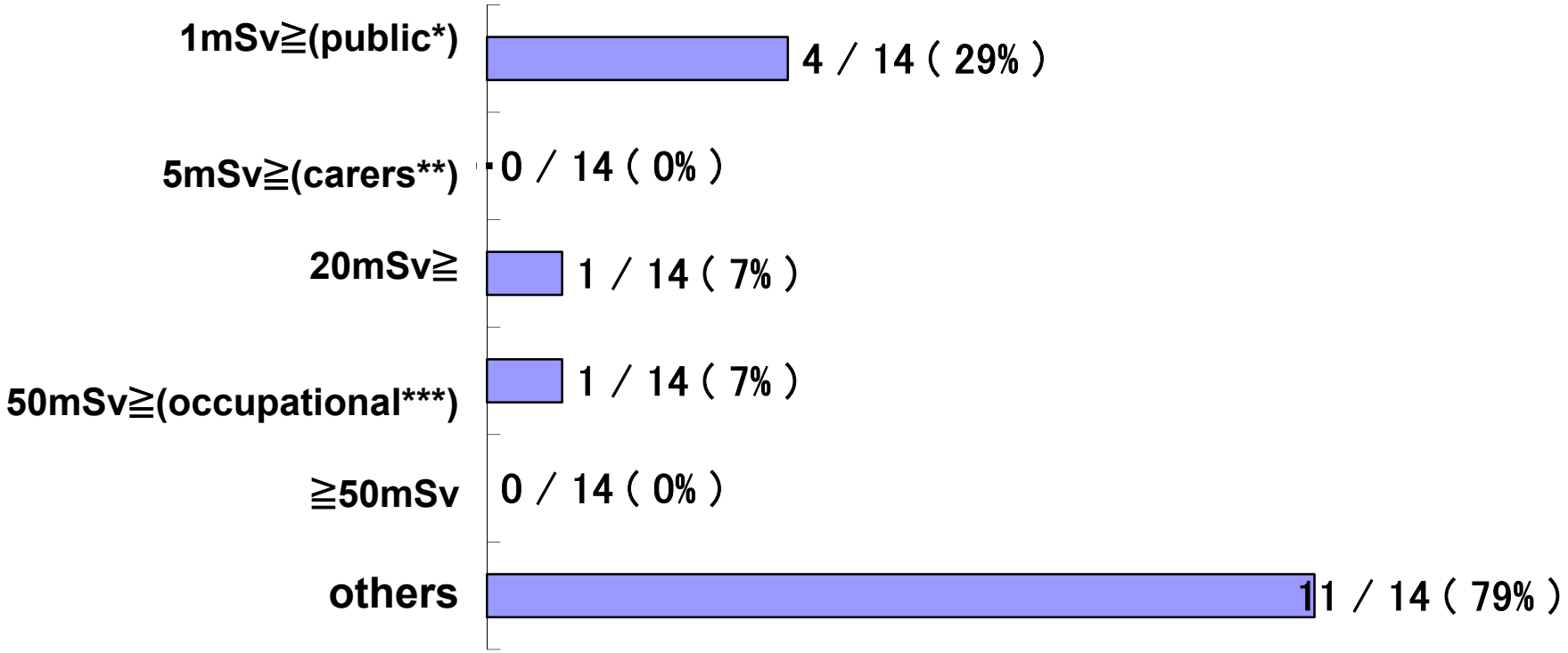
Quoted from *RADIOISOTOPES* 2010; 59: 659-673.

Is there any roughly described standards for dose limits defined by the ethics committee?



Quoted from *RADIOISOTOPES* 2010; 59: 659-673.

Among the site who answered “Yes”:



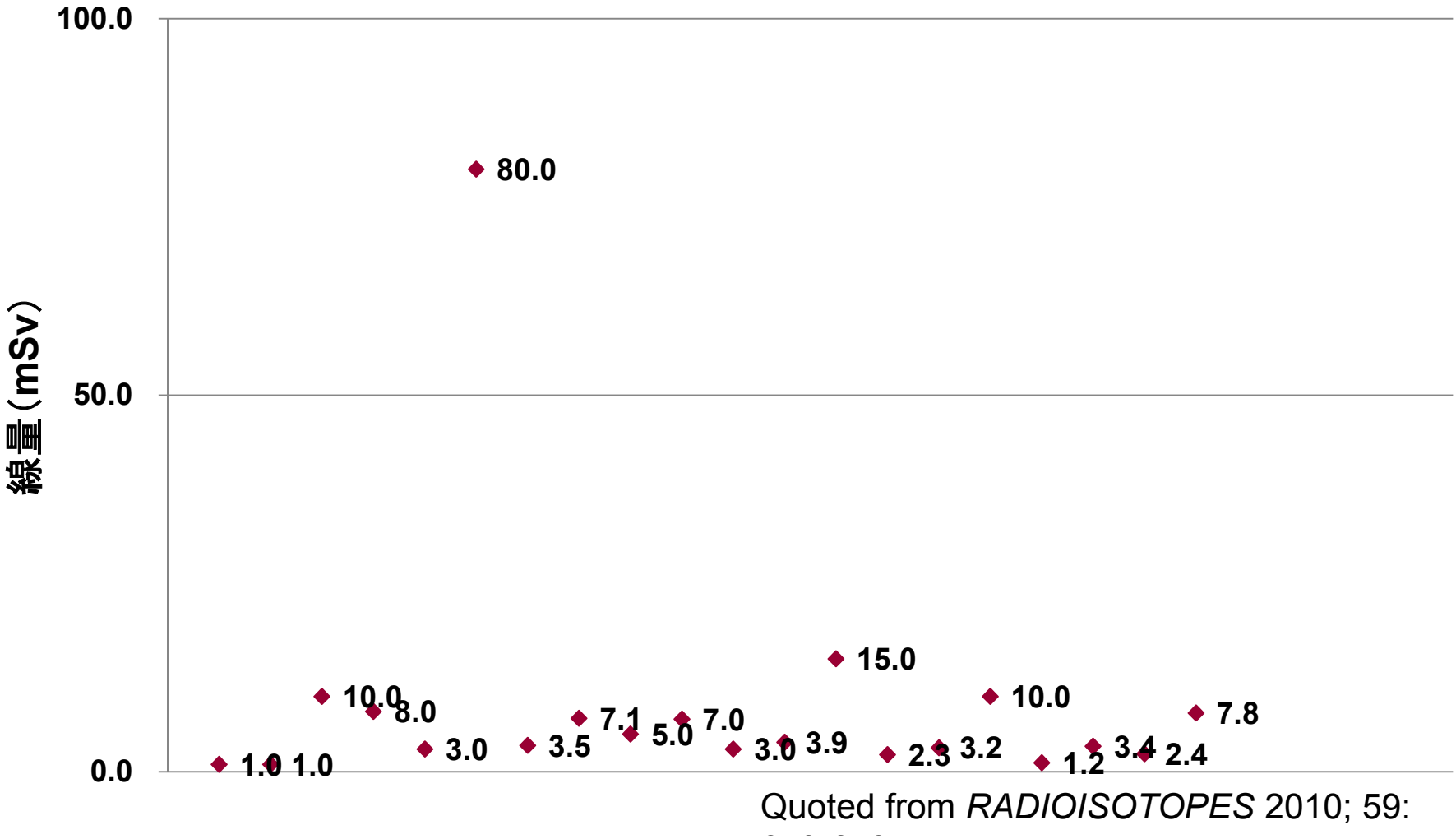
* equivalent to the annual dose limit for the general public in public exposure
** equivalent to the dose constraint for carers in medical exposure
*** equivalent to the annual dose limit for workers in occupational exposure

Quoted from *RADIOISOTOPES* 2010; 59: 659-673.

How much were the radiation doses (effective dose) in the protocols conducted in the past 2 years?（Healthy volunteers）

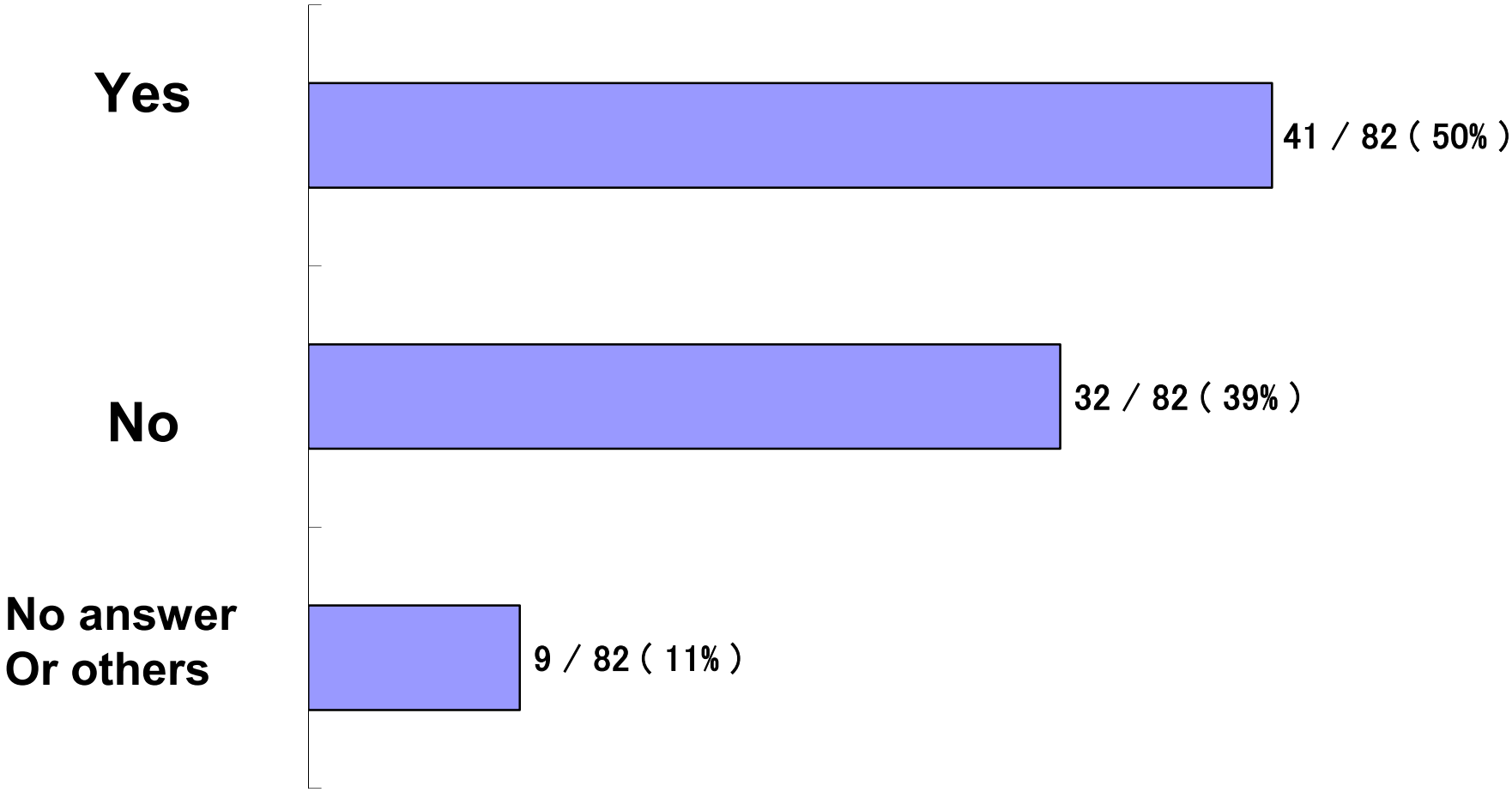
Quoted from *RADIOISOTOPES* 2010; 59: 659-673.

How much were the radiation doses (effective dose) in the protocols conducted in the past 2 years?（patient volunteers）



Quoted from *RADIOISOTOPES* 2010; 59:

Do you think it necessary to set an expert committee specifically evaluate radiation safety of administrating RIs to human research volunteers?



Quoted from *RADIOISOTOPES* 2010; 59:

Summary of “summary of results”

At the 76 institutes (81%) protocols including RI administration have been reviewed at the ordinary ethics committee not specific to RP.

At the 21 institutes (25%) expert of radiological science have not been included;

15 institutes did not call for experts even if necessary.

For all but 1 case the doses to volunteers were less than 50 mSv; informed consent process seemed to be appropriate.

International standards/recommendations have not been well recognized.

Quoted from *RADIOISOTOPES* 2010; 59: 659-673.

Proposal by J-SNM Oct 26, 2011

http://www.jsnm.org/tsuutatu/11-10-28

Ethics & regulations: Helsinki, CIOMS, domestic/community regulations

Volunteers selection: capability of risk

- **healthy:** considering age, past experience of participation
- **pregnant, child:** only necessary cases, discussed at ethics committee
- **patient:** only when direct/indirect benefit is prospected

Radiation dose control:

- **healthy:** enough consideration for optimization
- **patient:** dose-optimization based on pre-clinical test;
  considering dose when using CT; limitation of times

Informed consent:

enough information concerning no-benefit & risk of radiation

Radiological protection of and education for research stuff

Ethics committee: participation or consultation of specialist of radiological protection; additional consideration on dose minimization, risk information, alternative method, quality assurance

* Not mentioned about ICRP pub 62. FDA 21CFR361.1…..why?

How is the case in your country?

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Experience to provide educational lecture on research ethics at the Meeting of Japanese Society of Radiological Technology and following discussion:

“Our ethics committee does not approve a protocol only because radiation exposure is involved”

“I think it is NOT necessary to describe about radiation dose in a study protocol”

Too much sensitive …Too much negligent

Principles of bioethics and radiological protection

bioethics

1. Respect for persons
   - Respect for individual's decision making
   - Informed consent
2. Beneficence
   - Principle of "do no harm"
   - Maximize benefit, minimize risk
   - risk-benefit assessment
3. Justice
   - Fair balance of sharing risk and chance of participating in research and access to benefit of research results

The Belmont Report. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979.

RP

1. Justification
2. Optimization
   ALARA: as law as reasonably achievable
3. Limitation

Kurihara C. Research ethics and radiological protection: Reflecting the discussion at the Japanese Society of Radiological Technology Meeting. Japanese Journal of Radiological Technology. 2011; 67(6): 683-90.

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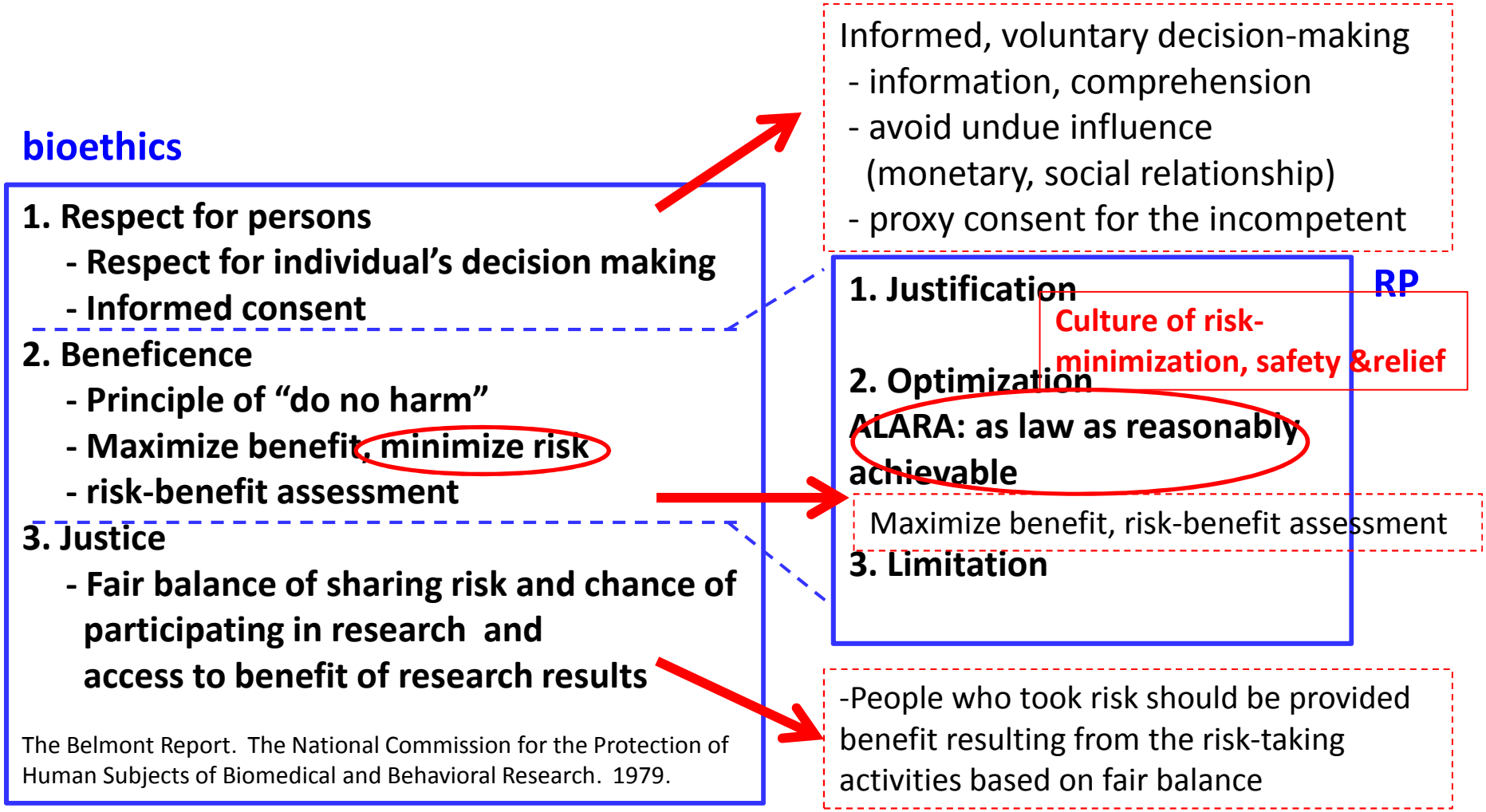
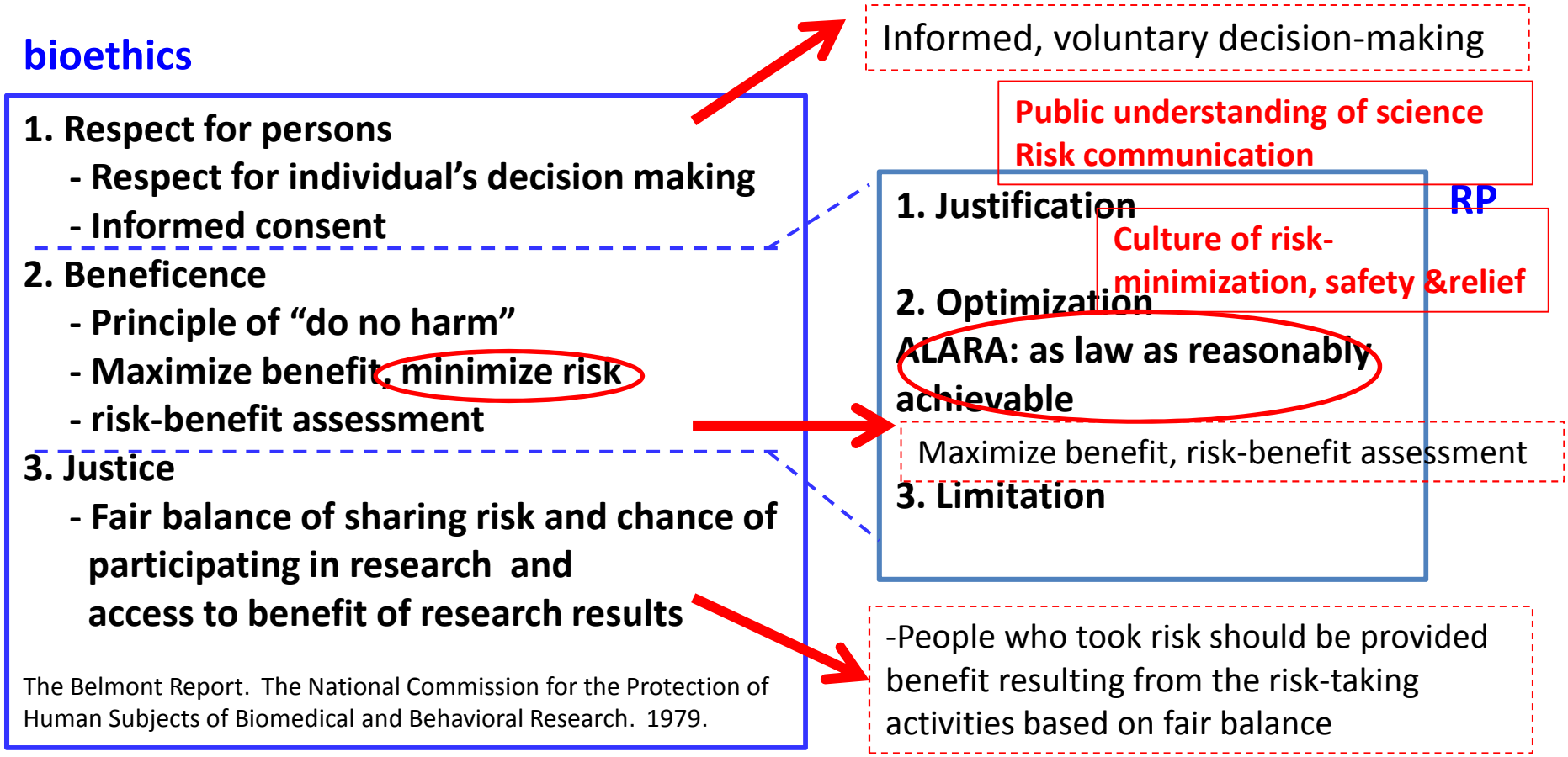
Principles of bioethics and radiological protection



Kurihara C. Research ethics and radiological protection: Reflecting the discussion at the Japanese Society of Radiological Technology Meeting. Japanese Journal of Radiological Technology. 2011; 67(6): 683-90.

Principles of bioethics and radiological protection

Core value=human dignity, right, welfare



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Principles of bioethics and radiological protection

Core value=human dignity, right, welfare

Anti-medicalization vs pro-medical technology

Anti-nuke vs pro-nuclear technology

bioethics

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- **Respect for individual's decision making**
- **Informed consent**

2. Beneficence
- **Principle of "do no harm"**
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3. Justice
- **Fair balance of sharing risk and chance of participating in research and access to benefit of research results**

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Informed, voluntary decision-making

Public understanding of science
Risk communication

RP

Culture of risk-minimization, safety &relief

1. Justification

2. Optimization
ALARA: as law as reasonably achievable

Maximize benefit, risk-benefit assessment

3. Limitation

-People who took risk should be provided benefit resulting from the risk-taking activities based on fair balance

Kurihara C. Research ethics and radiological protection: Reflecting the discussion at the Japanese Society of Radiological Technology Meeting. Japanese Journal of Radiological Technology. 2011; 67(6): 683-90.

Analogy of ethics of animal experimentation

Core value=human dignity, right, welfare VS animal right, welfare

Anti-medicalization vs pro-medical technology

Anti- vs pro- animal experimentation

bioethics

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Animal cannot give informed consent
Does guardian or community can give proxy consent?

1. Replacement

2. Reduction

3. Refinement

3Rs for animal experimentation

Does the research results from animal experimentation provide benefit to the tested animal or its population?

Kurihara C. Research ethics and radiological protection: Reflecting the discussion at the Japanese Society of Radiological Technology Meeting. Japanese Journal of Radiological Technology. 2011; 67(6): 683-90.

Environment Protection: for human?/environment?

Analogy of ethics of animal experimentation

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bioethics

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Questions

"Because all drugs have risks, the goal of pharmacotherapy cannot be to prescribe a risk-free regimen. Instead, it is to ensure that the risks of drug therapy are as low as possible and are acceptable in the context of a medication's clinical benefit."

"Principles of Pharmacology- The Pathophysiologic Basis of Drug Therapy 3rd edition"

Is it possible to shift the paradigm from the "risk-minimization culture" towards "acceptable risk" including emergent/harmful situation, balancing with benefit to the society?

Questions

"The physical and mental risks of living in an unfamiliar and foul environment are quite significant. The evacuation centers posed more urgent, direct and serious physical and mental risks for the elderly than the slightly increased risk of future cancer due to radiation exposure."

Akabayashi A, Hayashi Y. Mandatory evacuation of residents during the Fukushima nuclear disaster: an ethical analysis. Journal of Public Health. 2012; 34(3): 348-51.

Which kind of "voluntary" instead of "compulsory" decision-making algorism could be taken based on risk-benefit analysis comparing estimated health outcomes of two parallel worlds, based on epidemiological background information?

Questions

What is the directions of road ahead?
How is the timeline?

Which kinds/level of risk is acceptable for the society, including the case of emergency?;

which kind of benefit is expected balancing the risk?;

which kind of decision-making system is appropriate for each stakeholders?

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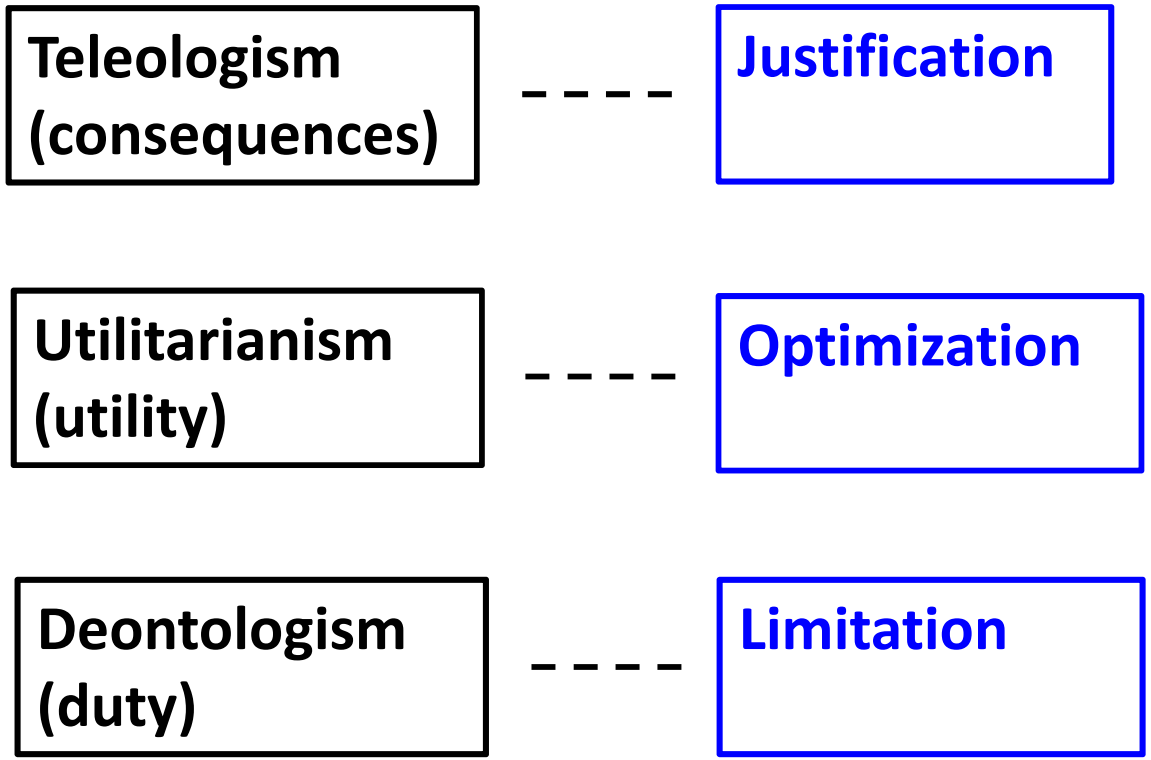
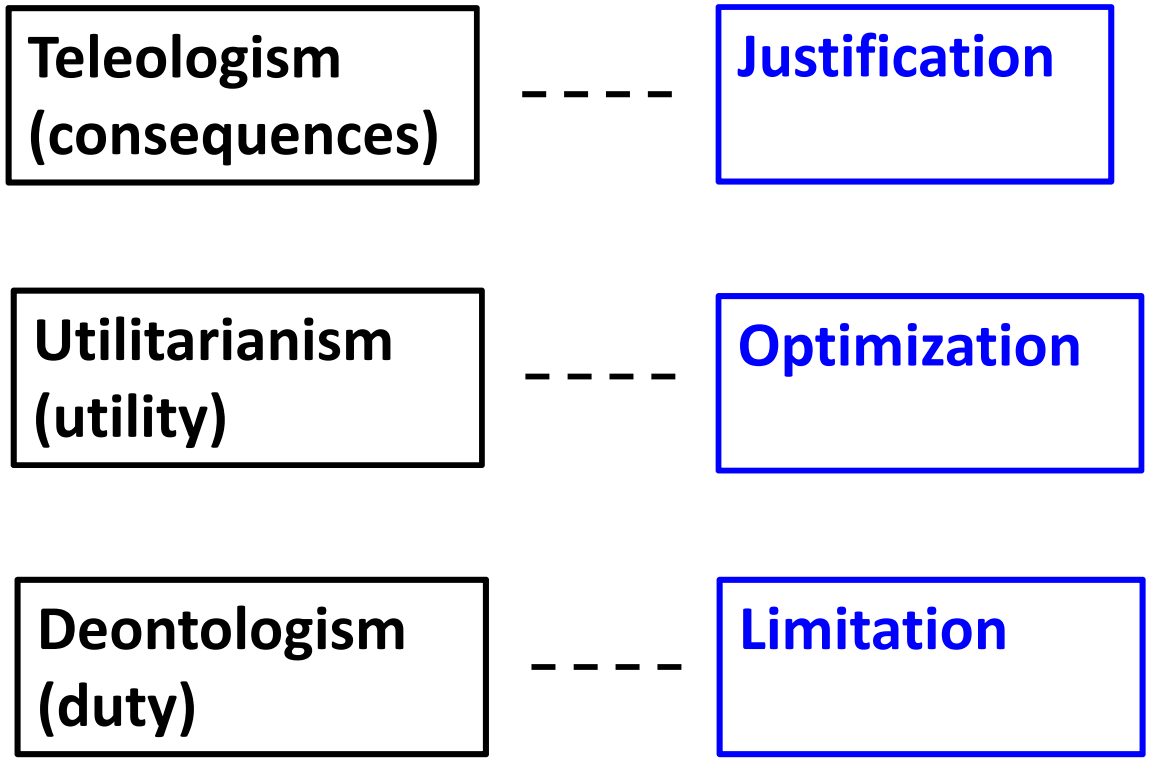
- Bioethics and radiological protection would be able to find common ground through discussion of case studies among bioethicists and RP experts, especially through evidence-based health policy development procedures.
- Principles of “respect for person” “justice” have not been well described in RP principles: These may be “double-edged” tool for “excuse” but same times work as the tool for “strictly fair balanced decision-making”.
- We hope to be able to share experience internationally which kind/level of risk is acceptable for society; which system is appropriate in the field of medical exposure; emergency exposure.

Theoretical consideration by Dr. Abel J. Gonzalez

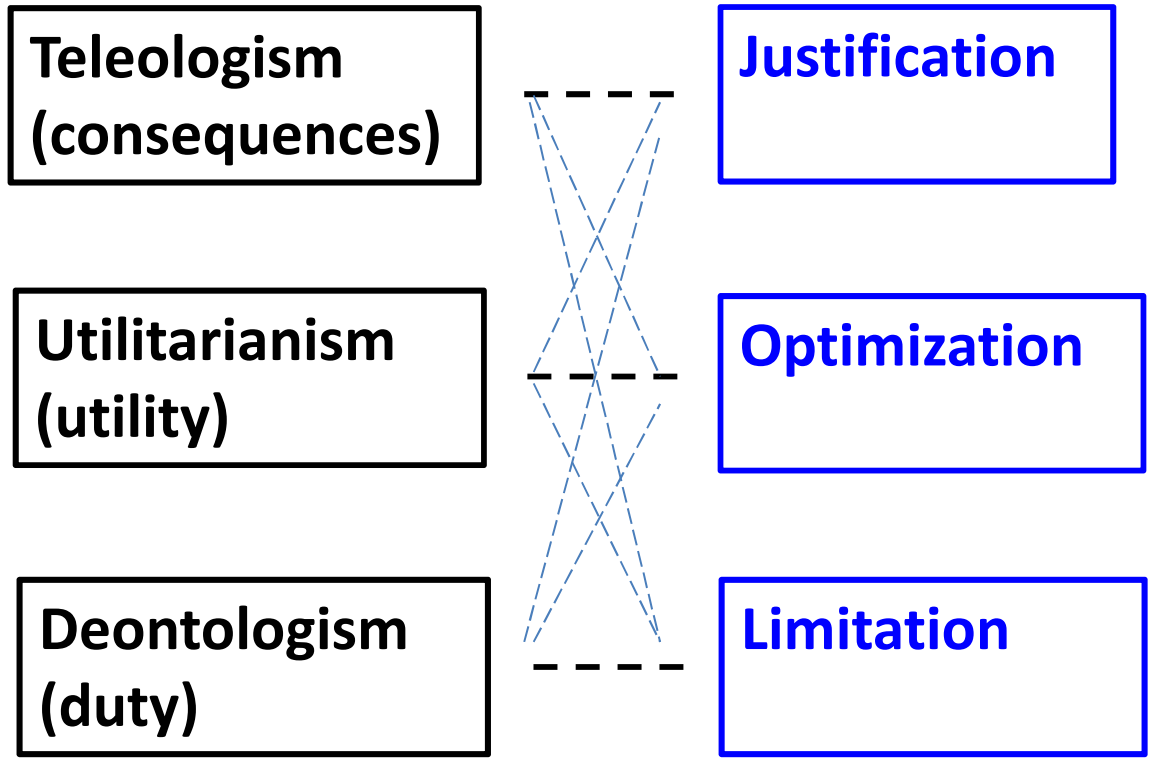


Theoretical consideration by Dr. Abel J. Gonzalez



I agree with this classification of the theories.

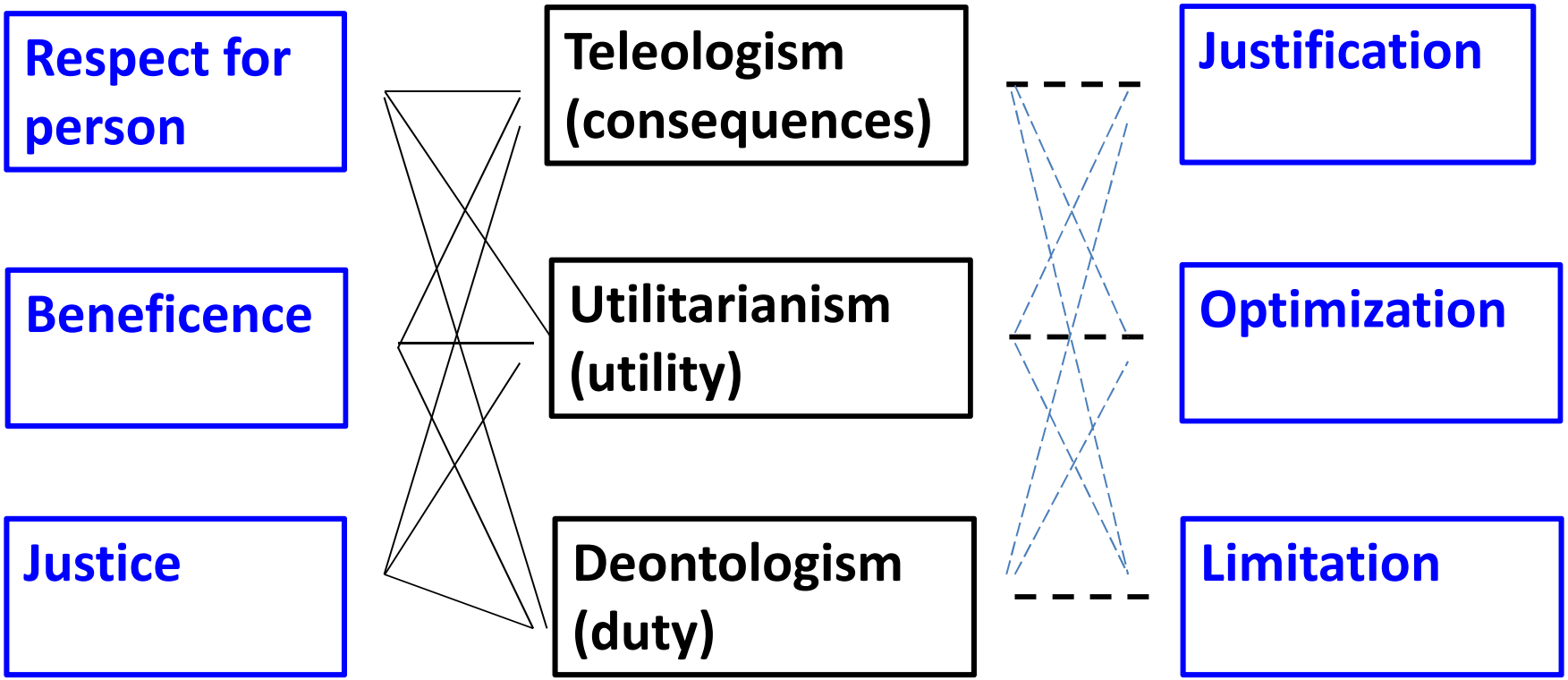
Theoretical consideration by Dr. Abel J. Gonzalez



I agree with this classification of the theories.

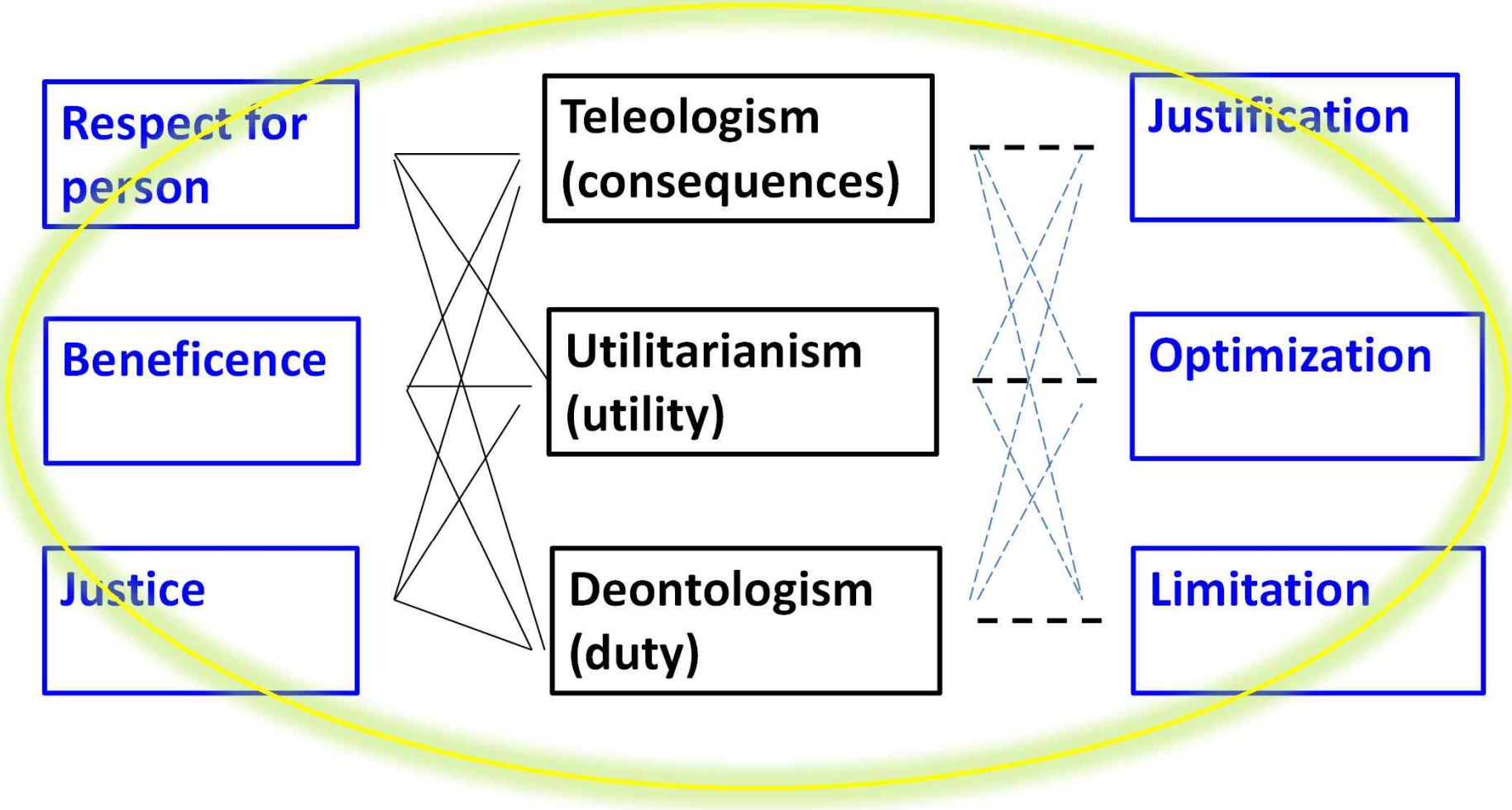
I more greatly agree with his idea: Moral dilemmas have been resolved by amalgamation of principles into common integrated system.

Theoretical consideration by Dr. Abel J. Gonzalez



Well-trained bioethicists take this kind of approach to use these principles as analytical tools to solve ethical dilemma, balancing and integrating the values based on scientific evidence.

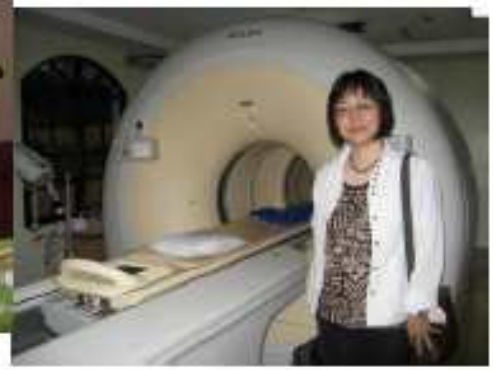
Theoretical consideration by Dr. Abel J. Gonzalez



It seems to be possible to integrate all of these principles to solve actual problems and to achieve common core value.

Ethics Committee of University of the Philippines

St. Lukes Hospital, Philippines



Administrative staff,
Dept of Nuclear Medicine,
Seoul National university

Thank you for your attention!!

My memories good friends in Asian countries Conference of Declaration of Helsinki in Tokyo with Asian people

Tokyo Sky Tree, dinner session of the DoH Conference

DoH Conference, Tokyo

IRB meeting of Seoul National University

More discussion!
Reach to common ground!