INTRODUCTION

There remains considerable debate concerning the risks of malignancies from low levels of radiation exposure. The current paradigm for all medical, occupational or public exposures is to maintain radiation doses 'as low as reasonably achievable, economic and societal factors being taken into account' (ALARA), based on the 'Linear-no-Threshold' model for radiation protection. This assumes that even very low levels of radiation exposure can cause secondary malignancies. This model has significant implications for diagnostic medical procedures involving radiation due to the potential health risks to patients, the obligation to communicate that risk, the costs of providing radiation protection and the impact on optimising the balance between the levels of activity administered and the duration of scans. Although studies have investigated risks from low levels of exposure over previous decades, no studies have as yet investigated the risk within the context of nuclear medicine across multiple centres.

The Simplification of Low Level Internal Dosimetry (SOLLID) study is a single centre, prospective, non-interventional pilot study. The overall aim is to evaluate the potential to investigate this issue within nuclear medicine. Over 600,000 diagnostic and therapeutic nuclear medicine oncological and non-oncological procedures are performed each year in England. Procedures are performed following administrations of standard levels of radiotracers that may...
be modified by patient weight. Average radiation absorbed doses delivered in these procedures are available from International Commission on Radiological Protection (ICRP) publications. \(^6\)\(^7\) These are calculated using kinetic models derived from limited data, often obtained from a very small cohort of patients or from animal studies. While these values are sufficient to satisfy regulations, there is abundant evidence from dosimetry studies with therapeutic radiopharmaceuticals that the interpatient variation in the absorbed doses delivered to healthy organs from a fixed level administration of a radionuclide can vary by up to 2 orders of magnitude. \(^8\) It is a reasonable assumption that a similar range of radiation dose levels will exist for diagnostic studies although it is accepted that data are scarce. \(^7\)\(^9\) The effective dose delivered from an administration of \(^{18}\)F-FDG has been shown to range from 0.0132 to 0.0291 mSv/MBq. \(^10\) The effective dose delivered from \(^{99m}\)Tc- MDP scans has not been calculated.

**TRIAL DESIGN**

The aim of the SOLLID study is to develop the methodology to enable a large-scale epidemiological investigation of the effect of radiopharmaceutical administrations to patients undergoing diagnostic nuclear medicine. Radiation dosimetry will be performed from a series of scans following administration in addition to the standard of care scan that is routinely acquired. This will enable the effective half-life of decay to be measured. The primary end point of the study is to determine the uncertainty on the absorbed doses calculated to normal organs and the whole-body (WB) as a function of the number of scans and WB counts acquired.

The secondary end points are to determine the range of doses delivered to normal organs. Seven diagnostic procedures will be studied: \(^{99m}\)Tc-MDP bone imaging, \(^{99m}\)Tc-DMSA kidney function, MAG3 renograms, \(^{99m}\)Tc-Pertechnetate thyroid imaging and PET imaging using \(^{18}\)F-FDG, \(^{68}\)Ga-PSMA and \(^{68}\)Ga DOTATATE (Table 1). Five patients will be recruited for each procedure, totalling 35 patients. A further exploratory end point is to determine the range of risk estimates for the development of secondary cancers associated with these procedures, based on the absorbed doses delivered.

Imaging regimens for SOLLID were developed to obtain the optimum information on tracer kinetics. For PET investigations, patients are imaged up to five times following intravenous injection of the PET tracer. A single bed position dynamic PET/CT image of the myocardium is acquired for 4 min, followed by a 40 min half-body dynamic whole body scan. WB measurements using a ceiling-mounted scintillation detector are acquired to determine radioactive excretion from the first and subsequent bladder voids. The clinical PET/CT scan is acquired at 1 h following further imaging at 2 and 4 h post-administration.

The most demanding imaging regimen is the Tc99m-MDP bone scan, for which patients are imaged up to seven times following intravenous injection of the tracer. A single field-of-view (FOV) dynamic image of the pelvis and kidneys is acquired for 30 min, followed by WB counting pre- and post-bladder voiding. WB imaging is performed at 1, 2, 3, 4, 5 and 24 h and a WB single photon emission tomography (SPECT)/CT performed at 3.5 h. Between each WB acquisition, further WB counting is performed to determine tracer excretion.

**DOSIOMETRY DATA**

Organ segmentation is performed using the CT images. Quantification of SPECT and PET data is performed using recovery coefficients derived from phantom experiments, whereby known concentrations of activity for each of the radionuclides under investigation are imaged in a series of spheres of increasing diameters. This approach has been used successfully for a multicentre trial to evaluate the absorbed doses delivered to patients undergoing radioiodine treatments for thyroid cancer. \(^12\) Radioisotope concentration in the relevant organs is plotted as a function of time and exponential functions are fitted to the data to model the biokinetics using non-linear regression and F-Test statistics. Time integrated activity for each organ is determined by

| Procedure          | Tc-99m MDP | Tc-99m DMSA | MAG3 (renogram) | Tc-99m Pertechnetate | F-18 FDG | Ga-68 DOTATATE | Ga-68 PSMA |
|--------------------|------------|------------|----------------|---------------------|---------|----------------|-----------|
| Use                | Bone imaging | Kidney Imaging | Kidney Imaging | Thyroid imaging | Disease metabolism | Neuroendocrine tumour imaging | Metastatic Prostate Cancer imaging |
| Dynamic imaging   | 30 min over pelvis | 30 min over kidneys and bladder | | 4 min over heart | 4 min over heart | 4 min over heart | |
| Static \(\gamma\) camera imaging | 5 WB sweeps up to 24 hours p.i. | Five images of abdomen up to 24 hours p.i. | Five images of abdomen up to 24 hours p.i. | 5 WB sweeps up to 24 hours p.i. | |
| Tomographic imaging | SPECT/CT at 3 h p.i. | SPECT/CT at 2 h p.i. | SPECT/CT at 2 h p.i. | SPECT/CT at 3 h p.i. | 6 x PET/CT up to 4 hours p.i. | 6 x PET/CT up to 4 hours p.i. | 6 x PET/CT up to 4 hours p.i. |

**Table 1. Scanning procedures for the SOLLID study**
integrating the fitted functions. Patient-specific organ absorbed doses are then generated using the MIRD schema and reference S-values from OLINDA/EXM and IDAC dosimetry software.\(^\text{13,14}\) Patient-specific organ S values will also be determined using mass-adjusted values.\(^\text{15}\) Uncertainty analysis, subject to increasing research,\(^\text{16}\) will be based on European Association of Nuclear Medicine (EANM) guidelines.\(^\text{17}\) The variation in absorbed doses calculated using different subsets of scan acquisitions will be investigated to identify the minimum number of scans required to achieve statistically significant results.

**STUDY POPULATION**

Trial subjects will be over 18 years and male or female. Pregnant females will be excluded. Each subject will have been referred for the relevant nuclear medicine scans and must have satisfied the inclusion criteria for those scans. They must also be willing and able to undergo the extra procedures necessary to acquire sufficient data for the dosimetry calculations. This may entail up to 7 nuclear medicine scans and 10 activity retention measurements in the 24 h following administration of the radiopharmaceutical.

**PUBLIC PATIENT INVOLVEMENT (PPI)**

To obtain the most accurate dosimetry in a small patient cohort, a relatively demanding scanning schedule is asked of patients. In addition, the effects of radiation are often poorly understood and risks from exposure may be greatly under- or overestimated.\(^\text{18}\) PPI is therefore a key element in all aspects of the study and imaging protocols were developed with the involvement of patient representatives. A patient forum was organised to discuss the methodology of the study, to consider how best to communicate the rationale and hypotheses underlying the study, and to ascertain the impact of the scanning schedules required. The trial was costed in line with INVOLVE guidelines.\(^\text{19}\) Prior to the study commencing a patient volunteer was asked to undergo the full procedure without an administration in a ‘dummy run’, to identify any details to be addressed. Patients enrolled on the study are asked to complete a questionnaire to record their comments and suggestions. These data will inform future study design.

**OUTCOMES AND FUTURE AIMS**

For each of the seven imaging procedures, the following will be calculated: (i) effective dose to whole body (mSv), with associated uncertainties, (ii) the absorbed dose delivered to individual organs (mGy), with associated uncertainties, (iii) the increased uncertainty as a function of the extent of data acquisition. The trial will identify the minimum number of scans and measurements required to enable accurate dosimetry to be performed and will highlight particular studies that will be more or less suitable for continued investigation. Taken in conjunction with patient feedback a protocol for a large-scale multicentre epidemiological study will be developed, focussed on nuclear medicine diagnostic imaging.

**DISCUSSION**

The European Basic Safety Standards directive, incorporated into national regulations including the UK Ionising Radiation (Medical Exposure) Regulations (IR(ME)ER), mandate communication of risk to patients from diagnostic exposures.\(^\text{20,21}\) Current risk estimates from medical examinations involving ionising radiation have been extrapolated from data obtained from the nuclear bombs dropped in WW2 and from nuclear incidents, which entailed high levels of exposure.\(^\text{22}\) There are increasing arguments that the LNT model may overestimate the effect of low levels of radiation.\(^\text{23}\)

The CT component of the procedures will enable attenuation corrected organ dosimetry with anatomical outlining. These will deliver radiation doses that may be of the order of those delivered from the SPECT and PET scans and must be taken into account for the calculation of effective doses.

It is intended that this study will inform a subsequent multicentre epidemiological investigation into the effects of low levels of radiation exposure by evaluation of the absorbed doses delivered and by monitoring primary and secondary outcomes. In recent years, two networks have been developed to perform multicentre studies of quantitative imaging of I-131 for the treatment of thyroid cancer. The ‘Selimetry’ study has investigated the use of the MEK inhibitor selumetinib to enable possible re-treatment of iodine refractory patients in eight UK centres.\(^\text{12,24–26}\) and the EU funded ‘Medirad’ study is currently underway in four centres in Germany, France and the UK.\(^\text{27}\) Both studies have entailed characterisation of γ cameras for sensitivity, recovery coefficients and dead-time using phantom studies and site visits. Data transfer, archiving, and centralised image processing have been set up to ensure that dosimetry data may be acquired and collated from different centres. An improved understanding of the effect of low levels of radiation exposure will lead to more cost-effective practice in radiation protection. This would enable optimised activities to be used for nuclear medicine procedures that may in turn improve diagnostic accuracy.

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REFERENCES

1. Ross JC, Vilíc D, Fongenie B. Reforming the debate around radiation risk. J Radiol Prot 2019; 39: 635–40. doi: https://doi.org/10.1088/1361-6598/ab1698

2. Weber W, Zanzonico P. The controversial linear No-Threshold model. J Nucl Med 2017; 58: 7–8. doi: https://doi.org/10.2967/jnumed.116.182667

3. ICRP publication 105. radiation protection in medicine. Ann ICRP 2007; 37: 1–63. doi: https://doi.org/10.1016/j.icrp.2008.08.001

4. Shore RE, Beck HL, Boice JD, Caffrey EA, Davis S, Groghan HA, et al. Recent epidemiologic studies and the linear No-Threshold model for radiation Protection-Considerations regarding NCRP release-2013-14. pdf. [Available from: http://www.england.nhs.uk/statistics/Radiodiagnostic activity. 2014. Available from: https://doi.org/10.1007/s00259-018-4136-7]

5. NHSNHS England Imaging and Radiodiagnostic activity. 2014. Available from: https://www.nhsengland.nhs.uk/statistics/wp-content/uploads/sites/2/2013/04/KH12-release-2013-14.pdf.

6. ICRP Radiation dose to patients from radiopharmaceuticals. ICRP publication 53 Ann ICRP1988: 18(1–4).

7. ICRP Radiation dose to patients from radiopharmaceuticals Addendum 3 to ICRP publication 53. ICRP publication 106... Ann ICRP 2008; 38(1-2): 1–197 Approved by the Commission in October 2007.

8. Strigari L, Konijnemberg M, Chiesa C, Bardies M, Du Y, Gleisner KS, et al. The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy. Eur J Nucl Med Mol Imaging 2014; 41: 1976–88. doi: https://doi.org/10.1007/s00259-014-2824-5

9. Eberlein U, Bröer JH, Vanvoorde C, Santos P, Bardies M, Bacher K, et al. Biokinetics and dosimetry of commonly used radiopharmaceuticals in diagnostic nuclear medicine - a review. Eur J Nucl Med Mol Imaging 2011; 38: 2269–81. doi: https://doi.org/10.1007/s00259-011-1904-2

10. Quinn B, Dauer Z, Pandit-Taskar N, Schoder H, Dauer LT. Radiation dosimetry of 18F-FDG PET/CT: incorporating exam-specific parameters in dose estimates. BMC Med Imaging 2016; 16: 41. doi: https://doi.org/10.1186/s12880-016-0143-y

11. Pfob CH, Ziegler S, Graner FP, Köhner M, Schachoff S, Blehert B, et al. Biodistribution and radiation dosimetry of (68)Ga-PSMA HBED CC- a PSMA specific probe for PET imaging of prostate cancer. Eur J Nucl Med Mol Imaging 2016; 43: 1962–70. doi: https://doi.org/10.1007/s00259-016-3424-3

12. Gregory RA, Murray I, Gear J, Leek F, Chittenden S, Fenwick A, et al. Standardised quantitative radioiodine SPECT/CT imaging for multicentre dosimetry trials in molecular radiotherapy. Phys Med Biol 2019; 64: 245013. doi: https://doi.org/10.1088/1361-6560/ab5b6c

13. Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. J Nucl Med 2005; 46: 1023–7.

14. Andersson M, Johansson L, Eckerman K, Mattsson S. IDAC-Dose 2.1, an internal dosimetry program for diagnostic nuclear medicine based on the ICRP adult reference voxel phantoms. EUNMIM Res 2017; 7: 88. doi: https://doi.org/10.1186/s13550-017-0339-3

15. Divoli A, Chiavassa S, Ferrer L, Barbet J, Flux et al. EANM: briefing notes for researchers: public involvement in NHS, engagement of patients and the public: commitment towards involvement and practical guidance on uncertainty analysis for multicentre dosimetry trials in molecular imaging. Eur J Nucl Med Mol Imaging 2016; 43: 1976–88. doi: https://doi.org/10.1007/s00259-018-4136-7

16. Spielmann V, Li WB, Zankl M, Oeh U, Hoeschen C. Uncertainty quantification in internal dose calculations for seven selected radiopharmaceuticals. J Nucl Med 2016; 57: 122–8. doi: https://doi.org/10.2967/jnumed.115.160713

17. Gear JI, Cox MG, Gustafsson J, Gleisner KS, Murray I, Glatting G, et al. EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations. Eur J Nucl Med Mol Imaging 2018; 45: 2456–74. doi: https://doi.org/10.1007/s00259-018-4136-7

18. Ribeiro AS, Lee M, Oyen WJJ. EANM commitment towards involvement and engagement of patients and the public: learning from the UK experience. Eur J Nucl Med Mol Imaging 2019; 46: 2218–9. doi: https://doi.org/10.1007/s00259-019-04457-7

19. INVOLVEINVOLVE: briefing notes for researchers: public involvement in NHS, public health and social care research. Available from: http://www.involve.org.uk/wp-content/uploads/2014/11/INVOLVE_Briefing_Notes_WEB.pdf.

20. The Ionising Radiation (Medical Exposure) Regulations. 2017Regulation 12 (7) b [Available from: Available from: http://www.legislation.gov.uk/uksi/2017/1322/contents/made.

21. European Council directive 2013/59/ Euratom on basic safety standards for protection against the dangers arising from exposure to ionising radiation. Of the EU 2014;.: 1–73Chapter 2, Article 4 (13)L13; 57.

22. Little MP, Wakeford T, Tawn EJ, Bouffler SD, Berrington de Gonzalez A. Risks associated with low doses and low dose rates of ionizing radiation: why linearity may be (almost) the best we can do. Radiology 2009; 251: 6–12. doi: https://doi.org/10.1148/radiol.2511081868

23. Siegel JA, Pennington CW, Sacks B. Subjecting radiologic imaging to the linear No-Threshold hypothesis: a non Sequitur of Non-Trivial proportion. J Nucl Med 2017; 58: 1–6. doi: https://doi.org/10.2967/jnumed.116.180182

24. Wadsley J, Gregory R, Flux G, Newbold K, Du Y, Moss L, et al. SELIMETRY-a multicentre I-131 dosimetry trial: a clinical perspective. Br J Radiol 2017; 90: 20160637. doi: https://doi.org/10.1259/bjr.20160637

25. Taprogge J, Leek F, Flux GD. Physics aspects of setting up a multicenter clinical trial involving internal dosimetry of radioiodine treatment of differentiated thyroid cancer. Q J Nucl Med Mol Imaging 2019; 63: 271–7. doi: https://doi.org/10.23736/S1824-4785.19.03202-3

26. Brown SR, Hall A, Buckley HL, Flanagan L, Gonzalez de Castro D, Farnell K, et al. Investigating the potential clinical benefit of selumetinib in resensitising advanced iodine refractory differentiated thyroid cancer to radioiodine therapy (SEL-1-METRY): protocol for a multicentre UK single arm phase II trial. BMC Cancer 2019; 19: 582. doi: https://doi.org/10.1186/s12885-019-5541-4

27. Grande S, Palma A, Cisbani E, De Angelis C, Della Monaca S, Dini V, et al. MEDIRAD project “implications of medical low-dose radiation exposure”: Enhancing the protection of patients and health professionals from exposure to low-dose medical radiation. Nuovo Cim C- Colloq C 2018; 41.