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Role of Reference Levels in Nuclear Medicine: A Report of the SNMMI Dose Optimization Task Force

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Running Title: Role of Reference Levels in NM

BACKGROUND

The concept of reference levels (RLs) has had a long history in diagnostic imaging (*1*). In general, RLs provide guidance in medical imaging regarding appropriate or conventional levels of radiation dose to be delivered to patients. In Europe, the concept has origins in the 1950's with x-ray examination surveys in UK (*2*). In the US, the use of reference levels began in 1973 with the Nationwide Evaluation of X-ray Trends survey (*3*). Since then, concepts have been more formalized by the international community with publications from the ICRP (*4-7*) and in the US from the NCRP (*8*). With increased awareness of potential risks from ionizing radiation, there have been numerous recent publications addressing and suggesting RLs. These publications offer some differing definitions of RLs and raise some philosophical questions about their origin, purpose and appropriate use (*9-14*). In this article, we seek to discuss some of the considerations for application of RLs to nuclear medicine in response to the recommendations of ICRP Committee 3 that encouraged "authorised bodies to set diagnostic reference levels that best meet their specific needs and that are consistent for the regional, national, or local area to which they apply (*7*)."

For the purpose of this article, we focus on two widely-accepted concepts regarding RLs: Diagnostic Reference Levels (DRLs) and Achievable Doses (ADs). The DRLs are set at the 75th percentile of radiation doses for exams (*5*) and DRLs provide an investigational level to help identify unusually high doses. The ADs are set at the median (50^{th} percentile) of radiation doses for exams (*8*) and are intended to identify common practice. For the purpose of establishing DRLs and ADs, the distribution of radiation doses is typically determined by a survey of clinical sites based on protocol reviews, actual patient data, or phantom experiments. In this article, we will refer to both DRLs and ADs as RLs. This terminology is not to be confused with some publications that use "Reference Level" to describe interventional radiologic exams and "diagnostic reference level" to describe diagnostic exams (*8*).

Along with a growing consensus of the definitions of DRLs and ADs, there is also general agreement that these should not be interpreted as absolute measures of appropriate use of medical radiation (*5,9*). RLs should only be used as supplements to and not replacements for professional judgment and do not provide a dividing line between good and bad medicine. They are not intended for regulatory or commercial purposes or to establish legal standards of care. Even with these agreed constraints on the role of RLs in diagnostic imaging, there remain several open philosophical and practical questions about RLs. Should all clinics follow the same national RLs? Is there some leeway within which a clinic would be considered to be compliant with the RLs? What is the appropriate source for setting RLs? Are RLs set solely for radiation protection or should they also guide appropriate image quality? How can clinics use RLs for protocol optimization and ultimately improved patient care?

ROLE OF REFERENCE LEVELS IN IMAGING

Educational

In a broad sense, RLs offer a tool to educate imaging clinics on best practices. National RLs can be used to move national imaging practice to be more unified. Local RLs, potentially set by each clinic to meet unique needs, could be used to ensure appropriate, consistent practice for radiation safety and optimal image quality.

Optimum Range
Application of RLs "promotes attainment of an optimum range of values for a specified medical imaging protocol (*7*)"

Action Levels
Diagnostic Reference Levels can be used as suggested action levels. If a patient did or will receive more radiation than the DRL, the facility should review this patient's dosing and determine if an improvement is possible. This improvement could come in the form of a different dosing, improved equipment, or other protocol modification. In some instances, the site might determine that this level of exposure was, in fact, appropriate for this particular patient.

Normative Levels
Achievable Doses can be used to help define normal practice to help insure that most examinations are performed near the AD level.

As mentioned above, it is widely agreed that RLs are not intended to replace good judgment. Each clinic has a unique set of factors (scanner technology, time for exams, patient populations, physician preference, *etc*.) that could dictate radiation doses (and local reference levels) that deviate from published levels. As clearly stated in the ACR-AAPM practice parameter "The specific purpose of the diagnostic reference level is to provide a benchmark for comparison, not to define a maximum or minimum dose limit (*9*)."

NATIONAL OR LOCAL LEVELS

The ICRP defines the DRL as a level set by professional advisory bodies and/or societies implying a national or regional value that applies to numerous imaging centers (*5*). Many European countries have published RLs for a variety of diagnostic exams (*1,11,15*). In the US, the NCRP Report 172 suggested recommended RLs for many ionizing radiation exams from dental x-rays to nuclear medicine(*8*). In this context, the RLs must be applicable to a wide-range of clinics. Therefore, as Wall and Shrimpton suggest, the RL "should not be set at an 'optimum' or 'minimum achievable' level but more at the borderline between acceptable and unacceptable practice (*1*)." Because of the need to set the level at the high end of acceptable, our view is that national RLs serve primarily as guidance to ensure that excessive radiation doses are not delivered. Consequently, we assert that national RLs have a limited role in promoting optimal practice—i.e. sufficient image quality at the minimum dose.

In contrast, local RLs could be set by each clinic based on the local resources (imaging equipment, time for exams, physician experience, etc). Local RLs can also evolve based on practice changes (improvements in imaging equipment, changes in physician experience, etc.), and thus should be reviewed regularly.

In brief, national RLs primarily serve as guidance to ensure certain radiation doses are not exceeded and local reference levels could serve as a protocol improvement/optimization tool. One could argue that DRLs are the radiation protection measure (message: do not exceed the DRL) and AD's are the normative practice/improvement measure (message: try to practice close to AD). When both of these levels are set by national/regional bodies, they must still be fixed at the high end of acceptable practice limiting their ability to refine protocols to be close to the "as low as reasonable achievable" limit (*16*).

RADIATION DOSE VERSUS PROTOCOL DESIGN

Many publications support the role of RLs to help "optimize patient radiation dose *and* image quality" (*9*) and similarly "represent an important tool to optimize image quality and the radiation dose delivered to patients (*8*)." DRLs are defined as upper thresholds for dose and ADs are defined as middle targets for dose. Both of these imply that radiation doses should not be exceeded; this is primarily a radiation protection view. These levels do not explicitly provide insight into cases where the dose may be too low for quality images. Basically, they do not offer a lower threshold for dose (only an upper threshold). In short, RLs are limited in helping with ensuring sufficient radiation dose to achieve sufficient diagnostic quality.

With the image quality limitation acknowledged, the upper limit RLs can still be a useful tool. We assert that its value is increased if the levels are set close to the optimal operating point for a particular clinic. In this context, optimal is defined as providing sufficient diagnostic quality at the minimum necessary radiation dose. This is another reason to promote local RLs over national levels. That is, a clinic with rationally selected RLs that match their clinical resources can use these measures as tools for radiation protection (usually practice below local DRL) and general image quality assurance (practice close to local AD's as reasonable). The development of review tools and templates by national and international organizations to assist clinics in the deriving local RLs specific to their practice would be of significant value.

CONSIDERATIONS FOR NM REFERENCE LEVELS

To see an exhaustive list of recommended national RLs in the US for numerous modalities, readers are referred to NCRP 172 (*8*). RLs should be set based on an easily measured and standardized quantity. For NM, all of the RLs have been defined on administered activity. Administered activity provides a good measure for ensuring radiation protection. The radiation dose to the patient, while dependent on numerous factors (patient size, biokinetics, etc), is linearly related to administered activity.

For ensuring image quality in NM, administered activity does not tell the whole story. For x-ray based imaging modalities, RLs are based on accepted measures of dose indices from each modality. For example, in CT, RLs are based on $CTDI_{vol}$ (absorbed dose to standard phantom) (*13*). These absorbed dose indices are directly proportional to image quality, specifically to the photon density in the images. In other words, for x-ray modalities, the absorbed dose information is a strong predictor of image quality and therefore serves as a good metric for image quality assurance. In contrast, in NM, the photon density in the image is directly proportional to administered activity <u>but also to acquisition duration</u>. In some respects, administered activity tells less than half the story about the quality associated with a study. Furthermore, unlike CT scanners and diagnostic radiographs, which have sensitivity variations on the order of 0-40% between similar systems, there can be greater variations in sensitivity in NM due to different system geometries and collimators. For example, a dual-head camera will have a two-fold increase in sensitivity compared to a single-head camera. The wide range of NM equipment means that the same activity administered to all patients at all clinics will not equate to an equivalent image quality for all patients. This reality limits the role of administered activity RLs for ensuring appropriate image quality in NM practice.

We suggest using RLs based on administered activity for the purpose of radiation protection guidance. To overcome some of the image quality limitation, we also propose using a new quantity, administered Activity Duration Product (ADP) [MBq*min], to help ensure image quality is

achieved for an exam. The ADP in MBq*min can be easily calculated for an exam by multiplying the Administered Activity [MBq] by the study duration [min]. For SPECT imaging, considering most systems are dual head cameras, we will define this measure for duration of a dual head acquisition. If a single or triple head camera was used for acquisition, the local value should be normalized accordingly, i.e. ($ADP_{single\ head}$ = ADP*2; $ADP_{triple\ head}$ = ADP * 2/3).

ORIGIN OF NM REFERENCE LEVELS

Recommended doses for NM diagnostic exams were based on the initial trials with each tracer. Typically, these doses were set by the initial investigators to achieve sufficient diagnostic quality and eventually led to the recommended doses on package inserts. In general, there have been very limited or no adjustments to recommended doses over the years. The recommended doses are often over a wide range and the adherence to these levels is generally not known at clinics in the US.

The NM community does not have sufficient data to determine common dosing and acquisition strategies at clinics in the US. As stated in NCRP 172 page 73, "Determining RLs for commonly performed nuclear medicine studies is challenging due to limited available survey data..." (*8*). In the absence of sufficient survey data, the NCRP published suggested adult reference levels based on a small survey of 9 academic centers. It is unlikely that these few sites offer sufficient sampling to provide administered activities indicative of the broader practice of nuclear medicine in the US.

NEW SURVEY DATA FOR MDP AND FDG

In an effort to better understand normative practice in the US, we evaluated the administration schemes of clinics that submitted accreditation applications to Intersocietal Accreditation Commission (IAC) between February 2008 and December 2012. We evaluated dosing for ^{99m}Tc-methylene diphosphonate (MDP) bone scans and ^{18}F-fluorodeoxyglucose (FDG) whole-body PET scans. This study did not require IRB approval because it does not involve protected health information; The included data were fully de-identified according to standards set by the HIPAA Privacy Rule section 164.514(a)-(c). The average administered activity for each facility was calculated from patient case reports. Sites were categorized based on their type (hospital, private, mobile, etc.), region of the country, and their reported dosing strategy (fixed, range or weight-based dosing).

Tables 1 and 2 summarize the dosing strategies for MDP and FDG scans categorized by type of facility. **Figure 1 presents histograms of injected activity for all cases submitted to IAC in accreditation materials.** For MDP scans, 225 facilities were evaluated. For each facility, the average administered activity for that facility was calculated from the patient cases submitted for accreditation. Each facility submitted 1-4 cases with an average of 2.2 +/- 0.8 cases contributing to the facility average. The average MDP activity across facilities was 930 +/- 118 MBq (25.1 +/- 3.2 mCi), with a dosing range of 710-1315 MBq (19.2-35.5 mCi). In addition, 58% of facilities self-reported that they employed a range based dosing strategy, while the rest of facilities reported using fixed dosing. Comparing average administered activity across five different clinic types (hospital to free-standing clinics), there were no significant or clinically relevant differences in dosing strategies. The single mobile clinic is noted for using 40% more activity than other types of sites. Likewise, there were no significant differences between different regions of the country (no differences between Southeast, Southwest, Northeast, Northwest, or Midwest.

For FDG scans, 95 facilities were evaluated. Each facility submitted 1-5 FDG cases with an average of 4.3 +/- 1.3 cases submitted per facility. The average FDG activity across facilities was

508 +/- 117 [108-875] MBq (13.7 +/- 3.2 mCi). For dosing strategies, 64% of clinics self-reported using a range of doses, 29% reported using fixed dosing, and 7% use weight-based dosing. Like MDP, there was no relevant difference in average dosing across clinic types. Again, the 3 mobile centers are noted for using roughly 30% more activity than the other types of clinics. Likewise, there were no relevant differences between regions of the country.

From these data, we derived the DRLs and ADs from the 75th and 50th percentiles of the facility distributions of average dosing. Table 3 summarizes the SNMMI recommended dosing ranges, the NCRP RLs, and the IAC values discussed above for MDP and FDG. The ADs are similar between NCRP and our IAC survey. The DRLs suggested in the NCRP document are higher than the 75 percentile in the IAC survey. Our understanding is that the 9-site survey that contributed to the NCRP levels did not include a survey of actual patient dosings from which the 75 percentile dose levels could be extracted. Rather, this survey queried the minimum, maximum, mean and median dosing based on prescribed practice. With this data set, the NCRP suggested the DRL to be the 75% of the maximum levels (this is not representative of the 75% of all injected activities). This DRL level (75% of maximum values) will most certainly be higher than the ICRP defined DRL (75th percentile of all values) and helps explains the deviation of the DRL's from NCRP and from our IAC survey.

Table 3 also includes suggested Activity Duration Product (ADP) RLs. For the MDP SPECT exams, we use a total acquisition duration of 25 minutes times the IAC survey results to present AD and DRL levels for ADP. For FDG, we use an acquisition duration of 3 minutes per bed position for the ADP levels. It should be stressed that these represent suggested national levels that could be refined by clinics to provide local levels.

DISCUSSION

Reference levels are primarily intended to offer benchmark values as a rough guideline for appropriate practice. With this goal in mind, one could argue that RLs do not need to be exact, but rather be general suggestions for appropriate, normative practice. We would argue that the more general, and rough the RLs are, the less value they offer for determining appropriate practice. For example, if the ^{99m}Tc MDP DRL is 1185 MBq (32 mCi), as suggested by NCRP 172, this number is sufficiently high that a large majority of clinics will never need to consider improvements, leading to little value to the field. In contrast, if the ^{99m}Tc MDP DRL is 999 MBq (27 mCi), more clinics will have cause for reflection and potential improvements. Furthermore, if a clinic decides that local resources dictate a local MDP DRL of 1050 MBq (28 mCi), then the site has a tailored, rational value to ensure good practice for their patients.

For national RLs intended to reflect normal practice, there is currently limited data on nuclear medicine practice in the US. We present survey data from two common exams, whole-body FDG PET and MDP bone scans. This type of analysis needs to be expanded to more exams in order to better understand practice patterns around the US and provide US-wide national RLs.

Finally, RLs could also be employed for pediatric imaging. The NCRP document reported survey results from the 2007 survey of 13 pediatric hospitals of Treves *et al.* (*17*). Caution should be used in basing reference levels on this older survey data. The intention of that survey was not to suggest appropriate dosing, but rather to highlight the variability amongst pediatric NM clinics. That survey led to the NA Consensus Guidelines, which were recently updated (*18,19*). A follow-up to the 2007 survey performed after the adoption of the NA Consensus Guidelines has been recently published (*20*). Furthermore, given the wide-range of pediatric sizes and appropriate

dosing, a single reference level for pediatric NM is arguably of little value. Pediatric patient dosing (and procedures for ensuring safe dosing) should be tailored for the patient; The North American guidelines and European guidelines recommend weight-based dosing schemes (*19,21*).

IMPLEMENTATION OF NM REFERENCE LEVELS

In brief, we recommend that clinics adopt local NM reference levels for administered activity and ADP as a tool for radiation protection, protocol improvement and to ensure best practices. One suggested approach is initially to set local DRLs and ADs based on national standards (such as values presented in Table 3) and then to refine these local levels to meet the demands and evolution of the local clinical practice. Local levels should be reviewed and modified if necessary during structured protocol reviews to determine if improvements are necessary or possible. For example, if image quality is consistently higher or lower than deemed necessary, then doses and acquisition durations should be modified accordingly. Likewise, if clinical resources change (more/less time for each imaging session, improved equipment, different physician preference/experience), then reference levels should be modified.

CONCLUSION

The main points of this work are that National RLs can provide guidance and an educational tool for comparison with regional practice. Local RLs, based on unique resources and conditions of the particular clinic, should be employed if the intention is to inform local protocol selection. For NM, RLs based on administered activity offer a tool for radiation protection, but have a limited role in ensuring appropriate image quality. For NM, RLs based on both radiation dose and acquisition duration could be used to help ensure radiation protection and appropriate image quality.

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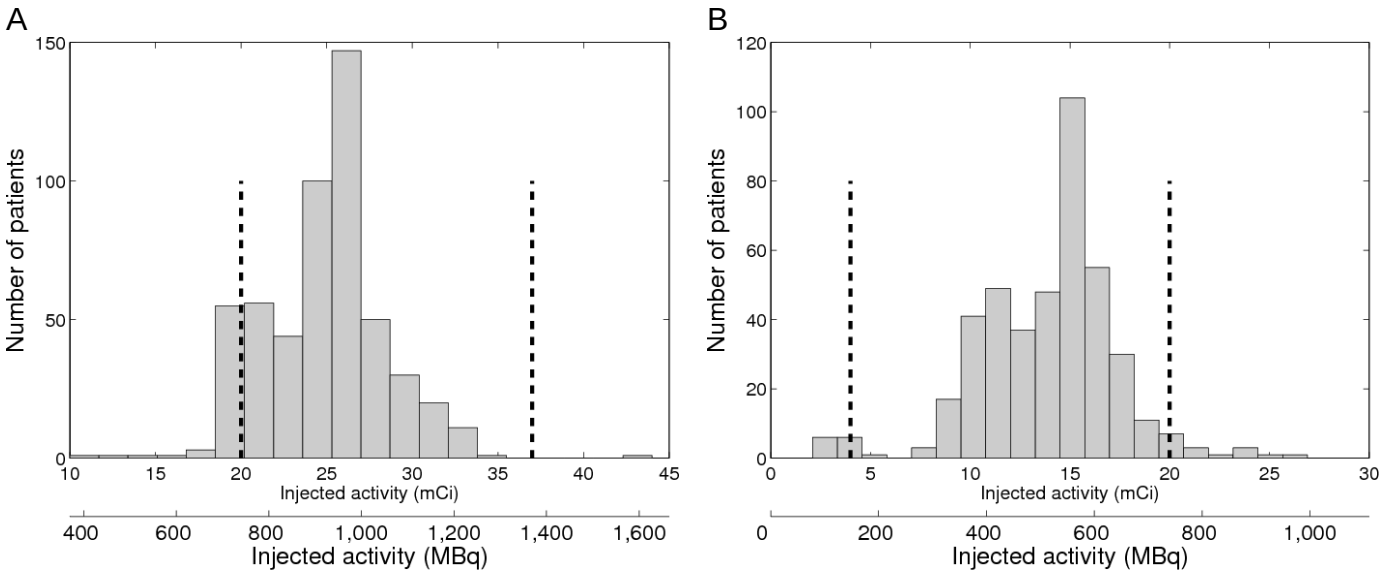

Figure 1. Histogram of injected activity for all MDP (A) and FDG (B) cases submitted to IAC in accreditation materials. MDP histogram from N=522 patient cases from 225 separate facility applications. FDG histogram from N=424 patient cases from 95 separate facility applications. The vertical dashed lines mark the lower and upper recommended range from SNMMI Guidelines.

Table 1. Summary of average dosing for Tc-99m MDP Bone Scans from IAC Survey data.

Site Type	# Sites	Average # Bone/Year	Dosing (% Range to Fixed)	MDP Dose
Hospital	111	759	61%	905 +- 112 [710-1236] MBq *24.5 +- 3.0 [19.2-33.4] mCi*
Private	50	220.2	53%	973 +- 125 [738-1215] MBq *26.3 +- 3.4 [20.0-32.9] mCi*
Free-standing	36	490.6	68%	918 +- 107 [740-1180] MBq *24.8 +- 2.9 [20.0-31.9] mCi*
Multispecialty	27	278.1	38%	953 +- 98 [740-1206] MBq *25.7 +- 2.6 [20.0-32.6] mCi*
Mobile	1	78.3	100%	1315 MBq *35.5 mCi*
Total	225	543.8	58%	930 +- 118 [710-1315] MBq *25.1 +- 3.2 [19.2-35.5] mCi*

Doses presented as mean +- standard deviation [minimum to maximum].

Table 2. Summary of average dosing for Whole-Body F-18 FDG PET from IAC Survey data.

Site Type	# Sites	Average # PET/Year	Dosing (Range:Fix:Weight)	FDG Dose
Hospital	41	1345.8	25:10:5	532 +- 102 [372-875] MBq *14.4 +- 2.8 [10.1-23.7] mCi*
Private	16	653	12:3:1	519 +- 73 [360-620] MBq *14.0 +- 2.0 [9.7-16.8] mCi*
Free-standing	27	1036	14:10:0	476 +- 114 [134-761] MBq *12.9 +- 3.1 [3.6-20.6] mCi*
Multispecialty	8	513.1	5:2:0	421 +- 204 [108-622] MBq *11.4 +- 5.5 [2.9-16.8] mCi*
Mobile	3	4661.2	2:1:0	632 +- 39 [608-677] MBq *17.1 +- 1.1 [16.4-18.3] mCi*
Total	95	1274	58:26:6	508 +- 117 [108-875] MBq *13.7 +- 3.2 [2.9-23.7] mCi*

Doses presented as mean +- standard deviation [minimum to maximum].

Table 3. Comparison of Recommended Adult Reference Levels for Tc-99m MDP Bone Scans and Whole-Body F-18 FDG

		Radiation Protection: Injected Activity [MBq] (mCi)				Image Quality: Activity Duration Product [MBq*min] [#]	
	SNMMI Guidelines Range	NCRP 172		IAC Survey			
Exam	Min to Max [MBq (mCi)]	AD	DRL	AD	DRL	AD	DRL
MDP Bone SPECT	740 – 1110 (20-37)	833 (23)	1185 (32)	925 (25)	999 (27)	23,100 (625 mCi*min)	25,000 (675 mCi*min)
FDG Whole Body	148 – 740 (4-20)	555 (15)	710 (19)	518 (14)	592 (16)	1554 (42 mCi*min)	1776 (48 mCi*min)

[#]The MDP Bone SPECT values assume the use a dual-headed system with a 25-minute study duration. The FDG Whole Body values assume an acquisition with 3 minutes per bed position.