PROCEDURE V.3 AUG. 2020

BIOMEDICAL RESEARCH USING IONIZING RADIATION IN HUMAN TEST SUBJECTS

PURPOSE

The purpose of this internal procedure is to offer a further elaboration of the *Radiation Protection Act* (Dutch: '*Besluit basisveiligheidsnormen stralingsbescherming*' or *Bbs*) in terms of biomedical research in human test subjects, in accordance with the provisions stated in *ICRP-62*, and the report of the Netherlands Commission on Radiation Dosimetry ('Nederlandse Commissie voor Stralingsdosimetrie' or NCS) regarding new directives for the justification of studies in human test subjects, in which these test subjects are exposed to sources of ionising radiation.

This procedure is intended for radiation protection experts (RPE), supervisory radiation protection officers (RPO) and other persons who in any way can be involved with biomedical research in human test subjects.

LEGAL FRAMEWORK

Exposure of human beings to sources of ionising radiation for the purpose of scientific medical research, hereinafter called biomedical research, may only occur in compliance with dose limits and criteria as stated in the Declaration of Helsinki (DoH). This declaration has been developed by the World Medical Association (WMA) in Helsinki in 1964, and has been revised in 2013. The most important change concerns the protection of vulnerable groups. Furthermore, extra attention should be paid to minimising and monitoring risks for test subjects during the course of the research.

Publication 62 of the International Commission on Radiological Protection (*ICRP-62*, 1992) refers to radiation protection as a part of biomedical research, and ties in with the provisions stated by the DoH. *ICRP-62* describes the applications that are frequently used in biomedical research. Additionally, the biological effects of the doses, to which the test subject is exposed, are derived from various scientific studies. Based on this, recommendations are issued for the classification of test subjects into risk categories, in which the risk is related to the potential benefit for the test subject himself.

ICRP-103 (2007) adds to *ICRP-62*, by specifying that a participant in biomedical research can also be a healthy volunteer.

The complex license issued to the Randwyck institutes, allows practices using ionising radiation in test subjects for the purpose of (bio)medical research, provided that the recommendations stated by *ICRP-62* (Chapter 4, section V, C) are observed.

Based mainly on aforementioned reports, the NCS published a directive for the justification process connected to the use of sources of ionising radiation in biomedical research. This directive is adapted to the latest state of technology and science. Therefore, the Radiation Protection Unit Randwyck ('Stralingsbeschermingseenheid' or SBE Randwyck) uses this as a guideline for the justification of studies.

METC APPLICATION

An independent, accredited Medical Ethics Review Committee ('Medisch-Ethische Toetsingscommissie' or METC) assesses every study on quality and relevance, and also on the associated strain and risks for the participants in the study. This review also includes verification of the fact that a study falls within the established legal frameworks. The METC issues an assessment, but can choose to be advised by experts in the field, who have no direct interest in the study. Permission is granted for each study, and is generally valid throughout the Netherlands.

The assessment of the radiation safety aspects of the study, based on *ICRP-62*, among other things, occurs according to the format described below, in accordance with the 'Radiation Safety Regulation Randwyck' ('Regeling Stralingshygiëne Randwyck'), and runs in parallel to the METC application.

The SBE assesses these studies according to the radiation safety principle of the ICRP, taking in account the justification, dose control, as well as the optimisation of the application. If necessary, the SBE consults with the researcher, RPE and/or RPO of the department at which the study is performed, to put additional provisions and/or measures into practice with the purpose of limiting the radiation risk. The final approval concerning the justified use of ionising radiation is issued by the General Coordinating Expert ('Algemeen Coördinerend Deskundige' or ACD) in the form of a written internal approval ('Schriftelijke Interne Goedkeuring' or SIG).

The Clinical Trial Center Maastricht (CTCM) facilitates human-related research, and manages the approvals related to a certain study, including those from the board of the institute where the study is performed. Only after necessary approvals have been acquired, a researcher may execute his study.

PRINCIPLES ICRP & NCS

Dose control

In *ICRP-53* and *ICRP-62*, extensive tables are included, in which the effective doses are calculated for the administration of radioactive sources in dispersible form to patients. These tables translate into the 'Recommendations Nuclear Medicine' ('Aanbevelingen Nucleaire Geneeskunde'), in which the standard protocols and thus standard doses for frequently used applications are presented. The purpose of these 'Recommendations' is to improve the quality of research and healthcare, and fundamentally contribute to the radiation protection of patients. This objective is served by striving for standardisation in the procedures of the various institutes.

For X-ray applications within the specialisms of Imaging and Cardiology, diagnostic reference levels ('diagnostische referentieniveaus' or DRNs) have been established within Europe. The DRN is a measure for the exposure or dose of standard patients in a routine test under circumstances, that in general meet the requirements of 'good medical practice'. In the case of common clinical issues, provided good diagnostic and technical performance of the used equipment is ensured, these DRNs should not be exceeded.

Justification

If equal or comparable results can be obtained by using alternative methods, an assessment is made to determine if the expected beneficial effects of the use of ionising radiation outweighs the detrimental effect (the health risk, amongst others). In this assessment, the risks that come with the use of the alternative physical or chemical alternatives are considered as well.

Optimization

In the context of optimization, administered doses should be as low as reasonably achievable (ALARA). For this, the latest scientific findings, use of state-of-the-art techniques, optimal quality control of equipment and statistical arguments regarding the number of test subjects must be considered in the study.

Execution of the study also needs to occur according to 'good medical practice'.

Classification into risk categories based on principles ICRP

ICRP-62 and *ICRP-103* assign classifications for the extent of the effective dose to which study participants are subjected during the course of the study. For this, the extent of the exposure is associated with a minimal benefit which the test subject is supposed to gain by participating in the study.

In the report of the NCS, titled "Human exposure to ionising radiation for clinical and research purposes: radiation dose & risk estimates" (*NCS-26*, 2016), new directives are stated, in addition to the classifications as advised by the ICRP, for the justification of studies with human test subjects in which these will be exposed to sources of ionising radiation. These additional directives are based on the current state of technology and science, and result in the addition of a new category. The necessity of this addition is mainly a result of the advance of imaging techniques in patient diagnostics. Because of this, the use of imaging techniques in biomedical research has increased significantly. As a result, the radiation exposure, which goes along with participation in a study, has increased at the same time. This classification in categories as proposed by NCS is shown in *Table 1*.

Table 1: Classification into risk categories based on principles ICRP

Effective dose [mSv]	Risk category	Benefit
<0.1	I (<$5{\cdot}10^{-6}$)	Obtaining fundamental scientific or medical knowledge
0.1-1	IIa ($5{\cdot}10^{-6}$ - $5{\cdot}10^{-5}$)	Obtaining fundamental scientific or medical knowledge, resulting in a health benefit
1-10	IIb ($5{\cdot}10^{-5}$ - $5{\cdot}10^{-4}$)	Obtaining fundamental scientific or medical knowledge, directly resulting in prevention or cure of the condition for the test subject
10-20	IIIa ($5{\cdot}10^{-4}$ - $1{\cdot}10^{-3}$)	Obtaining fundamental scientific or medical knowledge, directly resulting in prevention or cure of the severe condition for the test subject
>20	IIIb (>$1{\cdot}10^{-3}$)	Obtaining fundamental scientific or medical knowledge, directly resulting in the saving of lives or the prevention of new cases of disease

Correction of risk categories according to gender and age

Besides introducing an extra category, the NCS proposes to correct risk categories according to gender and age (see *Table 2*).

Table 2: Correction of risk categories according to gender and age

Gender	Age	Risk category			
		I	IIa	IIb	IIIa
Male	0-9	0.1	0.5	5.0	10.0
	10-19	0.1	0.6	6.3	12.5
	20-29	0.1	0.8	8.0	16.1
	30-39	0.1	1.0	9.8	19.5
	40-49	0.1	1.2	11.8	23.7
	50-59	0.2	1.5	15.3	30.6
	60-69	0.2	2.2	22.4	44.8
	70-79	0.4	3.8	37.9	75.8
	80-89	0.9	9.1	90.9	181.8
	90-99	12.5	125	1250	2500
Female	0-9	0.0	0.3	3.5	6.9
	10-19	0.0	0.5	4.5	9.1
	20-29	0.1	0.6	5.9	11.7
	30-39	0.1	0.7	7.4	14.7
	40-49	0.1	0.9	8.7	17.4
	50-59	0.1	1.1	11.3	22.7
	60-69	0.2	1.6	16.1	32.3
	70-79	0.3	2.7	27.3	54.6
	80-89	0.7	7.1	71.4	142.9
	90-99	12.5	125	1250	2500

The effective doses shown in *Table 1*, can thus be replaced by the doses shown in *Table 2*, if a clear demarcation of age group and/or gender is formulated in the study.

For all studies in which test subjects (male and/or female) between the age of 18 and 80 may be included, *Table 1* is used; this corresponds to the effective doses as defined for males in the age group of 30 to 39 years.

Assessment

The SBE uses above tables to apply a dose correction for both young children and the elderly.

When designing a study, if deemed necessary, a clinical physicist will be involved, who can provide or check the needed dosimetric patient data. Radioactive labelled compounds must meet the pharmaceutical quality requirements that apply for radiopharmaceuticals; X-ray equipment must meet the quality control that applies for application in patients.

The use of sources of ionising radiation as part of biomedical research is only allowed under the regime of a (or several) written internal permit ('Schriftelijk Interne Toestemming' or SIT) for the use of these sources at the department concerned, and within the framework of the Complex Licence Randwyck.

At all times, the execution of these practices occurs under supervision of the RPO of the department at which the practices are performed, after the researcher has discussed the specific details related to the use of ioinising radiation with this RPO.

Application (radiation safety) approval

If an approval needs to be acquired from the ACD, the study protocol, test subject information and the ABR form can be sent to straling-crisp@maastrichtuniversity.nl.

The processing time from the moment of acquiring the required documentation is two weeks at most.

LIST OF ABBREVIATIONS

Dutch		**English**	
ABR-formulier	algemeen beoordelings- en registratieformulier	ABR form	general assessment and registration form
ACD	algemeen coördinerend deskundige	-	general coordinating expert
ALARA	as low as reasonably achievable	ALARA	as low as reasonably achievable
Bbs	Besluit basisveiligheidsnormen stralingsbescherming	-	-
CTCM	Clinical Trial Center Maastricht	CTCM	Clinical Trial Center Maastricht
DRN	diagnostische referentieniveau	DRL	diagnostic reference level
ICRP	International Commission on Radiological Protection	ICRP	International Commission on Radiological Protection
METC	Medisch-Ethische Toetsingscommissie	-	Medical Ethics Review Committee
NCS	Nederlandse Commissie voor Stralingsdosimetrie	-	Netherlands Commission on Radiation Dosimetry
SBE	stralingsbeschermingseenheid	RPU	radiation protection unit

REFERENCES

- Besluit basisveiligheidsnormen stralingsbescherming: https://wetten.overheid.nl/BWBR0040179/2018-07-01
- ICRP-53 (1992)
- ICRP-62 (1992)
- ICRP-103 (2007)
- NCS-26 (1992)
- Regeling Stralingshygiëne Randwyck