Institution: University of Birmingham

Unit of Assessment: UoA1

Title of case study: Refining the role and optimizing delivery of radioiodine in the treatment of thyrotoxicosis and thyroid cancer

1. Summary of the impact (indicative maximum 100 words)

Thyrotoxicosis (over-activity of the thyroid) affects up to 5% of the UK population and causes excess mortality, especially from vascular diseases, even in its mildest form. Thyroid cancer is the commonest endocrine cancer, its treatment being associated with adverse consequences which need to be minimised. A large programme of thyroid research in Birmingham led by Prof Jayne Franklyn has made major contributions to improving the management of thyrotoxicosis, specifically through optimal use of radioiodine treatment. Her group has developed and delivered a national training scheme to allow endocrinologists (hormone specialists) to give this treatment safely and effectively. Radioiodine is also a crucial part of treatment of thyroid cancer; Franklyn helped deliver a major trial showing that lower doses are as effective as higher doses in most cases but with fewer days in hospital and side effects. This research has changed clinical practice regarding more effective and safe use of radioiodine in thyrotoxicosis and thyroid cancer. It has been incorporated in **national and international clinical guidance, patient information sources, and has directly affected clinician training and patient care pathways.**

2. Underpinning research (indicative maximum 500 words)

A substantial programme of thyroid research of national and international repute has been delivered at the University of Birmingham over the last two decades, led by Prof Jayne Franklyn (at UoB since 1988) and her team, including Dr Kristien Boelaert (Senior Clinical Lecturer, at UoB since 2002). Birmingham is regarded as one of the principal centres for this activity in the UK and wider world. Research is underpinned by a uniquely large, detailed and longstanding database that records information about clinical phenotype, test results, treatment given and treatment outcomes for consecutive series of subjects with thyrotoxicosis (hyperthyroidism) and thyroid cancer. In addition, Prof Franklyn and Dr Boelaert manage the regional Birmingham Thyroid Follow-up Register of all subjects in the West Midlands treated with radioiodine for thyrotoxicosis since the 1950s, providing a further unique dataset for examining treatment outcomes. These large datasets of several thousand patients come from a high quality clinical service, forming the basis of important studies (since 1998) defining short- and medium-term treatment outcomes and long-term consequences of thyrotoxicosis and its treatment.

Thyrotoxicosis: treatment with radioiodine. Seminal findings from Birmingham have included definition of the long term consequences of obvious/overt thyrotoxicosis, particularly the finding of increased mortality from vascular disorders [1] and importantly the amelioration of this adverse outcome by treatment specifically with radioiodine [1,2]. Studies have compared the relative efficacy of different treatments (anti-thyroid drugs and radioiodine in different doses) and have shown the long-term safety of radioiodine treatment in terms of any potential later cancer risk [3].

Mild/subclinical thyrotoxicosis: adverse outcome and need for treatment with radioiodine. Collaborations with colleagues in primary care and cardiology have allowed community-based studies in the elderly of mild (subclinical) hyperthyroidism. Major findings published from 2001-2013 include the high prevalence in this age group and strong association of mild hyperthyroidism with risk of atrial fibrillation (AF) and vascular mortality [4].These findings have contributed to meta-analyses of clinical outcomes in mild hyperthyroidism [3] through Franklyn's participation in the International Thyroid Collaboration led by Prof Nicolas Rodondi. These findings have clarified the importance of treating mild hyperthyroidism, radioiodine being the treatment of choice for confirmed cases, a treatment now used increasingly in this condition.

Thyroid cancer: ablation of the thyroid remnant with radioiodine: Prof Franklyn's role as Chair of the National Cancer Research Institute Thyroid subgroup (2005-8) facilitated development of the HiLo trial comparing the effectiveness of different doses of radioiodine in destroying residual thyroid tissue after initial surgery (thyroidectomy) for thyroid cancer. This trial was supported by Cancer Research UK funding, Franklyn being a member of the trial management group. HiLo study findings clearly demonstrated that low-dose radioiodine was as effective as high-dose radioiodine in subjects at low risk of cancer recurrence, and with a lower rate of adverse events and shorter

hospital stay [6].

3. References to the research (indicative maximum of six references)

1. Franklyn JA, Sheppard MC, Maisonneuve P (2005) Thyroid function and mortality in patients treated for hyperthyroidism. *JAMA*; 294(1): 71-80. *DOI 10.1001/jama.294.1.71*
2. Boelaert K, Maisonneuve P, Torlinska B, Franklyn JA (2013). Comparison of mortality in hyperthyroidism during periods of treatment with thionamides and after radioiodine. *Journal of Clinical Endocrinology and Metabolism* 98(5):1869-82 *In REF2*
3. Franklyn JA, Maisonneuve P, Sheppard MC, Betteridge J, Boyle P. (1999) Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. *Lancet* ; 353(9170): 2111-2115. *doi:10.1016/S0140-6736(98)12295-X*
4. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascularmortality in elderly people from one low serum thyrotrophin: a 10-year cohort study. *Lancet* 2001; 358(9285): 861-65. *doi:10.1016/S0140-6736(01)06067-6*
5. Collet TH, Gussekloo J, Bauer DC, den Elzen WPJ, Balmer P, Iervasi G et al.et al. Subclinical hyperthyroidism and risk of coronary heart disease and mortality *Archives of Internal Medicine 2012*; 172(10): 799-809. *DOI 10.1001/jama.2010.1361*
6. Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss Let al. Ablation with low-dose radioiodine and thyrotropinalfa in Thyroid Cancer. *New England Journal of Medicine* 2012;366: 1674-85. *http://www.nejm.org/doi/pdf/10.1056/NEJMoa1109589*

4. Details of the impact (indicative maximum 750 words)

Research led by Prof Franklyn and Dr Boelaert has had a significant impact on clinical management ofthyrotoxicosis (over-activity of the thyroid) and thyroid cancer. This work continues to drive national and international guidance, professional training and clinician decisions, as well as those of patients, in the UK and beyond.

Thyrotoxicosis and its treatment with radioiodine

Obvious (overt) over-activity of the thyroid affects 5% of the UK population. Untreated, in addition to unpleasant symptoms, it is a significant risk factor for cardiovascular disorders, especially the heart rhythm abnormality atrial fibrillation (AF), as well as for osteoporosis (thin bones). Management is typically with anti-thyroid drugs, radioiodine therapy or occasionally surgery. Radioiodine is used to overcome the hyperactivity of the thyroid gland, but in many cases induces hypothyroidism, i.e. under-activity of the gland, which requires careful management with thyroxine as thyroid hormone replacement. Prof Franklyn and team's research has impacted upon:

Clinician awareness and national guidance regarding use of radioiodine:

- Highlighted and clarified the increased risks of vascular diseases associated with thyrotoxicosis, influencing current guidance in the UK and overseas in terms of recommending and hence driving earlier use of definitive therapy with radioiodine to improve long-term prognosis [1,2].
- Driven current national guidance for the use of radioiodine in benign thyroid disease (Franklyn co-author and Birmingham work explicitly referenced [3] in guidance published 2007 which has driven practice 2008-13), which underpins safe and effective delivery of radioiodine treatment in conjunction with Medical Physics Departments, and subsequent follow-up of patients to promptly identify development of hypothyroidism and to manage it with the correct dose of thyroxine. Franklyn contributed to the 2011 Royal College of Physicians multi-professional guidance statement on diagnosis and treatment of hypothyroidism [4].

Training in the administration of radioiodine with associated cost savings and patient benefit:

To support clinician training and maximise patient benefit from this work, the team used their expertise to innovate in postgraduate medical education nationally. Franklyn led a team in 2006 that included the Royal College of Radiologists, the Institute of Physics and Engineering in Medicine and ARSAC (the government licensing body) to create the first national curriculum and associated teaching and assessment materials for consultant endocrinologists (specialists who manage patients with thyroid problems) to acquire the knowledge and skills required for licensing by ARSAC to administer radioiodine therapy (guidance issued in 2006 and revised in 2011 [5]). Franklyn and Boelaert developed novel educational materials and have delivered teaching on this

national course 2-3 times per year for 264 attendees since 2008. Importantly, over 50 consultant endocrinologists from across the UK have been certified by ARSAC, with support from their NHS Trust medical physics departments, through this new training scheme, representing an increase in licensed endocrinologists of 35% since 2008. This has had the specific beneficial impact of reducing patient visits and NHS costs (estimated at £223 per unnecessary oncology clinic appointment) by eliminating the need for cross-referral of patients between endocrinology and either oncology or nuclear medicine specialists for radioiodine treatment, allowing better planning of timing of treatment and follow-up and thus improving and simplifying the care pathway to the benefit of both patients and clinicians [6].

Patient access to information about optimal treatment for thyrotoxicosis:
The team has worked directly with patient and carer groups to disseminate the findings of their work and to support patient awareness and decision-making. Franklyn was a Trustee (2008-11) of the British Thyroid Foundation (the major UK patient and carer support group), contributing to patient information literature, newsletters, website information (such as the revised patient information on thyrotoxicosis developed by Franklyn and Boelaert [7]). They have also attended meetings of patient support groups, sessions which are *"highly regarded"* and have resulted in excellent patient and carer feedback, as testified by the British Thyroid Foundation [8], who also commented that *"We strongly support the notion that the University of Birmingham Research Portfolio continues to have significant impact on the care of patients with thyroid disorders."*

Mild (subclinical) thyrotoxicosis and its treatment with radioiodine
Thyrotoxicosis is described as "subclinical" (or mild) when the measurement of thyrotrophin (TSH) from the pituitary in the blood/serum is low but the blood level of the actual thyroid hormone thyroxine (T4) is normal. This combination of blood test results indicates the earliest stages of thyrotoxicosis which can progress to obvious/overt disease, but importantly has its own specific associated health risks. Work on subclinical thyrotoxicosis (also termed subclinical hyperthyroidism) led by Franklyn and team has shown how common this disorder is, especially in the elderly and how it is associated with vascular disorders and mortality, and has:

- Been incorporated into current UK guidance [9],first published in 2006 and updated in a Lancet invited review in 2012 [1], which clarifies current best practice in terms the role of treatment of subclinical hyperthyroidism with radioiodine, which is now increasingly undertaken in the UK and abroad;
- Directly influenced international practice by being incorporated into the American Thyroid Association/American Association of Clinical Endocrinologists/US Endocrine Society consensus guidelines in 2004 [10], which remain current and have driven US and international practice 2008-13. Franklyn was the only invited overseas expert and consensus guideline panel member;
- Been incorporated into the most recent US guidance published in 2011/12 [2] directly citing Franklyn and her team's work

Thyroid cancer and adjunctive treatment with radioiodine
Thyroid nodules are very common, and can be identified by ultrasound scanning in up to 50% of the population, though only around 5% of the population have nodules that are noticed by patients or their doctors. Up to 10% of such nodules may be cancerous, thyroid cancer being the commonest endocrine cancer with more than 2000 new cases each year in the UK.

Birmingham work on radioiodine treatment has also extended to thyroid cancer. Surgery (thyroidectomy) is the initial treatment for thyroid cancer, but radioiodine is used subsequently to destroy any remaining thyroid tissue. Much higher doses of radioiodine are used than in treatment of thyrotoxicosis as described above. These high doses require significant hospital stays in isolation because of national radiation protection regulationsfor the general population and high doses are potentially harmful long-term in terms of risk of "second"/later malignancies; high doses of radioiodine were regarded as the best option to ensure ablation of all residual thyroid tissue. Franklyn played a key role in the development and delivery of the 'HiLo' trial of "high" versus "low" doses of radioiodine in thyroid cancer patients at relatively low risk of later recurrence (who represent 40-50% of those diagnosed each year), the trial results showing that low doses were just

as effective as high and caused fewer side effects (21% versus 33%), helping with quicker recovery and shorter hospital stays (13% given low dose radioiodine in the HiLo trial hospitalised for at least 3 days versus 36.3% for high dose). These findings have already:

- Led to reduction in the doses of radioiodine administered to those whose thyroid cancer is at low risk of recurrence, this being a significant proportion of those treated, as evident in our own local tertiary centre guidance and practice. In the year to October 2011 100% of 93 radioiodine doses administered for "remnant thyroid ablation" in the Queen Elizabeth Hospital Birmingham were "high" (3000 or 5500MBq) in contrast to only 73% of 102 doses in the year to October 2012 and 62% of 97 doses in the year to October 2013 [11], a change which was implemented as a result of the HiLo outcomes. These changes represent a saving of approximately 100 days of hospitalisation over a 2 year period in this single centre. More broadly for other centres adopting this recommended change in practice it was estimated within the HiLo study that there was a 24% cost reduction in care of patients treated within the NHS from reduction in hospital days in isolation, as well as associated reduction in days off work.
- This work has been widely disseminated amongst clinicians and patients through Cancer Research UK [12,13] and hailed as seminal results which are directly changing clinical practice.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Franklyn JA, Boelaert K. Thyrotoxicosis. *Lancet* 2012 379(9821): 1155-66. http://www.ncbi.nlm.nih.gov/pubmed/22394559 (invited review)
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3. Royal College of Physicians. Radioiodine in the management of benign thyroid disease. Clinical Guidelines. Report of a Working Party 2007. London: RCP; 2007. http://bookshop.rcplondon.ac.uk/contents/pub208-bdbb4220-3a14-401a-b298-c0d3f20cdd38.pdf
4. Royal College of Physicians. The Diagnosis and Management of Primary Hypothyroidism. Revised statement June 2011. *http://www.rcplondon.ac.uk/resources/clinical-resources/diagnosis-and-management-primary-hypothyroidism*
5. Notes for Guidance onthe Clinical Administrationof Radiopharmaceuticalsand Use of Sealed Radioactive Sources, 2011 update *http://www.arsac.org.uk/notes_for_guidance/documents/ARSACNFG2006Corrected2011.pdf*
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8. British Thyroid Foundation letter of support
9. Association for Clinical Biochemistry. UK Guidelines for the Use of Thyroid Function Tests. British Thyroid Association/ British Thyroid Foundation; 2006. http://www.acb.org.uk/docs/TFTguidelinefinal.pdf
10. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH et al.Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004; 291(2): 228-38. http://www.ncbi.nlm.nih.gov/pubmed/14722150
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12. http://www.cancerresearchuk.org/cancer-info/news/archive/pressrelease/2012-05-02-thyroid-cancer-trial-results
12. Cancer Research UK website – Cancer Help information under Trials and research: A trial looking at radioactive iodine treatment for thyroid cancer (HiLo): http://www.cancerresearchuk.org/cancer-help/trials/a-trial-looking-at-radioactive-iodine-treatment-for-thyroid-cancer