The American College of Radiology, with more than 30,000 members, is the principal organization of radiologists, radiation oncologists, and clinical medical physicists in the United States. The College is a nonprofit professional society whose primary purposes are to advance the science of radiology, improve radiologic services to the patient, study the socioeconomic aspects of the practice of radiology, and encourage continuing education for radiologists, radiation oncologists, medical physicists, and persons practicing in allied professional fields.

The American College of Radiology will periodically define new practice parameters and technical standards for radiologic practice to help advance the science of radiology and to improve the quality of service to patients throughout the United States. Existing practice parameters and technical standards will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.

Each practice parameter and technical standard, representing a policy statement by the College, has undergone a thorough consensus process in which it has been subjected to extensive review and approval. The practice parameters and technical standards recognize that the safe and effective use of diagnostic and therapeutic radiology requires specific training, skills, and techniques, as described in each document. Reproduction or modification of the published practice parameter and technical standard by those entities not providing these services is not authorized.

Revised 2019 (Resolution 40)*

ACR–SNMMI–SPR PRACTICE PARAMETER FOR THE PERFORMANCE OF SCINTIGRAPHY AND UPTAKE MEASUREMENTS FOR BENIGN AND MALIGNANT THYROID DISEASE

PREAMBLE

This document is an educational tool designed to assist practitioners in providing appropriate radiologic care for patients. Practice Parameters and Technical Standards are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, the American College of Radiology and our collaborating medical specialty societies caution against the use of these documents in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the practitioner in light of all the circumstances presented. Thus, an approach that differs from the guidance in this document, standing alone, does not necessarily imply that the approach was below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in this document when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of this document. However, a practitioner who employs an approach substantially different from the guidance in this document is advised to document in the patient record information sufficient to explain the approach taken.

The practice of medicine involves not only the science, but also the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to the guidance in this document will not assure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of this document is to assist practitioners in achieving this objective.

1 Iowa Medical Society and Iowa Society of Anesthesiologists v. Iowa Board of Nursing, ___ N.W.2d ___ (Iowa 2013) Iowa Supreme Court refuses to find that the ACR Technical Standard for Management of the Use of Radiation in Fluoroscopic Procedures (Revised 2008) sets a national standard for who may perform fluoroscopic procedures in light of the standard’s stated purpose that ACR standards are educational tools and not intended to establish a legal standard of care. See also, Stanley v. McCarver, 63 P.3d 1076 (Ariz. App. 2003) where in a concurring opinion the Court stated that “published standards or guidelines of specialty medical organizations are useful in determining the duty owed or the standard of care applicable in a given situation” even though ACR standards themselves do not establish the standard of care.
I. INTRODUCTION

This practice parameter was revised collaboratively by the American College of Radiology (ACR), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the Society for Pediatric Radiology (SPR).

This practice parameter is intended to guide interpreting physicians performing and interpreting thyroid scintigraphy, thyroid radioiodine uptake (RAIU) measurements, and whole-body radioiodine scintigraphy. Properly performed imaging and uptake examinations provide critical information on a variety of conditions that relate to the thyroid gland. Although results can suggest specific medical conditions or diseases, the examination should be correlated with clinical information, including thyroid function tests, thyroid physical examination, and recent medications or iodine ingestion. Findings should be correlated with other available imaging examinations, such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission/computed tomography (PET/CT), radiography, ultrasonography, and/or prior thyroid scintigraphy. Adherence to this practice parameter should optimize detection and characterization of abnormal thyroid morphology and function.

Application of this practice parameter should be in accordance with the ACR-ACNM-SNMMI-SPR Practice Parameter for the Use of Radiopharmaceuticals in Diagnostic Procedures [1].

Thyroid scintigraphy facilitates the detection of focal and/or diffuse abnormalities of thyroid morphology, correlation of morphology with function, and detection of aberrant or metastatic functioning thyroid tissue, or residual native tissue after therapy.

Thyroid uptake allows measurement of global function of the thyroid gland as reflected by the quantitative evaluation of radioiodine accumulation and kinetics.

II. INDICATIONS AND CONTRAINDICATIONS

A. Thyroid scintigraphy is useful in, but not limited to, the evaluation of the following:

1. Size and location of thyroid tissue
2. The cause of overt and subclinical thyrotoxicosis
3. Suspected focal masses or diffuse thyroid disease
4. Clinical laboratory tests suggestive of abnormal thyroid function
5. Function of thyroid nodules detected on clinical examination or other imaging examinations
6. Congenital thyroid abnormalities, including ectopia
7. Differentiating hyperthyroidism from other forms of thyrotoxicosis (eg, subacute or chronic thyroiditis and thyrotoxicosis factitia)

B. Thyroid uptake is useful for the following:

1. Differentiating hyperthyroidism from other forms of thyrotoxicosis (eg, subacute or chronic thyroiditis and thyrotoxicosis factitia)
2. Assessing the necessity and calculating iodine-131 sodium iodide administered activity for patients to be treated for hyperthyroidism (see the ACR Practice Parameter for the Performance of Therapy with Unsealed Radiopharmaceutical Sources) [2]

C. Whole-body imaging for thyroid carcinoma is useful for determination of presence and location of the following:

1. Residual functioning thyroid tissue or cancer after surgery for thyroid cancer or after ablative therapy with radioiodine
2. Metastases from iodine-avid forms of thyroid cancer
D. Contraindications

Administration of iodine-131 sodium iodide to pregnant or lactating patients (whether currently breastfeeding or not) is contraindicated. Complete cessation of breastfeeding 6 weeks prior to administration of iodine-131 sodium iodide is recommended to decrease the radiation absorbed dose to the maternal breast tissue and prevent the ingestion of radioactive breast milk by the nursing child [3-5]. After administration of I-131, breast feeding must completely cease for infant(s). Breastfeeding may occur for future children.

The ACR–SPR Practice Parameter for Imaging Pregnant or Potentially Pregnant Adolescents and Women with Ionizing Radiation provides useful information on radiation risks to the fetus regardless of source. Information on managing pregnant or potentially pregnant patients undergoing nuclear medicine procedures is available from the International Commission on Radiological Protection [6].

III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

See the ACR-ACNM-SNMMI-SPR Practice Parameter for the Use of Radiopharmaceuticals in Diagnostic Procedures [1].

IV. SPECIFICATIONS OF THE EXAMINATION

The written or electronic request for thyroid scintigraphy and uptake measurements should provide sufficient information to demonstrate the medical necessity of the examination and allow for its proper performance and interpretation.

Documentation that satisfies medical necessity includes 1) signs and symptoms and/or 2) relevant history (including known diagnoses). Additional information regarding the specific reason for the examination or a provisional diagnosis would be helpful and may at times be needed to allow for the proper performance and interpretation of the examination.

The request for the examination must be originated by a physician or other appropriately licensed health care provider. The accompanying clinical information should be provided by a physician or other appropriately licensed health care provider familiar with the patient’s clinical problem or question and consistent with the state’s scope of practice requirements. (ACR Resolution 35, adopted in 2006 – revised in 2016, Resolution 12-b)

A. Thyroid Scintigraphy

1. Radiopharmaceutical

The preferred radiopharmaceutical for thyroid scintigraphy for benign disease is iodine-123 sodium iodide administered orally in a capsule or as a liquid. In adults, the administered activity is 0.2 to 0.4 mCi (7.4-14.8 MBq). For children, the administered activity should be 0.0075 mCi/kg (0.28 MBq/kg) with a minimum administered activity of 0.027 mCi (1 MBq) and a maximum administered activity of 0.3 mCi (11 MBq) [7]. Use of iodine-131 sodium iodide is strongly discouraged for benign disease use because of its much greater radiation dose to the thyroid.

An alternative radiopharmaceutical is technetium-99m sodium pertechnetate administered intravenously. In adults, the administered activity is 2 to 10 mCi (74-370 MBq). For children, the administered activity is 0.03 mCi/kg (1.1 MBq/kg) with a minimum administered activity of 0.19 mCi (7 MBq) and maximum administered activity of 2.5 mCi (92.5 MBq) [7].

The choice between iodine-123 sodium iodide and technetium-99m sodium pertechnetate for thyroid scintigraphy depends on local practice and physician preference. The longer physical half-life (13.2 hours) and intrathyroidal organification of iodine-123 sodium iodide allows for improved target-to-background ratio, functional thyroid gland imaging, and RAIU. Technetium-99m has a higher photon flux, which results in shorter imaging times. It results in a lower radiation exposure to the thyroid, although the total body...
exposure is slightly higher. Technetium-99m is readily available from a molybdenum-99/technetium-99m generator and is less expensive than iodine-123 sodium iodide. Technetium-99m does not undergo thyroidal organification, and rapid thyroid washout of technetium-99m limits its use for quantitative assessment of thyroid uptake. Rarely, findings on radioiodine and technetium images may be discordant in nodular disease because pertechnetate is not handled by the same physiologic mechanism as iodine.

2. Pharmacologic considerations

Many medications interfere with the accumulation of radiopharmaceuticals in the thyroid gland.

Compounds That May Decrease Thyroid Iodine Uptake

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>TIME*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methimazole</td>
<td>3-5 days</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>3-5 days</td>
</tr>
<tr>
<td>Bromides</td>
<td>1 week</td>
</tr>
<tr>
<td>Mercurials</td>
<td>1 week</td>
</tr>
<tr>
<td>Nitrates</td>
<td>1 week</td>
</tr>
<tr>
<td>Perchlorate</td>
<td>1 week</td>
</tr>
<tr>
<td>Salicylates (large doses)</td>
<td>1 week</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>1 week</td>
</tr>
<tr>
<td>Thiocyanate</td>
<td>1 week</td>
</tr>
<tr>
<td>Iodine-containing cough medicines and vitamins</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Iodine solution (Lugol’s or SSKI**)</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Iodine-containing topical agents</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Kelp</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Tri-iodothyronine (T₃)</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Levothyroxine (T₄)</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td>Thyroid extracts (desiccated thyroid extracts)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Intravenous iodinated contrast materials</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td>Oil-based iodinated contrast materials</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>3-6 months</td>
</tr>
</tbody>
</table>

*Time that patients should wait after medication is discontinued in order to obtain accurate uptake

**Saturated solution of potassium iodide

A thorough medical history should be obtained prior to administering the radiopharmaceutical and, if necessary, the examination should be delayed appropriately.

3. Patient

The patient should be placed in a supine position, with the neck comfortably extended. It may be helpful to gently immobilize the head. When indicated, the physician should palpate the thyroid gland while the patient is in the imaging position as well as when the patient is upright.

4. Imaging

With iodine-123 sodium iodide, planar imaging in the anterior, LAO, and RAO positions can commence as early as 3 to 4 hours or as late as 24 hours after administration. For technetium-99m pertechnetate, imaging should commence 5 to 30 minutes after injection. Radioactive sources or lead markers may be used to identify anatomic landmarks, such as the sternal notch and thyroid cartilage. The location of palpable nodules should be confirmed with a marker for anatomic correlation.

B. Thyroid Uptake
1. Radiopharmaceutical

If thyroid RAIU is performed in conjunction with thyroid scintigraphy, the activity administered for the scan will suffice. If the uptake is performed separately or in conjunction with a technetium-99m pertechnetate scan, as little as 0.1 mCi (3.7 MBq) of iodine-123 sodium iodide or 0.004 to 0.005 mCi (0.15-0.185 MBq) of iodine-131 sodium iodide may be used. If only a thyroid uptake with iodine-131 sodium iodide is obtained, the administered activity should not exceed 0.01 mCi (0.37 MBq).

2. Pharmacologic considerations: See section IV.A.2

3. Procedure

The usual time of measurement is approximately 24 hours after radiopharmaceutical administration. An additional uptake measurement may be performed at 4 to 6 hours, particularly in cases of suspected rapid iodine turnover. The percent uptake should be compared to normal values measured at the same time after radiopharmaceutical administration, if available. The patient should sit or lie with neck extended; an open-faced collimated detector probe should be directed at the neck, with the crystal usually no more than 20 to 30 cm away.

There are several acceptable measurement and calculation techniques; the following is one example. Counts are acquired for 1 minute over the thyroid gland. Counts are then acquired over the patient’s mid-thigh for 1 minute and at the same distance (eg, 20-30 cm), taking care to exclude the urinary bladder from the detector field. A standard (source of the same radiopharmaceutical of identical activity to that administered to the patient) or the radioiodine capsule being administered to the patient is placed in a standardized Lucite scattering neck phantom and counts are acquired for 1 minute using the same geometry. The room background counts also are acquired for 1 minute.

The RAIU is calculated using the following formula:

\[
RAIU = \frac{\text{Neck Counts} - \text{Thigh Counts}}{\text{Phantom Counts} - \text{Background}} \times 100\%
\]

C. Imaging for Thyroid Carcinoma

1. Radiopharmaceutical

Anterior and posterior whole-body radioiodine imaging for thyroid cancer can be performed either as a diagnostic examination (after administration of activity of radioiodine in the diagnostic range) or after administration of a therapeutic administered activity of iodine-131 sodium iodide. Diagnostic whole-body imaging can be performed with either iodine-123 sodium iodide or iodine-131 sodium iodide. Image quality is better with iodine-123 sodium iodide, but its use may be limited by decreased sensitivity in detection of pulmonary metastases, commercial availability or cost [8,9].

a. Preparation

Thyroid hormone replacement should be withheld for a time sufficient to render the patient hypothyroid (serum thyroid-stimulating hormone [TSH] level greater than 30 mU/L), or recombinant human thyroid-stimulating hormone (rhTSH; thyrotropin alpha, such as Thyrogen®) stimulation should be used according to an established protocol.

The use of a low-iodine diet may increase the efficacy of iodine-131 sodium iodide ablation by decreasing serum iodine levels, which can increase RAIU [10-12]. Subsequently, use of a low-iodine diet may also increase the sensitivity of the imaging examination. Typically, the low-iodine diet is started 1 to 2 weeks prior to radioiodine administration [10].
b. Procedures

i. Diagnostic Whole-Body Radioiodine Scintigraphy

Administered activity of 1.0 to 5.0 mCi (37-185 MBq) of iodine-131 sodium iodide is given orally, and imaging of the neck and the whole body is performed 24 to 72 hours later using a high-energy collimator designed for iodine-131 sodium iodide. Possibility of “stunning” may be reduced with less than 3 mCi. Iodine-123 sodium iodide is considered an alternative radiopharmaceutical because of the “stunning” phenomenon that may be encountered when administering iodine-131 sodium iodide for pretherapy diagnostic scintigraphy [13]. Typically administered activity for iodine-123 sodium iodide is 1.5 to 5 mCi (55.5-185 MBq).

In addition to whole-body anterior and posterior parallel-hole collimator images, spot views of the thyroid bed and neck in the anterior and right and left lateral views are obtained with a pinhole collimator [14], and, as needed, anterior and posterior images of the chest and abdomen obtained with a parallel-hole collimator may improve lesion detection. Single photon emission computed tomography (SPECT) imaging may be performed as needed. SPECT/CT imaging may replace or complement planar and pinhole imaging by improving anatomical localization, lesion detection, and diagnostic accuracy [15,16].

Currently, consensus practice parameters for body weight–based administered activity of iodine-131 and iodine-123 for whole-body scintigraphy for children are not available. However, administered activity of 1.5 to 5 mCi, similar to adults, can be used. Activity range of 3 to 5 mCi of iodine-123 for whole-body scintigraphy has been used for children [17].

ii. Posttherapy Whole-Body Radioiodine Scintigraphy

Iodine-131 sodium iodide whole-body imaging may be performed 2 to 14 days (typically at 5-7 days) after thyroid ablative therapy to detect residual thyroid tissue in the neck and/or iodine-avid metastases that may not have been detected on pretherapy imaging examinations, if performed [18]. Uptake values may also be calculated for the residual thyroid tissue in the thyroid bed using the technique described in section IV.B.3.

c. Alternative protocols

Whole-body F-18-fluorodeoxyglucose-PET/CT (FDG-PET/CT) may be used to evaluate patients who have a history of differentiated thyroid cancer that is not iodine avid and have elevated thyroglobulin levels [10]. FDG-PET/CT can detect metastatic disease and change patient management in suspected thyroid cancer recurrence [19]. Studies have demonstrated that stimulated TSH levels with thyroid hormone withdrawal or rhTSH may increase the sensitivity of FDG PET/CT for the detection of metastatic thyroid cancer [20,21].

V. EQUIPMENT SPECIFICATIONS

A. Thyroid Imaging

Typically, a gamma camera equipped with a pinhole collimator is used. Images are acquired in the anterior, and often both anterior oblique, projections for a minimum of 100,000 counts or 8 minutes, whichever occurs first. The distance between the collimator aperture and the neck should be such that the thyroid occupies most of the field of view. With pinhole collimators, significant geometric distortion occurs. Additional views with a parallel-hole collimator may be useful when searching for ectopic tissue or estimating thyroid size. Collimator choice should be appropriate to the radiopharmaceutical used.

B. Thyroid Uptake
A thyroid probe is typically used. A gamma camera with a parallel-hole collimator may be used instead of a probe, but the use of a standardized neck phantom remains necessary.

C. Imaging for Thyroid Carcinoma

For iodine-131 sodium iodide imaging, a high-energy collimator should be used with an appropriately shielded detector head. Pinhole collimator imaging of the thyroid bed may also be useful.

Whole-body imaging examinations are acquired with a high-energy collimator for iodine-131 sodium iodide. For imaging with iodine-123 sodium iodide, using a medium-energy collimator rather than a low-energy collimator may improve image quality due to down scatter from a small amount of high-energy photons with photon energies greater than 300 keV [22,23]. If a low-energy collimator is used, down scatter correction should be applied [24,25]. The whole-body scan for iodine-123 sodium iodide may be performed 18 to 24 hours after administration at a scan speed of 8 cm per minute, matrix of 256 × 1,024. Typically for iodine-131 sodium iodide, whole-body imaging is performed in anterior and posterior images as a whole-body sweep (typically 4 cm per minute for approximately 30 minutes, from head to knees). Another protocol is 8 cm per minute with a 256 × 256 × 16 matrix for anterior and posterior images. In some patients, such as young children, it may be easier to acquire multiple planar images. If static planar images will be used, all images should be acquired for the same period of time to facilitate image comparison. Typically for iodine-131 sodium iodide, images of the torso are planned to acquire 300,000 to 500,000 counts. In some situations it may be helpful to image the thyroid bed with a pinhole collimator or to calculate thyroid bed RAIU as part of pretherapy imaging [14].

VI. DOCUMENTATION

Reporting should be in accordance with the ACR Practice Parameter for Communication of Diagnostic Imaging Findings [26].

The report should include the radiopharmaceutical used, the administered activity, and route of administration, any other pharmaceuticals administered, as well as the dose and route of administration.

VII. RADIATION SAFETY

Radiologists, medical physicists, registered radiologist assistants, radiologic technologists, and all supervising physicians have a responsibility for safety in the workplace by keeping radiation exposure to staff, and to society as a whole, “as low as reasonably achievable” (ALARA) and to assure that radiation doses to individual patients are appropriate, taking into account the possible risk from radiation exposure and the diagnostic image quality necessary to achieve the clinical objective. All personnel that work with ionizing radiation must understand the key principles of occupational and public radiation protection (justification, optimization of protection and application of dose limits) and the principles of proper management of radiation dose to patients (justification, optimization and the use of dose reference levels) http://www-pub.iaea.org/MTCD/Publications/PDF/Pub1578_web-57265295.pdf.

Facilities and their responsible staff should consult with the radiation safety officer to ensure that there are policies and procedures for the safe handling and administration of radiopharmaceuticals and that they are adhered to in accordance with ALARA. These policies and procedures must comply with all applicable radiation safety regulations and conditions of licensure imposed by the Nuclear Regulatory Commission (NRC) and by state and/or other regulatory agencies. Quantities of radiopharmaceuticals should be tailored to the individual patient by prescription or protocol.

Nationally developed guidelines, such as the ACR’s Appropriateness Criteria®, should be used to help choose the most appropriate imaging procedures to prevent unwarranted radiation exposure.

Additional information regarding patient radiation safety in imaging is available at the Image Gently® for children (www.imagegently.org) and Image Wisely® for adults (www.imagewisely.org) websites. These advocacy and awareness campaigns provide free educational materials for all stakeholders involved in imaging (patients, technologists, referring providers, medical physicists, and radiologists).
Radiation exposures or other dose indices should be measured and patient radiation dose estimated for representative examinations and types of patients by a Qualified Medical Physicist in accordance with the applicable ACR technical standards. Regular auditing of patient dose indices should be performed by comparing the facility’s dose information with national benchmarks, such as the ACR Dose Index Registry, the NCRP Report No. 172, Reference Levels and Achievable Doses in Medical and Dental Imaging: Recommendations for the United States or the Conference of Radiation Control Program Director’s National Evaluation of X-ray Trends. (ACR Resolution 17 adopted in 2006 – revised in 2009, 2013, Resolution 52).

VIII. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

Policies and procedures related to quality, patient education, infection control, and safety should be developed and implemented in accordance with the ACR Policy on Quality Control and Improvement, Safety, Infection Control, and Patient Education appearing under the heading Position Statement on QC & Improvement, Safety, Infection Control, and Patient Education on the ACR website (https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Quality-Control-and-Improvement).

Equipment performance monitoring should be in accordance with the ACR–AAPM Technical Standard for Nuclear Medical Physics Performance Monitoring of Gamma Cameras [27].

ACKNOWLEDGEMENTS

This practice parameter was revised according to the process described under the heading The Process for Developing ACR Practice Parameters and Technical Standards on the ACR website (https://www.acr.org/Clinical-Resources/Practice-Parameters-and-Technical-Standards) by the Committee on Practice Parameters and Technical Standards – Nuclear Medicine and Molecular Imaging of the ACR Commission on Nuclear Medicine and Molecular Imaging and the Committee on Practice Parameters – Pediatric Radiology of the ACR Commission on Pediatric Radiology in collaboration with the SNMMI, and the SPR.

Collaborative Committee – members represent their societies in the initial and final revision of this practice parameter

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PRACTICE PARAMETER

Thyroid Scintigraphy

REFERENCES


*Practice parameters and technical standards are published annually with an effective date of October 1 in the year in which amended, revised or approved by the ACR Council. For practice parameters and technical standards published before 1999, the effective date was January 1 following the year in which the practice parameter or technical standard was amended, revised, or approved by the ACR Council.
Development Chronology for this Practice Parameter
1995 (Resolution 26)
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Amended 2006 (Resolution 35)
Revised 2009 (Resolution 17)
Revised 2014 (Resolution 33)
Revised 2019 (Resolution 40)