Guidance for best practice from MetroMRT

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EMRP
European Metrology Research Programme
Programme of EURAMET

National Measurement Institutes

- MetroMRT is an NMI led European project looking to improve and provide tools for clinical implementation of dosimetry for Molecular Radiotherapy
- National standards for weights and measures are maintained by a National Measurement Institute (NMI) which provides the highest level of standards for the calibration and measurement traceability infrastructure in that country.
- MetroMRT set out to
  - provide tools for harmonisation of activity and dose measurements/estimates.
  - determine and improve accuracy and determine uncertainties in those measurements.
  - improve measurement techniques and nuclear data.

International Equivalence

NPL National Physical Laboratory

MRA (BIPM)

- Key comparisons (Ge/Ga-68 on-going)
- SIR system
  - Gamma emitters
  - Beta emitters
  - Short-lived radionuclides

Primary standards

- > 100 radionuclides
- Repeated and submitted to BIPM/CIPM every 10-20 years

Secondary standards

- Ionisation chamber
- Use of ICP-MS and gamma sp fo cl

Nuclear data

- Dedicated gamma and beta spectrometry and detector

The CIPM MRA has now been signed by the representatives of 92 institutes – from 52 Member States, 36 Associates of the CGPM, and 4 international organizations – and covers a further 147 institutes designated by the signatory bodies.

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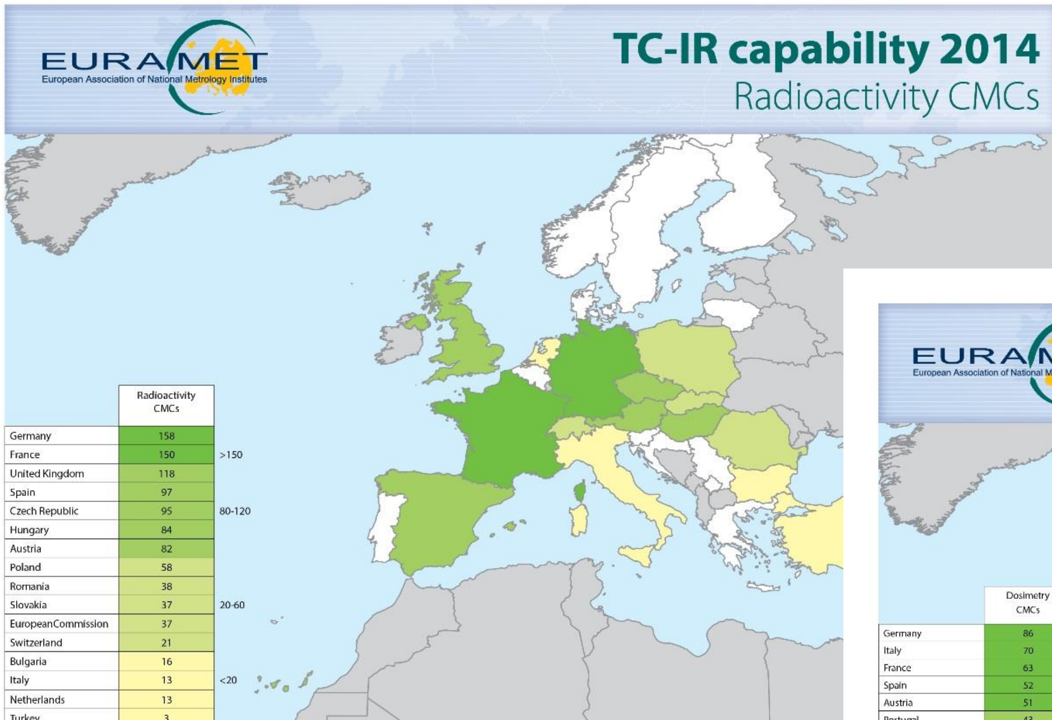

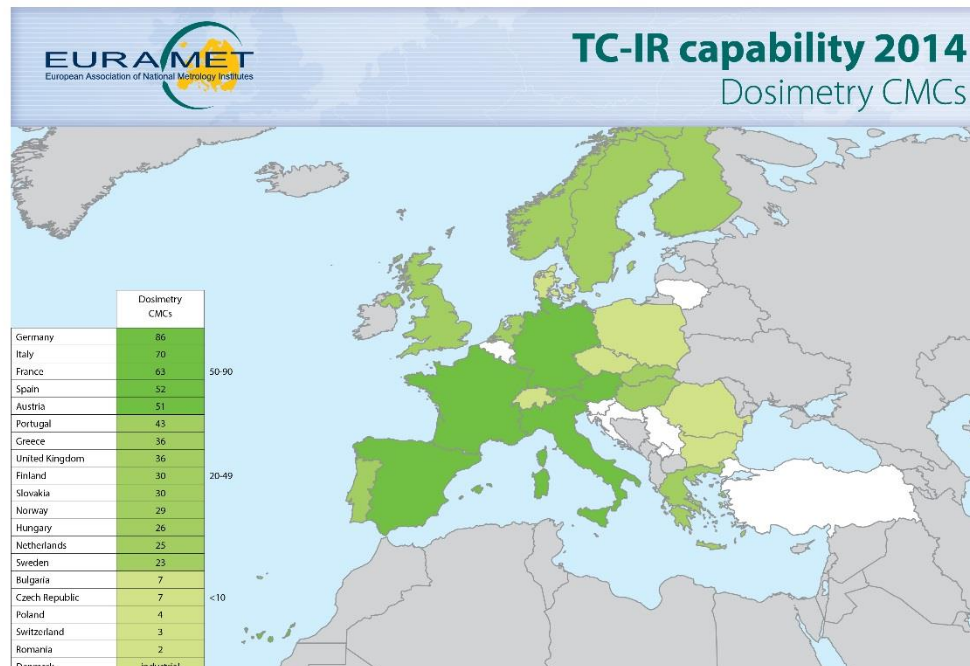

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Current guidance - example

A National Measurement Good Practice Guide No. 93

Protocol for Establishing and Maintaining the Calibration of Medical Radionuclide Calibrators and their Quality Control

+ e learning

MetroMRT Guidance deliverables

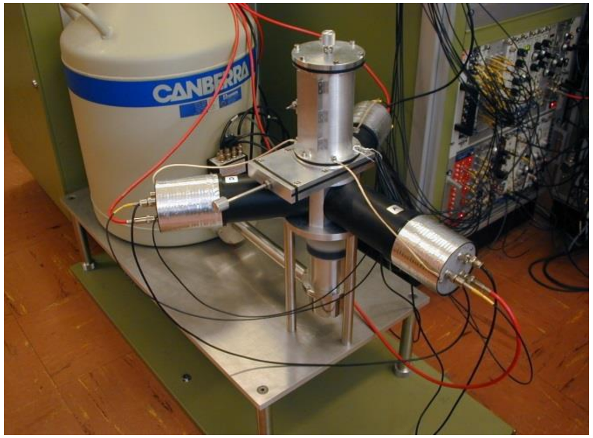
National Physical Laboratory

- Standard transfer protocol for ^{90}Y microspheres (**NPL**, CEA, ENEA)
- Recommended techniques for the use of quantitative imaging to measure radionuclide uptake and retention (**NPL**, CMI, VSL, AUSL, Christie, ICR, IFO, ISS, LUND, UCL, Velindre)
- Recommended techniques for obtaining absorbed dose to target and critical normal tissues (**ENEA**, CMI, NPL, VSL, AUSL, Christie, ICR, IFO, ISS, LUND, UCL, Velindre)
- Recommended methodology for deriving the uncertainty in an absorbed dose evaluation (**NPL**, AUSL, Christie, ICR, IFO, ISS, LUND, UCL, Velindre)
- Advice on measures to reduce the uncertainty in MRT dosimetry and the implications for clinical practice and research (**NPL,** CMI, ENEA, ICR, LUND, UCL)

MetroMRT - Activity measurements

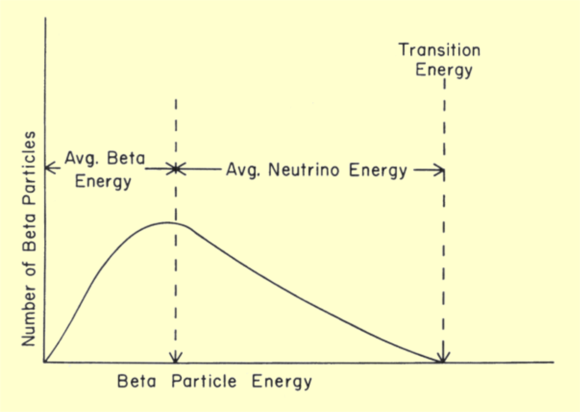
National Physical Laboratory

- Development of the TDCR-Cerenkov technique for direct standardisation of radiopharmaceuticals



- Development of standardisation and transfer methods for ^{90}Y microsphere samples

- Determination of beta spectra



(LNHB)

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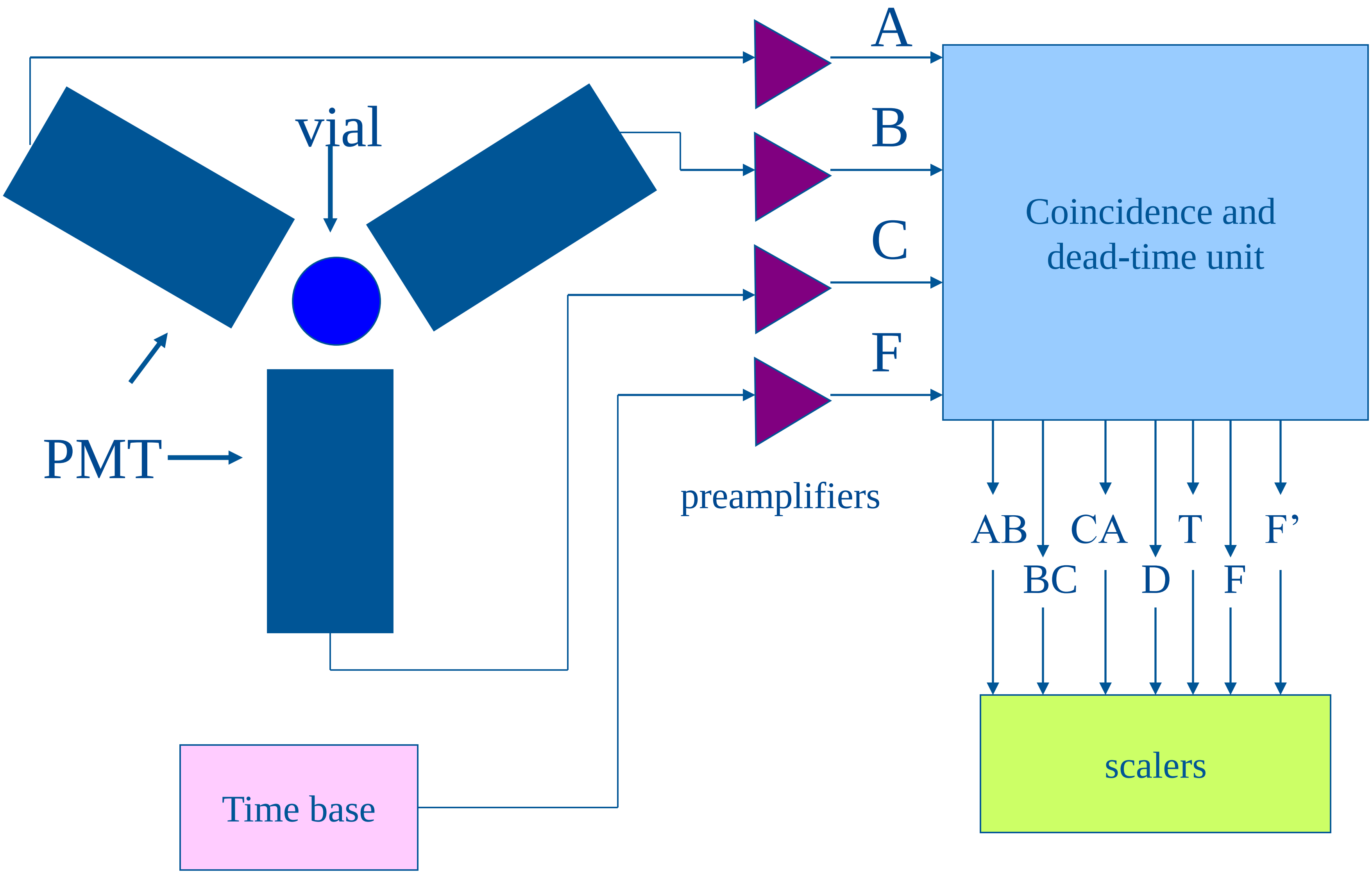
Triple to Double Coincidence Ratio



TDCR
Free parameter model

TDCR method (3 PMTs):

$$\varepsilon_{\mathrm{D}} = \int_0^{\mathrm{E_{max}}} S(\mathrm{E})\left(3\left(1-e^{-\frac{\mathrm{Q(E)E}}{2\mathrm{M}}}\right)^2 - 2\left(1-e^{-\frac{\mathrm{Q(E)E}}{3\mathrm{M}}}\right)^3\right)dE$$

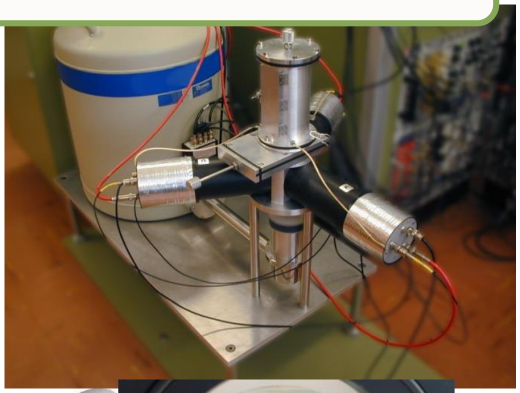
$$\varepsilon_{\mathrm{T}} = \int_0^{\mathrm{E_{max}}} S(\mathrm{E})\left(1-e^{-\frac{\mathrm{Q(E)E}}{3\mathrm{M}}}\right)^3 dE$$

The free parameter *M* is derived from the ratio of the experimental counting rate.

$$TDCR = \frac{R_T}{R_D} = \frac{\varepsilon_T}{\varepsilon_D}$$

For primary <u>activity determination</u> using liquid scintillation, the TDCR method needs a model of light emission to establish a <u>relationship between the detection efficiency and the *TDCR* ratio</u>

3-photomultipliers TDCR set-up



- ✓ **Analytical modelling (classical)**

  Coincidence calculations based on an analytical expression using the mean number of photoelectrons in PMTs

  (Poissonian distribution for <u>photoelectrons</u>)

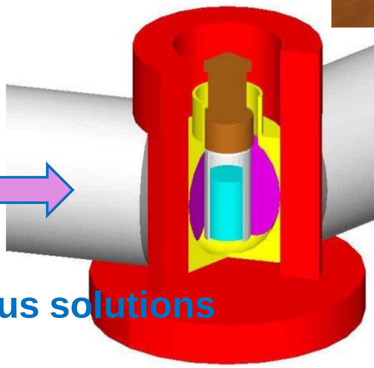
- ✓ **Monte Carlo modelling (using the Geant4 code)**

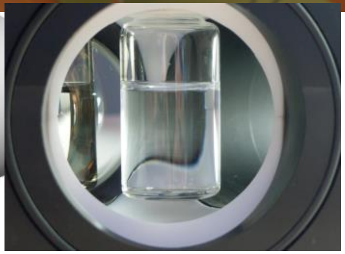
  Coincidence calculations based on the simulation of photon propagation from their creation to the production of photoelectrons in PMTs

  (using a Poissonian distribution for <u>optical photons</u>)

  Correlations between PMTs taken into account

TDCR-Geant4 model needs a comprehensive description of the geometry and optical properties of the detector

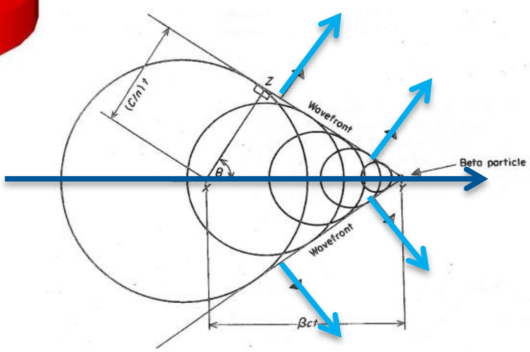




❑ **Cerenkov counting enables measurements in aqueous solutions**

the TDCR model has to be modified to take into account:

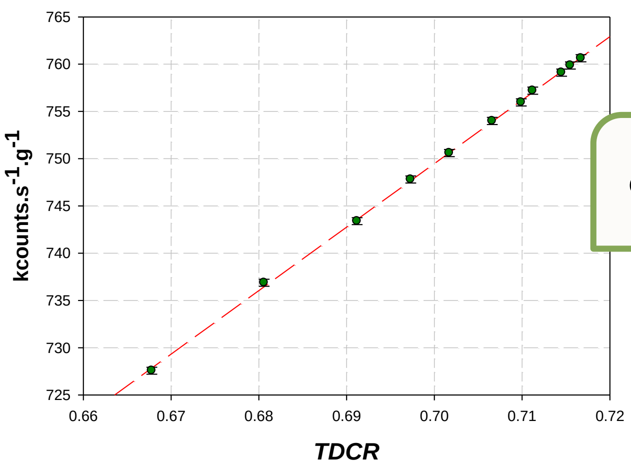
- **Anisotropy of Cerenkov light emission**
- **Threshold effect (260 keV in aqueous solution)**
- **Large spectral bandwidth of light (from UV to visible)**



- <u>**TDCR-Cerenkov technique in NMIs**</u>
  - ⇨ <u>**NPL:**</u> **Adaptation of the classical TDCR model (^{32}P, ^{90}Y, ^{56}Mn)**
  - ⇨ <u>**LNHB**</u>**: Monte Carlo modeling using the Geant4 code (^{32}P, ^{90}Y, ^{11}C)**

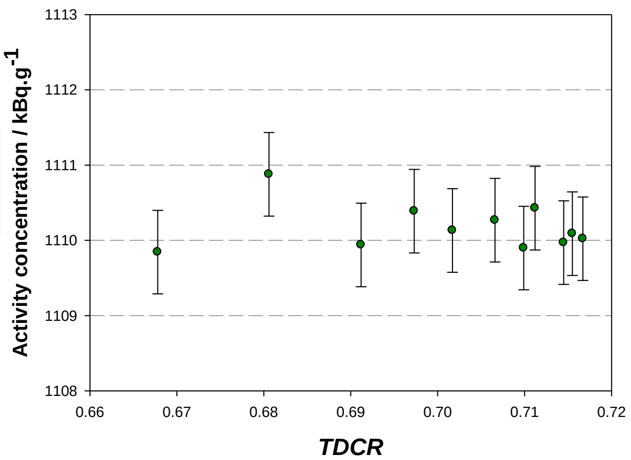
- TDCR-Cerenkov counting directly carried out in aqueous solution (no liquid scintillator)
- Variation of the detection efficiency implemented by defocusing the photomultipliers
- Activity calculated using the TDCR-Geant4 model first validated with aqueous solution of ^{90}Y in glass vials

Example of TDCR-Cerenkov measurements for one source



Double coincidence rate according to *TDCR*

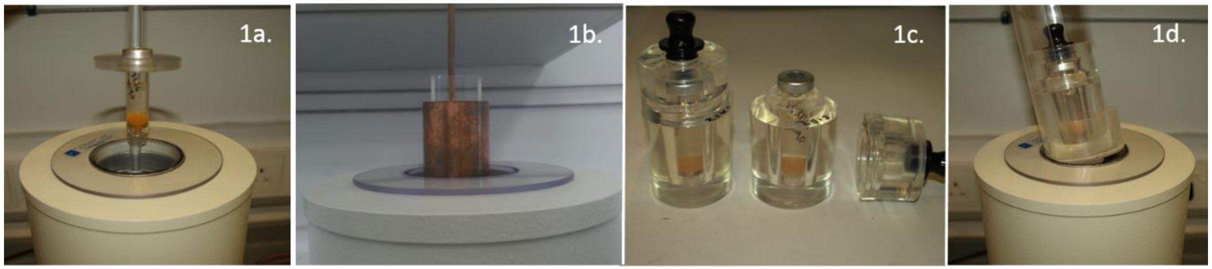
Detection efficiency calulated with the TDCR-Geant4 model

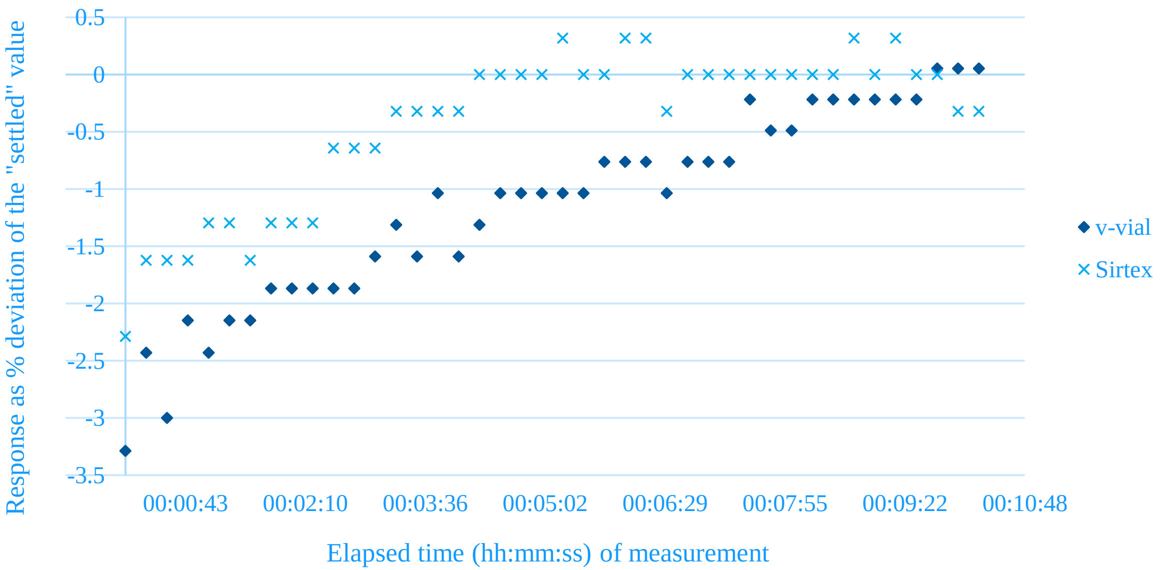


Activity concentration according to *TDCR*
No visible trend

^{90}Y SIR spheres transfer protocol

- Primary Standard can only be achieved when ^{90}Y is in solution – spheres have to be dissolved
- Secondary standards achieved by measurements of ^{90}Y spheres and the same matrix dissolved
- Influence of geometric parameters was determined due to strong attenuation of bremsstrahlung





MetroMRT – Quantitative Imaging

Current practice

The most basic imaging-based dosimetry would be based on whole body scans. The total counts in the whole body image can be extracted, and used to perform dosimetry calculations. Making this slightly more complicated, you can draw regions of interest around organs or lesions and use the count information within these regions to perform the dosimetry.

The next step up is to draw your regions of interest on the 3D SPECT/PET images to get the count information.

As far as performing the dosimetry calculations is concerned, the most basic method is to use the MIRD calculations, and consider only the dose to the organ of interest due to the activity in the organ of interest (assuming that the doses due to other organs is negligible in comparison). For some applications this is sufficient, but there is currently a large shift in thinking towards using Monte Carlo-based software to perform voxel based dosimetry instead.

Quantitative imaging - calibration

Investigation of methods calibrating a QI measurement with traceability to an activity standard

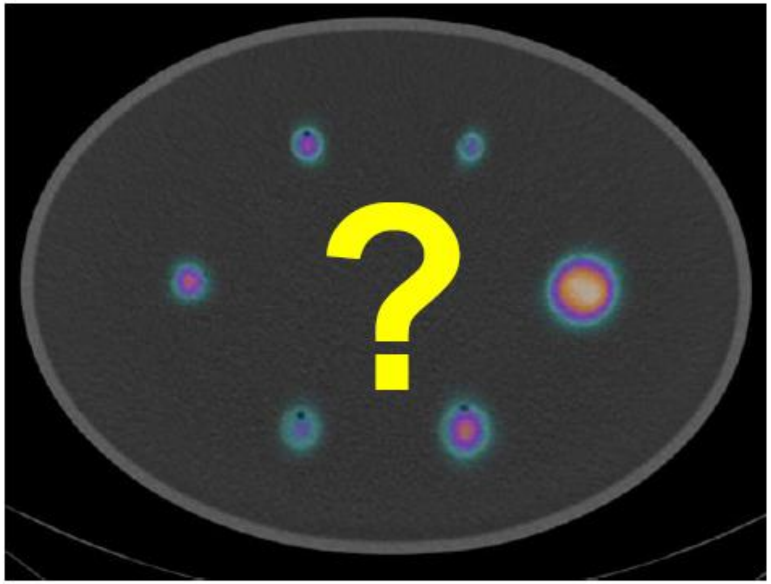
- Y-90, I-131, Lu-177
- Reference phantom: Elliptical Jaszczak phantom, 33mm dia. fillable sphere
- Reference conditions:
  - In air on axis
  - In water on axis
  - In water off axis
- Which gives the "calibration factor"?

Hospitals / cameras

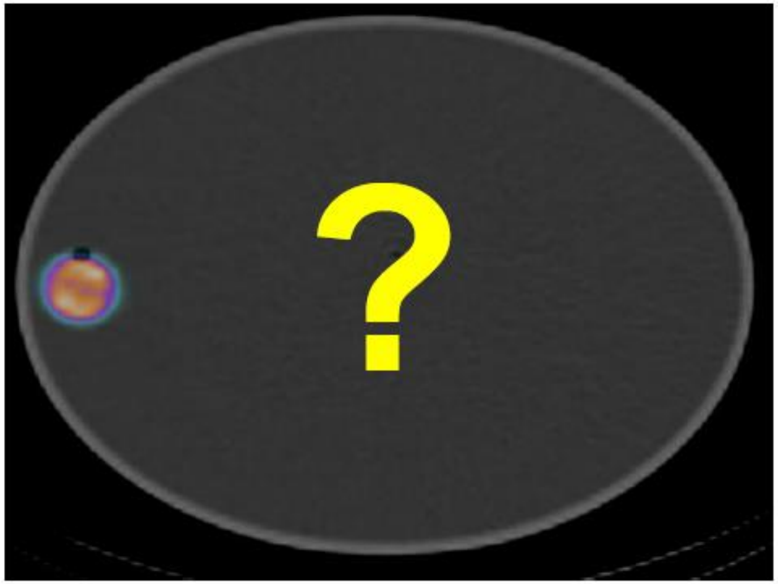
- **Lu-177**
  - Würzburg – Siemens Symbia (8ml sphere used)
  - Portsmouth – Siemens Symbia
  - (Frimley – Philips XCT)
- **I-131**
  - Manchester – GE Hawkeye
  - Southampton – GE Hawkeye
- **Lu-177 & I-131**
  - London – GE Discovery
  - Guildford – GE Hawkeye

National Physical Laboratory

What is "off-centre"??



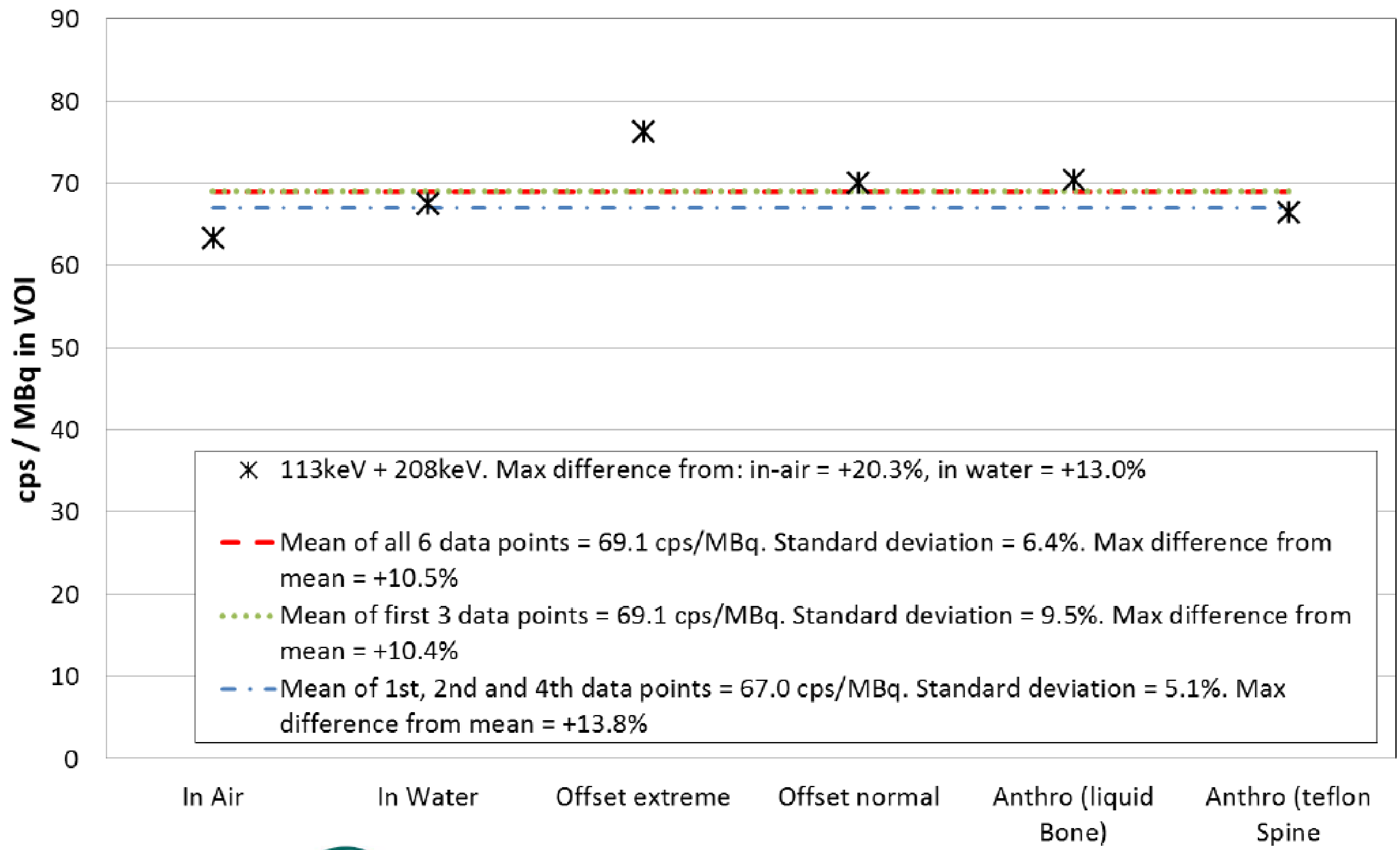
"Off-set" / "all spheres"



"Extreme off-set"

We tried both…….

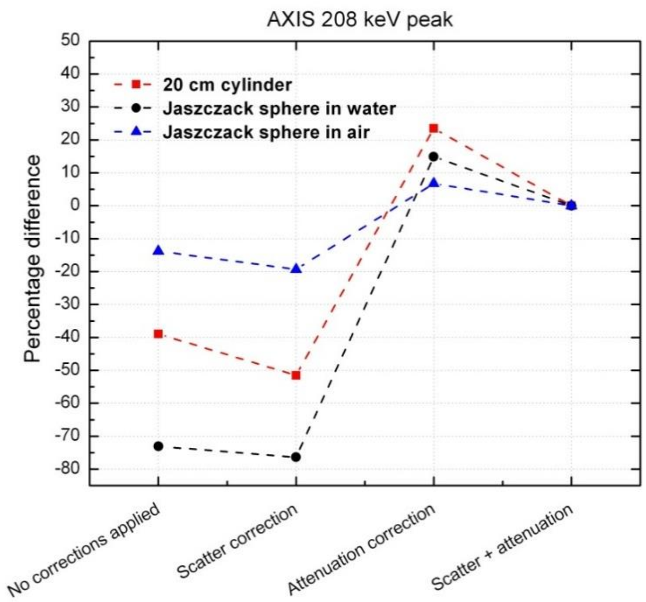
London, Lu-177, with Resolution Recovery: cps/MBq in VOI for 16ml sphere

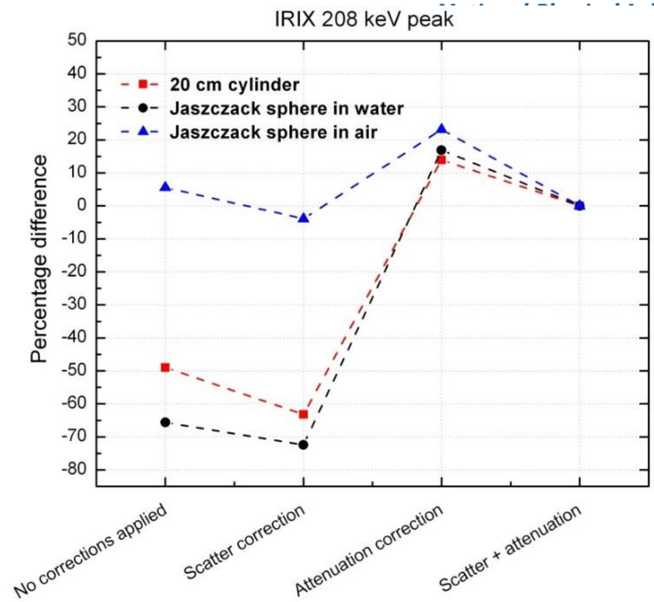


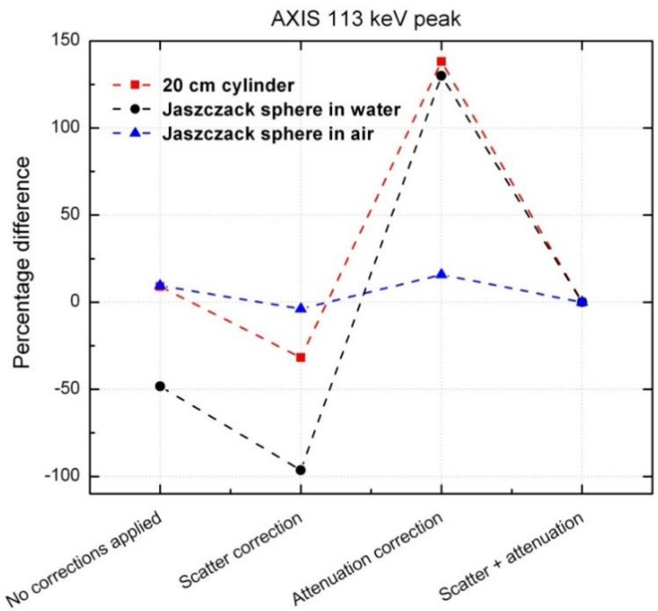
Full report at EANM conference 2014

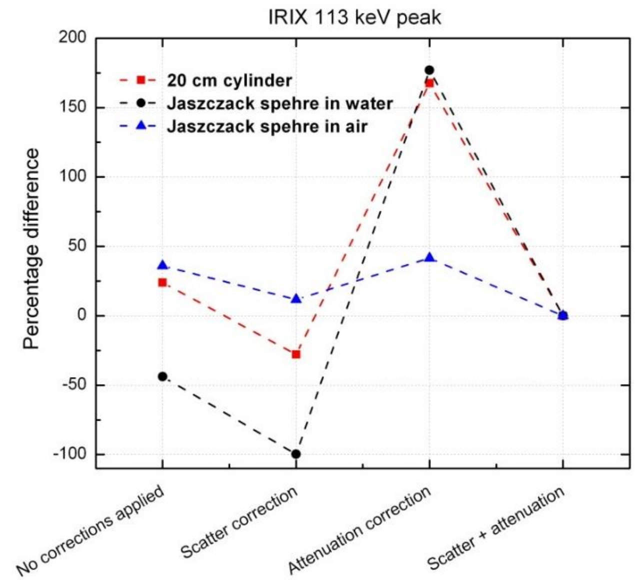
Jill Merrett et al. and Andrew Fenwick et al.

Impact of correction factors for different geometries (ENEA , IFO Hospital)









Preliminary results

- Gamma camera calibration is a prerequisite for absolute quantification studies via SPECT imaging, i.e. the system sensitivity must be preliminarily assessed to convert the reconstructed SPECT voxel values to absolute activity or activity concentration.

- Sensitivity values (cps/Bq) are geometry-dependent i.e. depend on the particular reference condition. In general, acquisitions performed with the **IRIX gamma camera provided good results at 208 keV, with agreement within 5% for all geometries**.

- **The use of a Jaszczak sphere in water provided sensitivity values capable of recovering the activity in anthropomorphic geometry within 1% for the 208 keV peak, for both gamma cameras.** The point source provided the poorest results (most likely because scatter and attenuation correction are not incorporated in the calibration factor?)

- As a general rule, acquisition at the lower photopeak provided results with larger deviation from the measured activity concentration. Acquisition on the Lu-177 main photopeak (208 keV) are therefore recommended in the clinical practice. **Scatter and attenuation play a major role at 113 keV and are likely to hinder an accurate absolute quantification**.

- For both gamma cameras all geometries provided sensitivity values capable of recovering the activity in anthropomorphic geometry within about 12% (range -11.9%/+7.1%) for acquisitions at the 208 keV photopeak.

Abolute quantification using a commercial software with advanced scatter and attenuation correction algorithms (ENEA , IFO Hospital)

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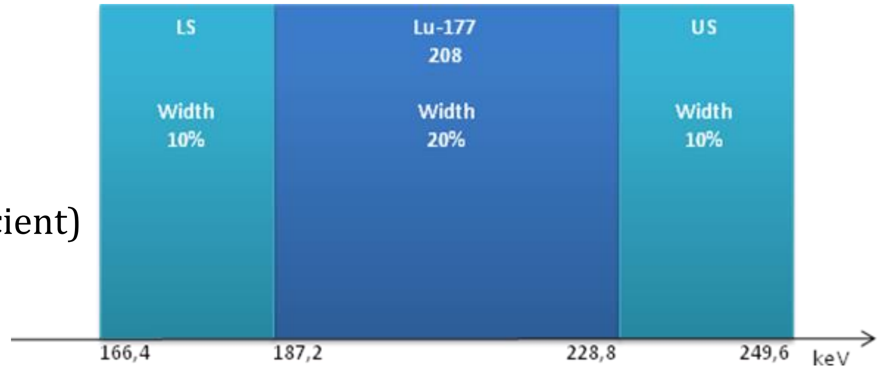
- Acquisition were performed in anthropomorphic geometry with Lu-177 supplied by Perkin-Elmer. A sample of the Lu-177 solution was shipped to ENEA for measurements of activity concentration both with ionization chambers and HpGe.
- Three different “tumour” to background activity concentration ratios were considered

	Activity conc. (1.1% uAc)		Tumor/background ratio
Insert concentration	7,14	MBq/mL	
Background concentration 1	0,50	MBq/mL	14,22
Background concentration 2	0,81	MBq/mL	8,81
Background concentration 3	1,19	MBq/mL	6,00

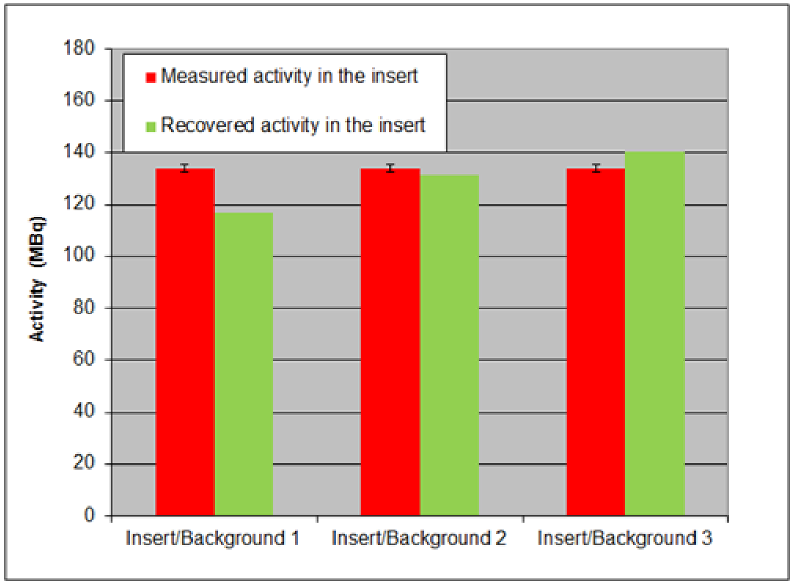
- Matrix size: 128 x 128
- Total projections: 90
- Projections per head: 45
- Seconds/projections: 10 sec
- OSEM reconstruction algorithm, 10 iterations, 10 substeps
- Partial volume correction applied (through recovery coefficient)
- Compensation for spill-in effect
- Correction for septal penetration

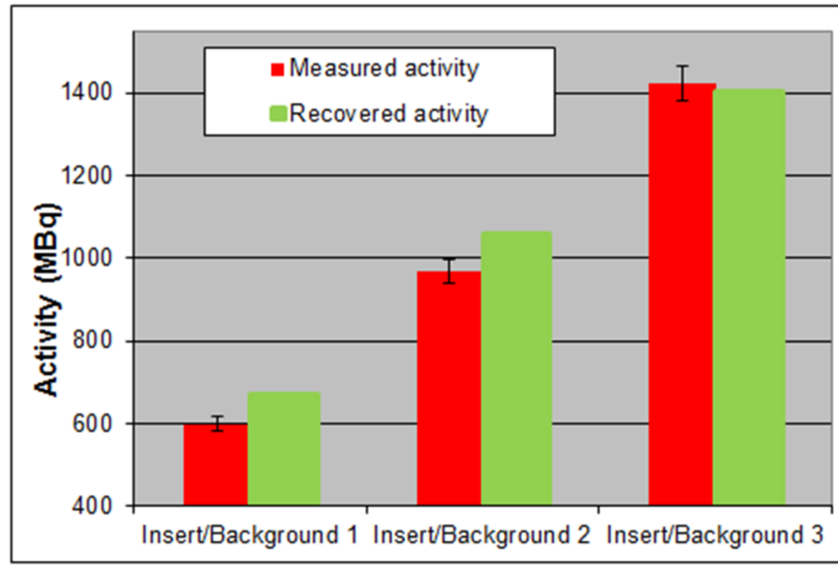


Measurements in anthropomorphic geometry : recovered activity into the insert

Deviation from measured activity (liver)	
Insert/Background 1	-12,8 %
Insert/Background 2	-1,9 %
Insert/Background 3	4,7 %

Deviation from measured activity (tumor)	
Insert/Background 1	11,8 %
Insert/Background 2	9,5 %
Insert/Background 3	-1,3 %





- Both the insert and the background activity concentrations were recovered with increasing accuracy for decreasing tumor to background ratio. The worst case scenario provided deviations approximately within 12% both for the background and for the tumor insert. **For a T/B ratio of about 6, the recovered activities were within 5%.**
- A Jaszczack sphere in water resulted a good reference condition capable of recovering activities in large and small target regions. Most likely because possible biases due to attenuation and scatter correction are included into the calibration factor.
- Advanced correction factor are likely to increase the accuracy in absolute activity quantification in SPECT. **QSPECT software proved good in recovering activity in anthropomorphic geometry.**

Protocol for Calibration of a SPECT/CT camera for use in Quantitative Imaging

ion)

hout the calibration procedure,
should allow a homogenous and
on of the measurements.
aining quantities of inactive
onent is not required however
ls being used. Some typical
tions prepared using peptides or

MetroMRT – QI Comparison Exercise

Participation so far:

The Christie (UK) *
Royal Surrey County Hospital (UK)
Royal Marsden Hospital (UK)
Bradford Teaching Hospital (UK)+
Lund University Hospital (Sweden)
Erasmus MC (the Netherlands)
Universitätsklinikum Würzburg (Germany)
FN MOTOL (Prague, Czech Rep)

Italian clinics are about to submit results as well.

MetroMRT calibration protocol also performed
+ Only calibration sphere images taken as shell damaged
* Additional measurements of calibration sphere in comparison source position taken

MetroMRT – guidance on Activity Measurements

National Physical Laboratory

Primary standard for Y-90 SIR spheres available

and

Calibration services for radionuclide calibrators and protocol for dissolution of SIR spheres available to clinics

Nuclear data to be published through NEA and DDEP

http://www.nucleide.org/DDEP_WG/DDEPdata.htm

MetroMRT – guidance on Quantitative Imaging

SPECT/CT camera Calibration Protocol available

and

Comparison exercise results underway

Report on influence of correction factors in quantitative imaging will be available

Next steps wish list

Further development of anthropomorphic phantoms for validation of QI.

Development of International Protocols for MRT (with IAEA and EANM?).

Build up phantom and image library for QI validation.

NMI contribution to clinical trials.

MetroMRT II (first round announced sometime in May 2015).

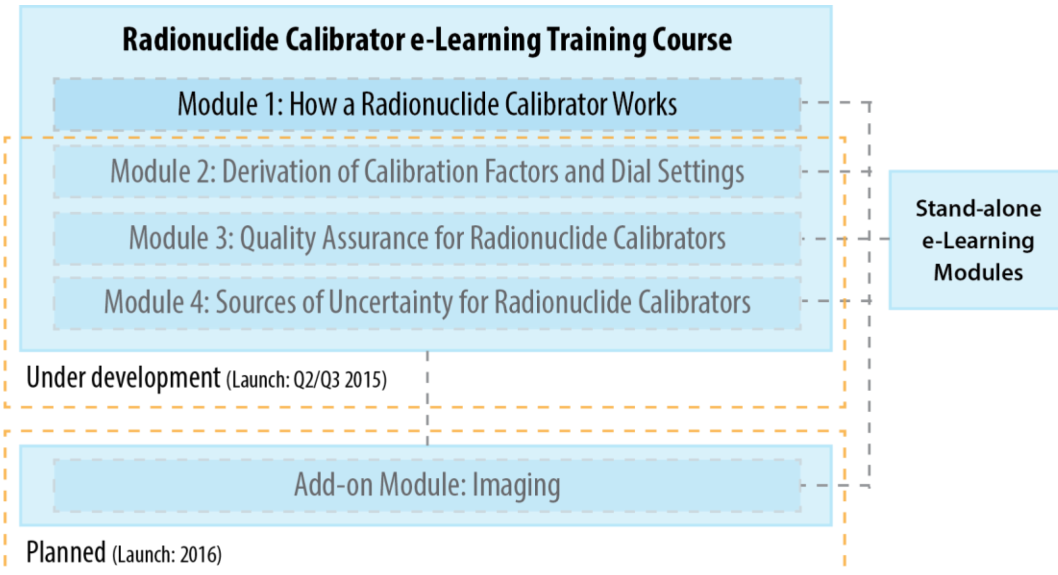
Radionuclide Calibrator e-Learning Course

NPL National Physical Laboratory

- Get the right skills to operate radionuclide calibrators
- Ensure their effective use, in a clinical setting
- Implement quality assurance tasks
- Identify sources of uncertainty, and improve your measurements

Radionuclide Calibrator e-Learning Course

NPL National Physical Laboratory



The first module is free!

***Register** now and give us your **feedback** at:*
www.npl.co.uk/e-learning

This course is aimed at:

- Medical physicists working in nuclear medicine.
- Nuclear medicine technologists & practitioners.
- Trainees on the NHS PTP or STP training programmes.
- Radiopharmacists & those working in radiopharmacies.

NPL National Physical Laboratory Training

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