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GUIDELINES & RECOMMENDATIONS

The internal dosimetry user group position statement on molecular radiotherapy

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ABSTRACT

The Internal Dosimetry User Group (IDUG) is an independent, non-profit group of medical professionals dedicated to the promotion of dosimetry in molecular radiotherapy (www.IDUG.org.uk). The Ionising Radiation (Medical Exposure) Regulations 2017, IR(ME)R, stipulate a requirement for optimisation and verification of molecular radiotherapy treatments, ensuring doses to non-target organs are as low as reasonably practicable. For many molecular radiotherapy treatments currently undertaken within the UK, this requirement is not being fully met. The growth of this field is such that we risk digressing further from IR(ME)R compliance potentially delivering suboptimal therapies that are not in the best interest of our patients. For this purpose, IDUG proposes ten points of action to aid in the successful implementation of this legislation. We urge stakeholders to support these proposals and ensure national provision is sufficient to meet the criteria necessary for compliance, and for the future advancement of molecular radiotherapy within the UK.

INTRODUCTION

The Internal Dosimetry User Group (IDUG) was conceived following the British Nuclear Medicine Society (BNMS) Spring congress of May 2011 and officially founded during its first independent meeting in September 2011. It is an independent, non-profit group of medical professionals comprising medical physicists, clinical and healthcare scientists, technologists and physicians, and is open to anyone working in the National Health Service or related industries. Currently, IDUG comprises more than 100 specialists from over 50 different healthcare centres across the UK.

The vision of IDUG is to optimise and advance molecular radiotherapy (MRT) for the benefit of patients using personalised treatments and dosimetry. . IDUG was initiated to act as a forum for discussion of the latest developments in internal dosimetry and for individual members to promote and provide advice for the rapidly evolving discipline of molecular radiotherapy, aligning to the requirements of personalised, safe and effective treatment. To date IDUG and its members have:

- Advocated for the need for personalised dosimetry;[1]
- Hosted regular scientific meetings on MRT dosimetry alongside The British Institute of Radiology (BIR);
- Provided training in MRT and dosimetry techniques in collaboration with The British Nuclear Medicine Society (BNMS);
- Established practical guidelines for MRT dosimetry[2];
- Established methods for standardisation in dosimetry practice for MRT across centres in the UK[3];
- Reviewed the development and evaluated current dosimetry practice across the UK;[4]
- Carried out and regularly published the only serial survey of MRT activity;[4–6]
- Raised the need for funding to be available for clinical trials incorporating dosimetry.[7]

EXISTING GUIDANCE AND LEGISLATION FOR MOLECULAR RADIOTHERAPY

In December 2013, the European Union (EU) [8]Council Directive 2013/59/Euratom[8] laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation. The directive integrated several previous directives on occupational, public and medical exposures and radiation protection. The system of radiation protection is based on the principles of justification, optimisation and dose limitation.

Aspects of the directive relating to medical radiation exposures were transposed into UK national legislation in the Ionising Radiation (Medical Exposure) regulations 2017, IR(ME)R.[9] Pertinent to MRT, section 12 of the regulations state that:

"*In relation to all radiotherapeutic exposures the practitioner must ensure that exposures of target volumes are individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues must be as low as reasonably practicable and consistent with the intended radiotherapeutic purpose of the exposure.*"

With specific definition of radiotherapeutic given in section 2:

"*radiotherapeutic" means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes;*

The role of a medical physics expert (MPE) is also defined in section 14, which states that the employer must ensure that a suitable medical physics expert is appointed and involved in relation to every type of exposure to which the regulations apply. The medical physics expert must be closely involved in all non-standard radiotherapeutic practices and involved as appropriate for standardised therapeutic nuclear medicine practices.

The MPE should be available to give consultation on optimisation and give advice on dosimetry and quality assurance matters pertaining to radiation protection, as well as the physical measurement and evaluation of doses delivered. The medical physics expert must also contribute to:

- Optimisation of the radiation protection of patients and other individuals subject to exposures
- The training of practitioners and other staff in relevant aspects of radiation protection;
- The provision of advice to an employer relating to compliance with IR(ME)R.

Guidance to provide a practical approach to implementing IR(ME)R across a range of radiotherapy services, including MRT, was published by the Radiotherapy Board in a Joint Report with representatives from The Institute of Physics and Engineering in Medicine, The Society of College of Radiographers and The Royal College of Radiologists.[10] Guidance for clinicians in the UK performing molecular radiotherapy is giving in a report from the Intercollegiate Standing Committee on Nuclear medicine.[11]

Both guidance documents recognise that MRT administrations are often prescribed as a fixed or weight-adjusted activity ([1011])

Theragnostic imaging is highlighted as a means to identify suitability of a treatment prior to MRT delivery and in some cases can be used to optimise the planned administered activity for therapy. In the absence of randomised clinical trial evidence, activities are prescribed according to published experience supported by clinical judgement and specialist expertise within the MDT. Other methods of dose prescription, for example, to a desired whole-body radiation absorbed dose are also suggested. The need for prospective clinical trials to establish whether dosimetry-based individual treatment planning improves outcomes is recognised.[11]

The Radiotherapy Board noted the challenges of dose verification, which often requires accurate quantitative imaging and modelling of the activity distribution over time. These have been used as arguments against performing dosimetry.[12,13] However, counter arguments, demonstrating the technical advances, feasibility and evidence for dose–response relationships are available.[14–17]

The Administration of Radioactive Substances Advisory Committee (ARSAC)[18] gives more specific guidance on when individual absorbed dose assessments are required. Current recommendations are that in cancer treatments, the absorbed dose to the tumour and non-target volumes and tissues following each administration should be measured and recorded. For benign conditions or where direct measurements are impossible, absorbed doses should still be estimated and recorded. Applications for ARSAC Practitioner licenses for therapy administrations are expected to specify what dosimetry will be performed on an individual basis for therapies and note that it is the employers responsibility to ensure that appropriate resources are available.

The European Association of Nuclear Medicine (EANM) recently produced a position statement on article 56 of the Council Directive 2013/59/Euratom pertaining to nuclear medicine therapy.[19] The position statement aimed to provide guidance on how to interpret the statements within the directive and provide definition for standardised and non-standardised treatments. In their article, it was suggested that standardised therapies were those using approved products (by EMA or by CE marking) being administered according to the package inserts or relevant guidelines. Non-standardised therapies were defined as those in development or approved radiopharmaceuticals being used off-label. The UK Radiotherapy Board suggested that standard and non-standard nuclear medicine therapies should be defined locally depending on the local expertise and caseload[10] . The availability and proximity of the MPE should also bear a direct relation to the radiation risk involved with the treatment.

The EANM defined three levels for optimisation and verification of nuclear medicine therapy: (i) activity-based prescription and cohort-averaged dosimetry; (ii) activity-based prescription and patient-specific dosimetry; and (iii) absorbed dose-based patient-specific prescription. A classification of therapies was then provided with recommendations for when dosimetry was optional, advisable or not feasible. Despite contradiction to the optimisation principle set out in the directive, EANM

recommendations were that dosimetry was not necessary for registered radiotherapeutic procedures and generally only required when being used off-label.[19]

THE POSITION OF IDUG

IDUG strongly supports the European directive 2013/59 and IR(ME)R legislation as they pertain to MRT. We regard this legislation as an opportunity to progress the field and ensure standardisation and optimisation of therapy for the benefit of our patients. We strongly support the recommendations of ARSAC and Guidance from the Radiotherapy Board to comply with IR(ME)R. We support the EANM view that any non-licenced therapeutic radiopharmaceutical should only be administered with careful post-therapeutic verification. However, we feel that practice in the UK for other therapies should not be limited to the lower tier of optimisation and verification defined by the EANM. The IR(ME)R regulations make no exceptions for optimisation or verification requirements for licenced therapies. There are a number of radiopharmaceuticals currently on the market with insufficient dosimetry and long-term toxicity data. There is a severe lack of dose escalation studies across the breadth of MRT treatments, even in established therapies. Licencing of a therapeutic radiopharmaceutical does not imply optimisation, certainly not on a patient-specific level.

It is clear that prescription optimisation will still necessitate following vendor posology or clinical judgement, specialist expertise and experience within the MDT. However, these activity prescriptions should still be made with a knowledge of the range of absorbed doses that could potentially be delivered to the individual. Treatment delivery within this "expected range" must still be verified and recorded.

Following administration of MRT, the sites of uptake of the radiopharmaceutical should be demonstrated on an appropriate scan. IDUG recommends that as a minimum, a single quantitative image is required to confirm targeted delivery of the agent. With the exception of SIRT therapies, serial imaging and/or probe measurements are strongly encouraged to permit dosimetry of tumours and organs-at-risk (OAR). Provision should be in place to perform serial scanning with appropriate dosimetry in case of abnormal or unexpected uptake (such as extravasation[20] or kidney obstruction).

When only a single image is acquired, absorbed doses should still be estimated and reported using population data of effective half-life. For this "patient cohort–averaged dosimetry data", the uncertainty in the absorbed dose estimate should be considered and there should be sufficient data available to make an informed decision on the efficacy of delivering the treatment.

We are privileged within the UK to have a strong and dedicated workforce with a passion and desire to develop this field. The national training scheme[21] for medical physicists is well versed in delivering the skill set and resources needed to support these therapies. We should be embracing this legislation by gathering the data necessary to further advance the field of molecular radiotherapy. We recognise that calculation of treatment doses requires specialist resourcing. This includes equipment such as radiation detectors, dedicated dosimetry software and sufficient imaging capability. Appropriate staffing levels across centres are required with sufficient training to undertake the necessary scanning and dosimetric measurements and perform the dosimetry calculations. The need to balance standardisation with the variation in resources across centres will be challenging, but not impossible. Methods to progress molecular radiotherapy were made by the National Cancer Research Institute,[7] and many of the proposed strategies could be implemented to help aid national provision. A topical report by IPEM reported results from a survey of molecular radiotherapy provision and provided essential guidance on setting up a dosimetry service.[22]

To support its members and the wider community, IDUG has identified ten points for action to aid in the successful implementation of this legislation. Its aim is to promote inclusion of dosimetry, quantitative imaging and physics expertise in all MRTs, so that the UK can build an infrastructure of excellence in cancer treatment.

IDUG will work to:

- Report on the status and requirements for resourcing and infrastructure for dosimetry and support national societies to obtain the resourcing required to sustain a clinical dosimetry service.
- Continue to provide guidance on methodologies for dosimetry including best practise and pragmatic approaches to reduce resource burden associated with dosimetry.
- Provide training in aspects of therapy and dosimetry for all relevant disciplines.
- Compile and disseminate dosimetric data for common and emerging therapies so that exposure to target volumes can be planned accordingly.
- Support national incentives such as the peptide receptor radionuclide therapy PRRT registry and National Radiotherapy database.
- Work alongside other stakeholder organisations to further define the role of the MPE and provide advice and training of MPE's and clinical scientists in fulfilling the role set out in IR(ME)R.
- Support investigations into the impact of dosimetry based treatments on health economics.
- Engage with commissioners to ensure that commissioning guidelines for MRT fully take into account the requirements of IR(ME)R legislation.
- Engage with funding bodies to solicit support for the prospective clinical trials necessary to gather the evidence on which optimised treatments should be based.
- Continue to foster research that eventually leads to treatment planning according to a personalised dosimetry.

FUTURE DIRECTION

In our biennial surveys, we have observed an 80% increase in the number of patients treated with molecular radiotherapy over the last 10 years across the UK. A review article in the Lancet in March 2020[23] predicted revenue growth in the international

radiotherapeutic field to exceed $5 billion over the next 5 years. The number of new radiopharmaceuticals being trialled and introduced into the UK are at an unprecedented high. Pressure from industry and commissioners will inevitably seek to deliver these therapies with a minimum of resourcing or burden to the NHS. However, we have a duty of care to our patients and the wider population to ensure that these therapies are compliant with IR(ME)R as we deem appropriate.

The commissioning of Lu-177 DOTATATE therapy was granted based on evidence provided by a single commercial led clinical trial.[24] Although dosimetry was performed in a minimum number of patients for safety reasons, no attempt was made to optimise treatments using dosimetry. At present, guidelines for this therapy are based on the methodology of fixed activity administration used in this trial,[25] despite well-defined procedures and guidelines for performing quantitative imaging and dosimetry of Lu-177.[26] Whilst a few studies have sought to implement dosimetry led therapies,[27] there is still a question of absorbed or biological dose limits to organs at risk. Current data are mainly based on external beam radiotherapy and are only now being investigated in MRT.[17]

The registration of Lu-177 PSMA by the FDA and EMA following the VISION trial (https://clinicaltrials.gov/ct2/show/NCT03511664) is greatly anticipated. This trial was conducted without dosimetry or quantitative or even qualitative assessment of the radiotherapeutic uptake. Patients were treated with up to six administrations of Lu-177 PSMA, in a treatment regimen spanning 6 months. Yet, no post-therapy verification imaging was required by the trial protocol, and so there were no checks during this radiotherapeutic treatment that the radiation exposure was delivered as intended. Drug licenses must necessarily reflect the methodology of the preceding clinical trials, and so the instructions for use of Lu-177 PSMA will likely not recommend any form of post-therapy verification imaging, in complete contradiction to the aforementioned legislation. The introduction of this therapy in the UK following such a methodology will undoubtedly contravene IR(ME)R. We rigorously oppose allowing this approach to MRT to become the standard within the UK and the divide between drug and radiotherapy prescription must be bridged.

It should be applauded that dosimetry is now the recommended administration regimen for two major selective internal radiation therapy products, despite Y-90 being one of the most challenging isotopes to image.[28,29] Action is required by all stakeholders to ensure that all our patients, across all our therapies, are treated following the ethical and legal obligations we as a nuclear medicine community need to embrace.

CONCLUSIONS

We would strongly insist that commissioning bodies take into account the requirements of the EU directive and IR(ME)R legislation when evaluating MRT treatments for use in the NHS. We recognise that for many patients, a burdensome dosimetry schedule may be inappropriate. Yet, the decision to exclude verification and optimisation must not be made based on perceived cost and ease of implementation. Strategies for treatment must be multidisciplinary and based on what is best for the individual, in this the decision must be informed, justified and fully transparent.

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REFERENCES

1. McGowan DR, Guy MJ. Time to demand dosimetry for molecular radiotherapy? *Br J Radiol* 2015; **88**: 20140720. doi: https://doi.org/10.1259/bjr.20140720
2. Internal Dosimetry User GroupWhole Body Dosimetry Guidance. 2015. Available from: http://www.idug.org.uk/wp-content/uploads/2017/05/IDUGI-131-Whole-Body-Dosimetry-Final.pdf.
3. 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
4. Rojas B, Hooker C, McGowan DR, Guy MJ. Five years of molecular radiotherapy growth in the UK: survey results from 2007 to 2012. *Nucl Med Commun* 2015; **36**: 761–5. doi: https://doi.org/10.1097/MNM.0000000000000306
5. Rojas B, Hooker C, McGowan DR, Guy MJ, Tipping J. Eight years of growth and change in UK molecular radiotherapy with implications for the future: internal dosimetry users group survey results from 2007 to 2015. *Nucl Med Commun* 2017; **38**: 201–4. doi: https://doi.org/10.1097/MNM.0000000000000642
6. Rojas B, McGowan DR, Guy MJ, Tipping J, Aldridge M, Gear J. Eighty per cent more patients in 10 years of UK molecular radiotherapy: internal dosimetry users group survey results from 2007 to 2017. *Nucl Med Commun* 2019; **40**: 657–61. doi: https://doi.org/10.1097/MNM.0000000000001020
7. National Cancer Research Institute (NCRI) CTRad: identifying opportunities to promote progress in molecular radiotherapy research in the UK. 2016;.
8. Council Directive 2013/59/Euratom Laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom. *Official Journal of the European Union* 2013;.
9. The ionising radiation (medical exposure) regulations 2017. 2017; **1322**.
10. Ionising radiation (medical exposure) regulation: implications for clinical practie in radiotherapy. *Guidance from the Radiotherapy Board* 2020;.
11. Molecular radiotherapy: guidance for clinicians: report from the Intercollegiate standing Committee on nuclear medicine. *The Royal College of Radiologists* 2019;Contract No.: BFCO(19)4.
12. Brans B, Bodei L, Giammarile F, Linden O, Luster M, Oyen WJG, et al. Clinical radionuclide therapy dosimetry: the quest for the "Holy Gray". *Eur J Nucl Med Mol Imaging* 2007; **34**: 772–86. doi: https://doi.org/10.1007/s00259-006-0338-5
13. Giammarile F, Muylle K, Delgado Bolton R, Kunikowska J, Haberkorn U, Oyen W. Dosimetry in clinical radionuclide therapy: the devil is in the detail. *Eur J Nucl Med Mol Imaging* 2017; **44**: 1–3. doi: https://doi.org/10.1007/s00259-017-3820-3
14. Bardiès M, Gear JI. Scientific developments in imaging and dosimetry for molecular radiotherapy. *Clin Oncol* 2021; **33**: 117–24. doi: https://doi.org/10.1016/j.clon.2020.11.005
15. Flux GD, Sjogreen Gleisner K, Chiesa C, Lassmann M, Chouin N, Gear J, et al. From fixed activities to personalized treatments in radionuclide therapy: lost in translation? *Eur J Nucl Med Mol Imaging* 2018; **45**: 152–4. doi: https://doi.org/10.1007/s00259-017-3859-1
16. Flux GD, Verburg FA, Chiesa C, Bardiès M, Gleisner KS, Hertz B, et al. Comparison of empiric versus Dosimetry-Guided radioiodine therapy: the devil is in the details. *J Nucl Med* 2017; **58**: 862. doi: https://doi.org/10.2967/jnumed.116.186643
17. Strigari L, Konijnenberg 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
18. Administration of Radioactive Substances Advisory Committee Notes for guidance on the clinical administration of radiopharmaceuticals and use of sealed radioactive sources. *PHE publications gateway number GW-* 2021; **1943**: 1–71.
19. Konijnenberg M, Herrmann K, Kobe C, Verburg F, Hindorf C, Hustinx R, et al. EANM position paper on article 56 of the Council directive 2013/59/Euratom (basic safety standards) for nuclear medicine therapy. *Eur J Nucl Med Mol Imaging* 2021; **48**: 67–72. doi: https://doi.org/10.1007/s00259-020-05038-9
20. van der Pol J, Voo S, Bucerius J, Mottaghy FM. Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review. *Eur J Nucl Med Mol Imaging* 2017; **44**: 1234–43. doi: https://doi.org/10.1007/s00259-017-3675-7
21. Scientists Training ProgrammeNational School of Heathcare Science, NHS Heath Education England.. Available from: https://nshcs.hee.nhs.uk/programmes/stp/.
22. Craig AJ, Rojas B, Wevrett JL, Hamer E, Fenwick A, Gregory R. IPEM topical report: current molecular radiotherapy service provision and guidance on the implications of setting up a dosimetry service. *Phys Med Biol* 2020; **65**: 245038. doi: https://doi.org/10.1088/1361-6560/abc707
23. Herrmann K, Schwaiger M, Lewis JS, Solomon SB, McNeil BJ, Baumann M, et al. Radiotheranostics: a roadmap for future development. *Lancet Oncol* 2020; **21**: e146–56. doi: https://doi.org/10.1016/S1470-2045(19)30821-6
24. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med* 2017; **376**: 125–35. doi: https://doi.org/10.1056/NEJMoa1607427
25. Bodei L, Mueller-Brand J, Baum RP, Pavel ME, Hörsch D, O'Dorisio MS, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 2013; **40**: 800–16. doi: https://doi.org/10.1007/s00259-012-2330-6
26. Ljungberg M, Celler A, Konijnenberg MW, Eckerman KF, Dewaraja YK, Sjögreen-Gleisner K, et al. MIRD Pamphlet No. 26: joint EANM/MIRD guidelines for quantitative 177Lu SPECT applied for dosimetry of radiopharmaceutical therapy. *J Nucl Med* 2016; **57**: 151–62. doi: https://doi.org/10.2967/jnumed.115.159012
27. Sundlöv A, Sjögreen-Gleisner K, Svensson J, Ljungberg M, Olsson T, Bernhardt P, et al. Individualised ^{177}Lu-DOTATATE treatment of neuroendocrine tumours based on kidney dosimetry. *Eur J Nucl Med Mol Imaging* 2017;

44: 1480–9. doi: https://doi.org/10.1007/s00259-017-3678-4

28. Garin E, Tselikas L, Guiu B, Chalaye J, Edeline J, de Baere T, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. *Lancet Gastroenterol Hepatol* 2021; **6**: 17–29. doi: https://doi.org/10.1016/S2468-1253(20)30290-9
29. Levillain H, Bagni O, Deroose CM, Dieudonné A, Gnesin S, Grosser OS, et al. International recommendations for personalised selective internal radiation therapy of primary and metastatic liver diseases with yttrium-90 resin microspheres. *Eur J Nucl Med Mol Imaging* 2021; **48**: 1570–84. doi: https://doi.org/10.1007/s00259-020-05163-5