A Review of the Supply of Molybdenum-99, the Impact of Recent Shortages and the Implications for Nuclear Medicine Services in the UK

Administration of Radioactive Substances Advisory Committee

Chairman: **Dr T Nunan**

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ARSAC Secretariat
www.arsac.org.uk

c/o Health Protection Agency
Centre for Radiation, Chemical and Environmental Hazards
Chilton, Didcot, Oxon OX11 0RQ

Preface

i The Administration of Radioactive Substances Advisory Committee (ARSAC) was established in 1978 under Regulation 3 of The Medicines (Administration of Radioactive Substances) Regulations 1978 (MARS). The terms of reference for the statutory function of ARSAC are defined as:

> "To advise Health Ministers with respect to the grant, renewal, suspension and revocation and variation of certificates in those cases where in the opinion of Health Ministers certificates should not be granted, renewed, suspended or varied without the advice of the said committee, and generally in connection with the system of prior authorisation envisaged by Article 5(a) of Council Directive 76/579/EURATOM"

ii ARSAC has a non-statutory role, the terms of reference of which are:

> "To provide general guidance and advice to the Health Departments on the use of radioactive medicinal products in clinical medicine and research and on the use of machine-produced radiation (e.g. X-rays) in research"

iii Over the past 30 years ARSAC has provided guidance on the clinical administration of radiopharmaceuticals and use of sealed radioactive sources. The ARSAC Notes for Guidance are based on national and international recommendations and are considered to be a guide to good clinical practice in the UK for nuclear medicine. The Notes for Guidance are revised every five to six years and the latest edition was published in 2006.

iv In recent years nuclear medicine services across the world have been drastically affected by shortages in the production of molybdenum-99 (^{99}Mo), the parent isotope of technetium-99m (^{99m}Tc). Nuclear medicine services rely heavily upon the use of ^{99m}Tc, which is used in more than 80% of nuclear medicine investigations worldwide.

v In 2009 the Department of Health requested that ARSAC provide a report on the current situation, the impact of the worldwide shortages of ^{99}Mo on UK nuclear medicine departments and any medium- to long-term solutions to ameliorate this.

vi To achieve a comprehensive review of the topic, ARSAC established its Strategic Report Subcommittee (SRS). The SRS incorporates members from ARSAC, former members and scientific experts.

vii The aim of this report has been to provide advice to the Department of Health on how the medium- to long-term shortage of ^{99}Mo might be responded to and managed at national and local level.

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Contents

Chapter 1

Introduction

1.1 Nuclear medicine imaging relies upon the tracer principle first established in 1913 by Georg de Hevesy and involves the administration of small quantities of a radioactive substance into the body which then distributes and accumulates in particular organs. The distribution depends upon the particular material administered which is chosen depending on the organ of interest. The gamma rays emitted by the radionuclide are detected and an image of the distribution of the radioactivity within the body is constructed.

1.2 In contrast to other imaging modalities, which provide anatomical detail, nuclear medicine imaging provides information about organ function and can be used to demonstrate physiological processes. Although not used as frequently as radiographic techniques such as plain film and fluoroscopy, ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI), nuclear medicine complements other modalities and provides a valuable diagnostic tool in a range of clinical conditions. The demand for nuclear medicine imaging continues to grow within the UK and across the world.

1.3 Since the 1970s, most conventional nuclear medicine imaging has been undertaken following the administration of pharmaceutical compounds labelled with technetium-99m (^{99m}Tc) using a gamma camera to produce planar or cross-sectional images of the body.

1.4 Technetium-99m is the most commonly used imaging radioisotope in the UK as it emits a gamma photon of 140 keV and has a half-life of approximately six hours. The energy is well suited to the gamma camera detection system and the short half-life allows sufficient time for imaging but does not result in excessive radiation dose to the patient. Technetium-99m is used in more than 80% of nuclear medicine studies worldwide.

1.5 Technetium-99m can be conveniently obtained from decay of molybdenum-99 (^{99}Mo); the two radionuclides are separated under aseptic conditions using a chromatographic column in a device called a generator. Molybdenum-99 has a half-life of 66 hours (i.e. the yield goes down by one-half every three days); thus, the generator has a useful life of one to two weeks and replacements are usually obtained once a week. Most ^{99m}Tc radiopharmaceuticals are prepared in the hospital, though in larger cities there may be a central radiopharmacy which supplies a number of hospitals. Molybdenum-99 itself is conventionally produced in nuclear research reactors.

1.6 Nuclear medicine imaging is the final stage of a complex process which involves off-site industrial production of radioactive substances and pharmaceuticals and, as such, is dependent on a robust production, manufacturing and supply process. In the past few years, the reliance at the beginning of this chain on ageing research reactors to produce ^{99}Mo has resulted in interruption of nuclear medicine services during breakdowns and scheduled reactor maintenance periods. In the future, the move for security reasons, from processes involving highly enriched uranium (HEU) to low enriched uranium (LEU), will bring further challenges and cost implications. The resulting challenges for nuclear medicine services imaging have become clear.

1.7 This report describes the production process and how ^{99m}Tc is used in nuclear medicine departments. Alternative technologies and imaging modalities are then considered. The legal framework for nuclear medicine is reviewed, followed by conclusions and recommendations. A glossary and methodology for a comprehensive review of software solutions are also provided.

Chapter 2

Production of Molybdenum-99/Technetium-99m

Introduction

2.1 The global demand for ^{99m}Tc products has been estimated at around 50 million doses per year, with the USA demand constituting almost half that number and Japan and Europe about one-fifth each [1]. A similar estimate of 10 million imaging procedures per year in Europe is reported in a European Association of Nuclear Medicine survey for 2009 [2]. Utilisation of nuclear medicine in the UK is relatively low by international standards, but remains significant, with approximately 500,000 procedures using ^{99m}Tc being undertaken each year [3].

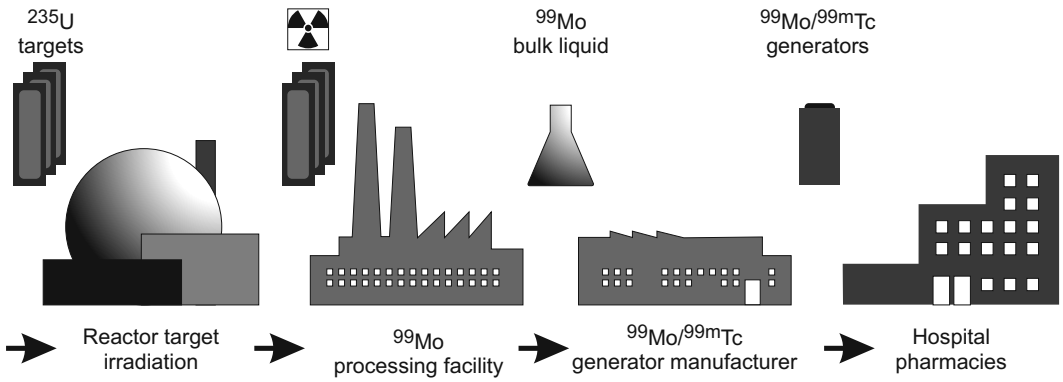
2.2 Despite the USA and Japan being the two largest nuclear medicine markets, neither has a domestic supply of ^{99}Mo. The USA decommissioned its last production reactor in 1989 and has since been relying largely upon Canadian supply. In response to recent shortages of ^{99}Mo, as described in detail below, the USA is looking at options for domestic supply. However, domestic supply for the USA will be of no direct benefit to the rest of the world as there is no intention to export ^{99}Mo from the USA. The Canadian reactor is due to be decommissioned in 2015 and the Canadian government does not plan to replace it. Therefore, a robust European plan of action for sustainability of ^{99}Mo supply in the medium to long term is essential.

2.3 The complex processes, exacting radiation safety requirements and the timelines for production associated with radioactive materials which decay over a matter of days dictates that there needs to be excess capacity for ^{99}Mo production in order to ensure continuity of supply through periods of routine maintenance. Thus the required capacity should be 200–250% of absolute requirements [4]. Coordination among producers regarding scheduling of downtime can help to alleviate supply problems but in the past this has not always been possible and ageing reactors will require increasing amounts of unscheduled downtime.

Supply chain – research nuclear reactor to healthcare facility

2.4 There are a number of steps in the supply chain for ^{99}Mo/^{99m}Tc generators, often requiring transport between steps. These steps are shown in Figure 2.1 below and summarised below.

Figure 2.1 ^{99}Mo/^{99m}Tc supply chain [4]



a *Irradiation of enriched uranium-235 (^{235}U) target in nuclear research reactor* (It should be noted that nuclear power reactors are not suitable for production of ^{99}Mo by fission due to the completely different technology employed.) The properties required of the target are that it is an appropriate size to fit the irradiation position in the reactor; contains a sufficient quantity of ^{235}U to produce the desired amount of ^{99}Mo; has good heat transfer properties to prevent overheating during irradiation; provides a barrier to the release of radioactive products, especially fission gases, during and after irradiation; and is compatible with the chemical processing steps that will be used to recover and purify ^{99}Mo after the target is irradiated. Most commonly this is an aluminium alloy [1].

b *Extraction of ^{99}Mo from target material* The main steps include dissolution of the target in sodium hydroxide (at this point iodine-131, ^{131}I, and xenon-133, ^{133}Xe, can be recovered) and filtration to remove solids. The waste contains 97% of the original ^{235}U, which is currently not economically feasible to be recovered.

c *Purification of ^{99}Mo is performed by ion exchange* The ^{99}Mo is trapped on an alumina column, washed with dilute ammonium hydroxide, and eluted with high concentration sodium chloride or ammonium hydroxide.

d *Loading of generators* Generator manufacturers obtain their bulk ^{99}Mo from any available suppliers. However, generator loading is another highly specialised operation, with most manufacturers having only one or two plants where this is carried out. The process ends with a trial elution. The generators are then shipped to their final users.

Table 2.1 Typical times required for steps in production of ^{99m}Tc generators

Process step	Time required (hours)
Target irradiation and cooling	130–168 (5–7 days)
Shipping and extraction of ^{99}Mo	6–28
Packaging and shipping of ^{99}Mo	6–12
Generator loading and packaging	12
Generator shipping	1–24
Clinical use of generator	168–336 (7–14 days)

Adapted from an NRC Committee Report [1]

2.5 As can be seen from Table 2.1, the total production process runs to very tight timelines. The time between ^{99}Mo targets being removed from the reactor and the $^{99}Mo/^{99m}Tc$ generator arriving at the hospital is a minimum of one day and is generally two or three days, which is equivalent to about one half-life of the ^{99}Mo produced. Therefore half of the manufactured activity has decayed before the generator goes into clinical use.

Transport problems

2.6 It can be seen that the supply chain involves transport of ^{99}Mo at up to three stages in the process: irradiation to purification, purification to generator loading, and generator loading to hospital. This transport often involves moving radioactive material across international borders which can affect reliability of supply, especially when air transport is involved [1]. Further details are given in Chapter 7. As a consequence, in times of supply disruption, alternative supply chains are not easy to establish even if alternative sources of ^{99}Mo can be found.

Production of $^{99}Mo/^{99m}Tc$

Conventional production of ^{99}Mo in nuclear research reactors

Existing research reactors

2.7 Most of the world's supply of ^{99}Mo for nuclear medicine is obtained by fission of ^{235}U and for many years was produced in only five nuclear reactors. Three more have entered service recently, two of these in response to shortages (see Table 2.2). All are research reactors and none is intended primarily for production of radionuclides for medical use; it is estimated that medical isotope production is around 10% of the business at a research reactor. Moreover, the five large reactors are all approaching the end of their useful lives.

Table 2.2 Research reactors used for large-scale production of ^{99}Mo

Reactor	Location	Date of first commissioning	Power (MW)	Operational days per year	Capacity (% of European needs)
NRU	Chalk River, Canada	1957	135	270	N/A
HFR	Petten, the Netherlands	1961	45	280	>100
BR2	Mol, Belgium	1961	100	140	>100 when operating
OSIRIS	Saclay, France	1966	70	180	~25 when operating
SAFARI	Pelindaba, South Africa	1965	20	310	N/A
OPAL *	Lucas Heights, Australia	2006	20	340	N/A
MARIA †	Swierk, Poland	1974	30	160	~10 when operating
LVR-15 †	Rez, Czech Republic	1957	10	210	~10

* Not yet exporting ^{99}Mo
† Began international supply of ^{99}Mo in 2010

2.8 It was expected that the ageing NRU reactor at Chalk River, Canada, would be replaced by the tandem MAPLE reactors (discussed in more detail below), which were designed for high capacity radionuclide production and would provide continuity of supply. Indeed, the USA decommissioned reactors on the understanding that MAPLE would ensure ^{99}Mo supply for the foreseeable future. Construction of MAPLE began in 1997 and commissioning commenced in 2000, but technical problems arose which could not be resolved and the project was cancelled in May 2008 after years of delay and cost over-runs. Despite the recommendation of an expert panel that a new conventional research reactor should be built [5], the Canadian government has announced that it will not replace the NRU reactor when it is decommissioned in 2015.

Recent problems

2.9 The age of the major reactors has significant impact on reliability and service schedules. In the past few years this has resulted in extended periods of interruption of ^{99}Mo supply. There have been three major emergency shutdowns in recent years as well as one prolonged planned closure for repairs.

2.10 In November 2007 the NRU reactor at Chalk River, which supplies the bulk of the ^{99}Mo for North America, was shut down for routine maintenance when the Canadian Nuclear Safety Commission (CNSC) noted that actions required from a previous safety inspection had not been completed and refused to allow the reactor to start up again. Over the course of two weeks, nuclear medicine in North America virtually ground to a halt. The nuclear medicine community was so successful in raising public awareness that there was an emergency debate in the Canadian parliament leading to passage within one day of legislation to allow the reactor to restart. This shutdown had very little impact in the UK.

2.11 In August 2008 the HFR reactor at Petten was shut down due to corroded pipes in the cooling system. In what was termed a 'perfect storm', all other reactors were down for unrelated reasons at the same time – most for maintenance but one because of a massive unintentional release of ^{131}I. After six months the HFR resumed operation in February 2009 but announced a further closure for several months in 2010 to allow for a more permanent repair [6]. This incident, too, raised interest at a political level. Indeed, political pressure ensured that the Dutch government allowed the reactor operation to be resumed in February 2009.

2.12 In May 2009 production at the NRU was interrupted again, this time because of a leak of heavy water from the reactor vessel, which continued at a rate of four litres per hour for several weeks. Repairs took well over a year and reactor operation resumed in August 2010. Even though NRU was not the primary source of ^{99}Mo for any of the UK suppliers, this has had a serious impact in the UK as a result of the global shortage which resulted when the largest supplier went down. In response to this shutdown, the HFR and SAFARI increased ^{99}Mo production and OPAL is coming online.

2.13 In February 2010 the planned six-month closure of the HFR reactor commenced for proper resolution of the problems encountered in 2008. Because the NRU was not back in operation by this time, worldwide supplies became extremely precarious. Even though both of these large reactors resumed production in August/September 2010, uncertainty remains about the continuity of supply due to the frailty of the limited network of ageing reactors.

Security issues regarding ^{99}Mo supply

2.14 Currently most ^{99}Mo is produced by irradiation of highly enriched ^{235}U targets (HEU). The natural abundance of ^{235}U is 0.7%. HEU is defined as over 20% ^{235}U, though in practice, the reactor targets contain over 90% ^{235}U to maximise the production of ^{99}Mo. HEU is considered to be weapons grade material and is subject to strict controls for storage and transport. International instability over the last ten years has raised the profile of security of radioactive sources where previously the major focus within radiation protection has been safety. This applies to all types of radioactive sources but the USA has now turned its attention to HEU and has declared a major policy change regarding the manufacture, use and availability of HEU. The USA intends to cease export of HEU in the next seven to ten years. While most nuclear power reactors have already switched to low enrichment ^{235}U (LEU) for their fuel, the targets remain HEU and this has major implications for the production of ^{99}Mo. Of the major reactors used for production of ^{99}Mo only SAFARI has converted to LEU targets. There is no scientific reason that LEU targets could not be used, but there are technical and economic implications. More irradiation space in the reactor core is required since the yield per target would be lower and there would need to be changes to processing, due to the larger amount of material irradiated and resultant greater volume of waste. In addition, there would be co-production of plutonium-239 (^{239}Pu) from the greater amount of ^{238}U. The US NRC Committee estimated that conversion would not increase the cost of ^{99}Mo by more than 10% [1], although the Society of Nuclear Medicine (SNM) Isotope Availability Task Group has disputed this [7].

Situation in the UK – generator supply

2.15 There are three suppliers of $^{99}Mo/^{99m}Tc$ generators in the UK, as summarised in Table 2.3.

2.16 As none of the European suppliers relies upon the NRU as a regular source of ^{99}Mo, the impact of the shutdown of the NRU was indirect and followed the diversion of European and South African reactor-produced ^{99}Mo to satisfy the North American market.

2.17 None of the three European companies manufactures generators during the weekend, which would enable delivery to UK hospitals on Monday morning. In contrast, the two large American companies (Lantheus and Covidien) manufacture on Sundays.

Table 2.3 UK generator suppliers

	GE Healthcare	Covidien	IBA/CisBio
Brand name of generator	Drytec	UltraTechnekow	Elumatic III
Site of manufacture of generators	UK	The Netherlands	France
Primary source of ^{99}Mo	SAFARI (South Africa)	HFR (the Netherlands)	OSIRIS (France)
Range of generator sizes (GBq ^{99}Mo)	2.5–100	2.15–43	2.4–24 *
Reference days per week	2	5	2 †
Market share by proportion of radioactivity	59%	28%	13%
Market share by proportion of generators	50%	25%	25%

* Range being expanded to 56 GBq
† Parent company produces five days a week but generators are only imported into the UK on two days of the week

2.18 During times of ^{99}Mo shortage there are complaints about inequities in supply. Although manufacturers claim to treat customers equally, both nationally and internationally, there are anecdotal reports that generator manufacturers ensure better supply to key markets, with larger central radiopharmacies being prioritised.

2.19 Each of the manufacturers has demonstrated different strategies for responding to shortages; GE Healthcare and Covidien make lower activity generators whereas IBA/CisBio brings forward the generator reference date. The end result is the same and neither strategy provides the activities required. IBA/CisBio also applies the French government policy of ensuring that each customer gets at least a minimal activity (currently 4 GBq ^{99m}Tc with four days pre-reference). A recurring problem has been the manufacturers' inability to provide information in advance regarding the activity that will be delivered. This makes it difficult for nuclear medicine services to plan their workload and to provide efficient patient scheduling.

Short-term responses to improve ^{99}Mo availability

2.20 Production has been increased at SAFARI and OPAL. During the closure of the HFR in 2010, production was increased at BR2 and OSIRIS to limit the number of weeks of extreme shortage of ^{99}Mo. A second small reactor at Saclay, Orphée, performed a number of irradiation cycles during 2010 at times when OSIRIS was unavailable. In addition, the MARIA reactor in Swierk, Poland, which currently supplies ^{99}Mo to Polatom, a Polish company established to address its domestic market only, has begun to produce ^{99}Mo for export, with the targets being transported to Petten for processing. Similarly, the LVR-15 reactor in Rez, Czech Republic, is sending targets to Mol, Belgium, for processing.

Upgrade of existing reactors

2.21 Despite being the world's largest consumer of ^{99}Mo, the USA has had no domestic production of ^{99}Mo since 1989 when its last reactor was decommissioned. However, the insecurity of ^{99}Mo supply in the last two years has led to the introduction of the American Medical Isotopes Production Act in November 2009, which allocates US$163 million to support production of ^{99}Mo without the use of HEU. It is expected that the University of Missouri Research Reactor (MURR) will be upgraded for ^{99}Mo production, although this will take about five years. However, MURR would only be able to provide 50% of the ^{99}Mo required for the USA, increasing to 70% for short periods, so alternative sources would be required.

2.22 The most likely European candidate for upgrade is the FRM-II reactor at the Technical University of Munich, Germany. However, it will probably be 2014 before it is able to supply ^{99}Mo. It has been suggested that this reactor has the capacity to supply around 50% of European requirements at very little cost [8].

Replacement of existing reactors

2.23 There are plans to replace many of the ageing reactors currently in use, shown in Table 2.4. Only the first of these programmes is actually underway, the second and third are highly likely to proceed, while the final one is uncertain.

Table 2.4 Status of replacement of existing production reactors

Country	Proposal	Capacity (% of European needs)	Projected completion
France to replace OSIRIS	JHR (Jules Horowitz Reactor) under construction since 2007 at Cadarache	~25 (could be expanded to 50)	2015 €500 million [9]
The Netherlands to replace HFR	PALLAS in planning at Petten site, construction contract being renegotiated	>100	2017 €500 million
Belgium to replace BR2	MYRRHA under construction since 1997 at Mol	>100 when operating	2022 €960 million total
Canada to replace NRU	Expert panel has recommended this option [5]	N/A	Current government has ruled out this option

2.24 In September 2010, the French Alternative Energies and Atomic Energy Commission (CEA), the Belgian National Institute for Radioelements (IRE) and IBA/CISBio signed an agreement aiming to secure the supply of ^{99m}Tc beyond 2015. The CEA will guarantee the irradiation of ^{235}U targets at the JHR reactor currently under construction. The IRE will extract ^{99}Mo following major renovations at its facility in Fleurus, Belgium, and deliver it to distributors of ^{99m}Tc generators. IBA/CISBio will manufacture and distribute ^{99m}Tc generators for hospitals from its new generator manufacturing lines in Saclay, France.

2.25 The European Commission is currently exploring two possible financing mechanisms to ensure a sustainable supply of radioisotopes within Europe. Loans to support isotope production projects may provide an incentive for appropriate investment in research reactors and/or in production facilities. European Investment Bank loans and guarantees may also serve this purpose. In addition, preliminary analysis is being undertaken into the possibility of a joint undertaking not only to achieve a regular and sustainable supply, but also to gain control of the entire ^{99}Mo production process [8].

Alternative routes to production of ^{99}Mo

2.26 A variety of alternative routes to production of ^{99}Mo have been investigated over the years but most have been discarded as uneconomical. However, the current shortages have changed perspectives and cost is no longer the most important factor. It is now acknowledged that the current model for the production of ^{99}Mo is not economically viable [4]. Four alternative routes to produce ^{99}Mo are described in Table 2.5, two involving reactors (conventional or novel) and two requiring novel high energy particle accelerators.

Table 2.5 Alternative routes to production of ^{99}Mo

Aqueous homogenous reactor (AHR)	
Technology	The AHR or uranyl nitrate medical isotope production system (MIPS) has been under development for some time but its utility for large-scale production has not been demonstrated. The AHR uses a LEU salt solution as both fuel and target. It is a very attractive concept. It is currently projected that a 200 kW reactor with a volume of 150 L could supply 10% of the world's ^{99}Mo requirement
Capacity	Expected to supply 50% of American market using ~6 AHRs
Cost	Received $9 million in January 2010 from the US National Nuclear Security Administration (NNSA)
Timeline	Currently under development by Covidien and Babcock & Wilcox 5–6 years
Advantages	Compact (150 L each) Safe (operates at 80°C and atmospheric pressure) Uses LEU, produces little radioactive waste Relatively short development time expected
Disadvantages	Unproven technology Technical problems possible Potential regulatory issues from both radiation and pharmaceutical viewpoints [1,10,11]
Assessment	Wait and see what progress is made Not aware of any proposals for this on a commercial scale in Europe
Neutron capture	
Technology	An early method for production of ^{99}Mo, still used in some parts of the world, was neutron irradiation of natural Mo targets utilising the ^{98}Mo(n,γ)^{99}Mo reaction. There are a number of disadvantages of this approach, leading to it being largely replaced by fission as a source of ^{99}Mo
Capacity	Large number of processing facilities required
Cost	Recently the US Department of Energy has awarded $2 million to GE-Hitachi to adapt this technology to the irradiation of ^{98}Mo targets in commercial nuclear power reactors. While the efficiency of this reaction is very low, the potential capacity is great [12]
Timeline	2 years
Advantages	Low risk, proven technology Could be enhanced by the use of enriched ^{98}Mo targets Might be possible to recover ^{98}Mo from spent generators Although lower specific activity ^{99}Mo could only be used for moderate size generators, it could be spiked with fission ^{99}Mo for high activity generators [11]
Disadvantages	Low yield Currently limited to small scale The specific activity of the resultant ^{99}Mo is low due to the presence of other isotopes of Mo. The natural abundance of ^{98}Mo is only 24% and the cross-section of the reaction is low, limiting the amount of ^{99}Mo which can be produced [12,13] The limitations imposed by low specific activity are the requirement for a larger column, which results in larger elution volumes and higher breakthrough of both ^{99}Mo and aluminium. Breakthrough also shortens the expiry date of the generator and therefore more generators (and more ^{99}Mo) would be required The large elution volumes and hence lower radioactivity concentration may require some radiopharmaceutical kits to be reformulated and relicensed. This would be extremely costly, as most are currently relatively inexpensive generic products
Assessment	No UK capacity (unless nuclear power reactor option proves feasible), limited interest in Europe

Table 2.5 ***Continued***

Photofission	
Technology	One proposal which has had a fair amount of publicity is production of ^{99}Mo using a particle accelerator for photofission of ^{238}U [14]. Because of the extremely low cross-section of this reaction, very high intensity photons from an accelerator with MW-level power are required. Such accelerators do not currently exist but their construction is feasible, although technology development and assessment will take several years
Capacity	2 or 3 accelerators would be required to supply UK market
Cost	Currently under development by MDS Nordion and Triumf $100 million per accelerator
Timeline	8 years
Advantages	Uses ^{238}U, not ^{235}U Does not require enriched ^{98}Mo targets
Disadvantages	Unproven technology Concerns about the reliability of sustained operation of very high power accelerators [11] New processing facilities would be required Radioactive waste
Assessment	Feasible but expensive as would require new, dedicated accelerators and processing
Transmutation	
Technology	The ^{100}Mo(γ,n)^{99}Mo reaction can be achieved by photo-conversion of a high energy electron beam, much as in the photofission option [13]
Capacity	The estimated capacity is 7,000–11,000 GBq per week and it is possible that one accelerator could supply the UK market
Cost	$100 million per accelerator
Timeline	5–8 years
Advantages	No radioactive waste
Disadvantages	Unproven technology Enriched targets required because the natural abundance of ^{100}Mo is only 9.6% Low specific activity may require new generator design and breakthrough may be a problem [5] (same problem as neutron activation) May require reformulation of kits
Assessment	Expensive as would require dedicated accelerators Being explored at CERN

Direct production of ^{99m}Tc by cyclotron

2.27 In addition to these well-described processes, direct production of ^{99m}Tc in a cyclotron, which was first described in 1971 [15], is being re-evaluated. This technology would be based on the ^{100}Mo(p,2n)^{99m}Tc reaction, which can be performed in current medical cyclotrons (around 10 MeV), although it is more efficient at somewhat higher energies (24 MeV) [15–18]. This approach relies upon the availability of enriched ^{100}Mo which is not yet commercially available. The Canadian government has funded a consortium of universities to explore ^{99m}Tc production using existing medical cyclotrons. Preliminary results have shown that ^{99m}Tc can be produced and that the resulting product behaves similarly to generator-produced ^{99m}Tc in labelling a range of kits used in nuclear medicine investigations [19].

2.28 Published yields from Takacs et al [17] and reported operational beam current data from the ACSI cyclotron indicate that it may be theoretically possible to produce all of the ^{99m}Tc required per day in the UK from two cyclotrons. Similar calculations have been obtained from Canada where preliminary work has been done. The cost of the 200 mg enriched ^{100}Mo target would be about $500 and it could be recycled. These estimates are supported in the publication by Guerin et al [19].

2.29 For reasons of both capacity and distribution, a network of cyclotrons would be required; however, this could be synergistic with positron emission tomography (PET) radionuclide production. Although a network of medical cyclotrons exists, they operate at lower energy than would be optimal for ^{99m}Tc production and most do not currently handle solid targets such as would be required for this route. Solid targets involve physical transfer of the target out of the cyclotron, dissolution, recovery of ^{100}Mo and purification of ^{99m}Tc, although we have many decades of experience in separating ^{99m}Tc from Mo.

2.30 One limitation of this route is the co-production of ^{99}Tc which could require the reformulation of radiopharmaceutical kits [12].

2.31 This is a very different model from those proposed for production of ^{99}Mo and is more akin to the supply of fluorine-18-labelled fluorodeoxyglucose (^{18}F-FDG), requiring immediate transport to a local region with the associated ongoing cost of daily transport.

Risks of unproven technology

2.32 While new technology may be attractive, development of existing established technology by experienced companies has not been without expensive and problematic issues and enthusiasm for new solutions should be tempered by these experiences.

2.33 MAPLE (Multipurpose Applied Physics Lattice Experiment) was a dedicated isotope production facility jointly developed by Atomic Energy of Canada Limited (AECL, a crown corporation) and MDS Nordion (a private company, formerly part of AECL). It was intended to include two identical 10 MW reactors, as well as the isotope processing facilities necessary to produce a large portion of the world's medical isotopes, in particular ^{99}Mo, ^{133}Xe, ^{131}I, cobalt-60 (^{60}Co) and iodine-125 (^{125}I). It was expected to replace the ageing NRU reactor. Construction began in 1997 and commissioning began in 2000, but technical problems started to emerge, and licensing and financial obstacles followed. In 2009 the Canadian government decided to mothball the project. There are still differing opinions as to whether MAPLE could be resurrected, and the cancellation is the subject of a lawsuit. However, the MAPLE project demonstrates the risks associated with over-reliance on a small number of plants and the expectation that this facility, had it proceeded to plan, would have provided the solution to the current challenges in ^{99}Mo supply internationally.

2.34 OPAL (Open Pool Australian Lightwater) was commissioned in 2006. Its design was based on the RA-3 reactor in Argentina and it uses LEU fuel and targets. RA-3 has been running for more than 40 years, switching to LEU fuel in the 1980s and LEU targets in 2002 [1]. This proven technology was expected to supply Australia and the Asia–Pacific region, followed by a ramping up of production for export to America. The manufacturer Lantheus has signed a supply agreement and has obtained approval from American and Canadian authorities to use Australian ^{99}Mo in its generators. However, OPAL has faced numerous operational problems, the ramp up of production has been very slow, and it is not yet exporting ^{99}Mo.

Other constraints on generator production

2.35 While most international high level concern has focussed on the small number of reactors producing ^{99}Mo, those within the nuclear medicine community have appreciated that the next link in the chain, generator loading, is also highly specialised and limited to a very few locations worldwide (see Table 2.6).

Table 2.6 Sites of large-scale generator production

Manufacturer	Location	Supply
GE Healthcare	UK	World
Covidien	The Netherlands	Europe
Covidien	USA	USA/Canada
IBA/CisBio	France	Europe
Lantheus	USA	USA/Canada
Fujifilm Pharma	Japan	Japan
NTP	South Africa	Africa/Asia
ANSTO	Australia	Australia/Asia

2.36 These relatively few facilities are not in the main co-located with the ^{99}Mo production sites and, as a result, there is significant loss of ^{99}Mo activity through decay during transport from sites of production/processing to generator loading. Cross-border issues can also result in problems. At present, the only major international generator producers co-located with their primary source of ^{99}Mo are Covidien and IBA/CisBio. (MDS Nordion formerly produced generators close to the NRU but stopped some years ago.) Proposals for more widespread but lower activity production of ^{99}Mo will have to be coupled to generator loading without excessive losses due to decay during transport.

2.37 Possible alternative generator technologies may offer solutions, including the Molyfill concept of a ^{99}Mo cartridge which the end-user would insert into a reusable generator. The cartridge would be easier to manufacture and ship than current generators. This is under development by Draximage and expected to be available by 2013.

Costs

2.38 It is extremely difficult to quantify the actual cost of ^{99}Mo production in a research reactor. The US NRC Committee report dealt with this in some depth and reported an average price of US$225 per 6-day curie (i.e. allowing six days from production to use) [1], although the relationship of this price to actual production costs is uncertain. Recently the Organisation for Economic Cooperation and Development (OECD) has released a comprehensive report on the economics of the ^{99}Mo supply chain which estimates a price of €295 per 6-day curie [4]. It should be noted that within the UK, the unit most commonly used to describe radioactivity is the becquerel (where 1 curie = 37 GBq).

2.39 The cost of ^{99}Mo is a significant contributor to the pricing of ^{99}Mo/^{99m}Tc generators to hospitals but there are many other factors, not least of all market forces. For many years it has been felt that manufacturers were using generators as a 'loss leader' in order to stimulate sales of radiopharmaceutical kits which are much more profitable. In some cases the two types of products were bundled together at a special price. Most manufacturers offered substantial discounts from their list prices, and some claimed to be losing money on generators, particularly when ^{99}Mo prices increased during shortages. In response to recent shortages, most manufacturers are now selling generators at list price and this has had an enormous impact on costs to hospitals, with generators increasing two or three fold in price. Discontinuation of discounting would appear to be the true reason for increased costs, with list price rises over the past five years being close to zero.

2.40 While any increases in costs are worthy of concern, it is important to put these into perspective. There is no direct connection between the cost of ^{99}Mo production and the total cost of a nuclear medicine investigation. It has been estimated that the radiopharmaceutical comprises only 5–10% of the cost of

the complete test [4,5]. Thus, a three-fold increase in the cost of ^{99m}Tc would translate into a 20% increase in the cost of the test.

2.41 The relative cost of ^{99m}Tc radiopharmaceuticals and ^{18}F-labelled tracers for PET is also a consideration. If the average component cost of a routine ^{99m}Tc agent is approximately £15, the minimum cost of ^{18}F-FDG or ^{18}F-fluoride at £150–£200 is at least ten times higher. However, it has been suggested that a five-fold increase in the cost of ^{99m}Tc would eliminate its cost advantage over PET, although many other factors would come into any decision to move to PET-based tracers [5].

Summary

2.42 The production of ^{99}Mo/^{99m}Tc generators for use within a hospital radiopharmacy involves many complex processes. Conventional production of ^{99}Mo is currently achieved through a small network of ageing research reactors. The supply of ^{99}Mo remains unstable.

2.43 There are plans to upgrade or replace some existing reactors but the production of ^{99}Mo from these reactors is not likely to start for a minimum of five years. A variety of alternative routes to production of ^{99}Mo and the direct production of ^{99m}Tc from a cyclotron are being evaluated, but much of this technology is unproven. These production methods are unlikely to be available within the next five years or more and, even if they are adopted, they are unlikely to be economically viable.

2.44 Moving to nuclear medicine services that use PET radiopharmaceuticals is likely to be uneconomic when considered against the current pricing structures of ^{99m}Tc-based services.

2.45 The planned closure of the NRU reactor in 2015 highlights the need for a robust European plan of action for a sustainable supply of ^{99}Mo.

Chapter 3

Preparation of Technetium-99m Radiopharmaceuticals in Hospitals

Introduction

3.1 Within the UK, most hospital radiopharmacies receive ^{99}Mo/^{99m}Tc generators on a weekly or twice weekly basis. Traditionally, generators are eluted each morning and the ^{99m}Tc obtained is used to prepare a variety of ^{99m}Tc-labelled radiopharmaceuticals by reconstituting kit vials. Most of these products have shelf-lives of six to eight hours after labelling and thus can be produced in a single batch per day; however, some require more immediate use. Preparation of ^{99m}Tc radiopharmaceuticals must be performed in an aseptic environment, generally in a laminar airflow hood or pharmaceutical isolator (glove box) located within a cleanroom.

3.2 The production model used for the manufacture of radiopharmaceuticals varies across the UK. These models have often developed from workload and staffing availability. In the past making the most efficient use of ^{99m}Tc was not the primary driver for the choice of production model.

3.3 The fact that service levels have been maintained despite recent shortages suggests that many hospitals have historically ordered generators of higher activity than they actually required. When ^{99}Mo was seemingly in abundant supply there was no incentive to optimise use.

3.4 Throughout the recent shortages of ^{99}Mo, nuclear medicine departments and radiopharmacies across the UK have adapted their practices to maximise the availability of ^{99m}Tc. Some of the proposals discussed in this chapter may already be in place in UK departments.

Optimising the use of generators

3.5 The design of ^{99}Mo generators has essentially enabled a simple traditional working pattern to develop. This would involve the delivery of a single generator per week and a single production session around one elution of the generator per day. While this has some economic and logistical advantages, this model may not be appropriate during current shortages and in future when costs may increase. Alternative strategies centre on generator size, frequency of delivery and elution.

Establishing minimum generator size requirements

Single generator, single elution daily, weekday working

3.6 The size of generator ordered is determined by the ^{99m}Tc activity requirements on the last day of use. This leads to an inevitable surplus of ^{99m}Tc on the days prior to the last day. This can be resolved in part by booking high activity investigations at the time when most activity is present in the department, but this may not always be possible for clinical reasons. The calculated efficiency of use of the generator varies slightly throughout the week depending on the day of generator production and the delivery schedule. However, it is clear that using a single generator per week with a 9 am – 5 pm weekday working pattern and current delivery schedules make inefficient usage of ^{99m}Tc: only about 50% of the available ^{99m}Tc is used.

3.7 Efficiency calculations can be used to determine the optimum delivery schedule for multiple generators per week. Some generator delivery schedules offered in the UK have been changed to improve the

average percentage utilisation of ^{99}Mo. This has advantages for both the generator manufacturers and their customers. However, further efficiency could be gained if the generator is delivered in time for first use on the day following production.

Two generators, single elution daily, weekday working

3.8 In place of one large generator, it may be more efficient to receive two generators per week with overlapping activity reference dates. This reduces the variation in daily activity of ^{99m}Tc eluted and thus a greater percentage of the available ^{99m}Tc will be utilised. It also reduces the amount of ^{99}Mo required by the manufacturer and spreads the demand through the week, although the total amount of ^{99}Mo required per week is not reduced appreciably. Purchasing two generators per week allows the option of obtaining generators from different suppliers, making the supply chain more robust, although there may be cost implications if generators are bundled with other products. There are also technical issues to address if more than one supplier is used as the physical dimensions of generators are not consistent among suppliers. The generator must be located in a shielded, aseptic environment and in many existing radiopharmacy units this is not readily adapted to different generator shapes. The optimal generator activity will depend on the generator production/reference day schedule.

Possible no-cost option: keeping the generator for a second week

3.9 Many customers return a generator on its reference day, long before its expiry. Keeping the generator for an extra week provides an additional 17% yield of ^{99m}Tc activity at no cost. However, there must be capacity for safe storage and elution of an additional generator. The Environment Agency permits/registrations for ^{99}Mo and depleted uranium (used as shielding in some generators) would have to be checked to ensure compliance. There may be costs associated with variation of Environment Agency permits/registrations.

Maximising elution yields

3.10 In most radiopharmacies in the UK the generator is eluted once per day. However, it is possible to re-elute after a few hours and receive a partial yield, although this reduces the next morning's yield somewhat. By modelling elutions at various times, an optimal time for re-elution and an overall reduction in generator activity can be determined [20]. Any financial savings made from reducing generator activity would have to be partially offset against the staffing and kit costs of a second production session.

3.11 The intentional use of multiple elutions on lower activity days has a significant impact on the operation of a radiopharmacy. The use of a single production session in the morning allows staff to move on to other responsibilities for the rest of the day. Multiple elution models may hinder this and can also result in less efficient use of kits and additional costs for microbiological monitoring.

Optimising production of ^{99m}Tc radiopharmaceuticals

Unit dose production

3.12 Most radiopharmaceutical kits are reconstituted in multidose vials. They can be supplied to the hospital as such or, alternatively, individual unit doses can be supplied in syringes or unit dose vials.

Advantages of unit dose

a *Most convenient for end-user* This is a very popular mode of supply in America where most of the commercial central radiopharmacies operate as unit dose suppliers. There is no excess activity on site. The radiopharmacy often takes back radioactive waste as well.

b *Traceability* Each syringe shield is labelled with a unique serial number which can be traced back to the production records in the event of an adverse incident.

c *All doses dispensed in an aseptic environment* Other areas within pharmacy are moving in this direction in accordance with guidance from the National Patient Safety Agency [21].

d *Reduces extremity radiation dose to nuclear medicine staff and reduces risk of radioactive contamination in nuclear medicine department* Less manipulation is required by nuclear medicine staff. The potential for radioactive contamination due to spillage/splashing is greatly reduced.

e *Makes most efficient use of available ^{99m}Tc* There is no need to allow extra volume in a vial in case doses are dispensed by inexperienced operators.

Disadvantages of unit dose

a *High extremity radiation doses to radiopharmacy staff* This is an extra process resulting in additional exposure. The time spent in adjusting doses contributes to this exposure. With multidose vials this radiation dose is shared among the staff preparing injections in the nuclear medicine department. Automated dose drawing devices are available but are slow and inaccurate for small volumes.

b *Loss of flexibility for end-user* For example, it would not be possible to adjust the administered activity for a patient's weight/body surface area in order to optimise count density and dosimetry. Additionally, if a patient arrives late or a study is delayed due to a camera being occupied or malfunctioning there is no leeway for increasing injection volume to account for the decay which has occurred.

c *Delays in obtaining extra doses* Extra doses or emergency requirements would have to be ordered from the central radiopharmacy, prepared, and then transported to the destination hospital. This may not be possible for all sites.

d *Potential stability issues* Doses in syringes could potentially be exposed to air which could result in oxidation, but this does not seem to be a major problem.

e *Losses in activity due to sticking to syringe/loss of activity in unit dose vial* Some products tend to stick in some brands of syringes, reducing the activity which the patient receives. Similarly, unit dose vials must have enough extra activity to account for losses in dead volumes and sticking to the vial and septum.

3.13 The supply of multidose vials has advantages in convenience, traceability and some degree of flexibility for the end-user. However, multidose vials require appropriate facilities and training for staff dispensing individual patient injections. Delays in obtaining extra doses and losses of activity sticking in vials are common disadvantages for multidose vials.

3.14 Although there is little direct evidence, it is felt that the most efficient and flexible distribution of ^{99m}Tc radiopharmaceuticals happens in centralised radiopharmacies because they can most efficiently match the timing of generator delivery to radiopharmaceutical demand. Large, centralised facilities receive a number of generator deliveries staggered throughout the week and have a large complement of staff to process materials and manage operations. This allows them to produce and distribute radiopharmaceuticals to a number of hospitals in either multidose vials or as single doses. Most nuclear medicine departments in smaller centres do not have access to a central radiopharmacy and, by necessity, prepare their own radiopharmaceuticals. Smaller nuclear medicine departments receive only a single generator from a single source weekly and, as a result, are far more vulnerable to a disruption in supply [22].

Challenges of centralisation of radiopharmacies

3.15 There are two types of challenges in centralisation of supply – logistical and regulatory/financial issues. The easier to address are the logistical issues. Many of these have been addressed on a smaller scale and would only require to be scaled up. The more difficult challenges are regulatory and financial, due to the involvement of multiple regulatory authorities and multiple healthcare institutions.

3.16 In 1996, Callahan estimated that 70–80% of radiopharmaceutical doses in the USA were supplied from central radiopharmacies, most of them commercial [23]. However, the economics are different in the UK. There have been only two commercial radiopharmacies in the UK, one of which has ceased to operate. The American chains have looked closely at the UK market but found it to be unprofitable, largely due to the level of regulation. There are some commercial radiopharmacies in other parts of Europe, but to a much lesser extent than in the USA.

3.17 Many central radiopharmacies in the UK were established 20–30 years ago for economic reasons. However, the situation has changed dramatically since then, with loss of crown immunity, tightening of regulatory controls and cost increases. Thus, old financial models may no longer apply. It is extremely complicated to work out the cost of operating a radiopharmacy. Charges to customers are generally based on historical models and zero-based budgeting has rarely been applied. Central hospital-based radiopharmacies are not supposed to make a profit from NHS customers. This should be contrasted with the requirement for full economic costing.

3.18 While there can be economies of scale in group tendering, there is also a need for flexibility to address individual requirements. In the past many NHS Trusts have created framework agreements and purchased through OJEU tenders processed either in house or by procurement hubs*. This results in common prices within specific districts or areas. However, a coordinated approach is becoming more difficult with the introduction of Foundation NHS Trusts where conflicting business models may apply.

Advantages of central radiopharmacies

a *Makes most efficient use of available ^{99m}Tc* The radiopharmacy generally has two or more generators delivered per week with different reference dates. This ensures a consistent amount of available activity and thus does not impose restrictions on which studies can be performed on certain days throughout the week.

b *Economies of scale in purchase and use of kits* In particular, it allows economic use of more expensive multidose vials.

c *Consistent quality of preparation in experienced centre* The radiopharmacy has full-time specialist staff who are not called away to other duties. This also allows multiple production sessions per day.

d *Capital costs minimised* There would be fewer centres requiring specialist facilities. Radiopharmacies are extremely expensive to build, with filtered air handling and radiation shielding requirements.

e *Smaller total number of specialised staff required* There is a shortage of radiopharmaceutical scientists due to an ageing workforce and lack of career pathway to attract new graduates.

f *Security of continuity of supply* Through purchase of generators from multiple suppliers.

g *Prioritised generator supply to central radiopharmacies* This should lead to most efficient use of available ^{99}Mo.

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* The OJEU (Official Journal of the European Union) is the journal in which all tenders from the public sector that are valued above a certain financial threshold, according to EU legislation, must be published.

Disadvantages of central radiopharmacies

a *High extremity radiation doses to radiopharmacy staff* This could be reduced by introduction of automation which may be economically feasible in a smaller number of specialist centres.

b *Reduced quality of life for central radiopharmacy staff* Due to early start – this could lead to problems in recruitment and retention of staff.

c *Loss of scientific role of radiopharmaceutical scientist* As provision becomes primarily a technical service, although this would probably be more of a problem in the commercial sector. Within the NHS the scientific role would remain, particularly if large radiopharmacies were located within clinical and research environments.

d *Dependence upon transport* Transport introduces a source of uncertainty due to traffic conditions and reliance upon the availability of trained drivers and equipped vehicles.

e *Ongoing cost of daily transport* There is a trade off between the timeliness of delivery and the number of vehicles and drivers. This could require multiple deliveries per day depending on workload and emergencies.

f *Decay during transport* ^{99m}Tc decays by 10% per hour. The dispensed activity must account for losses before the doses arrive at the destination hospital.

g *Loss of portion of shelf-life during transport* This is more significant for products with the shortest shelf-lives as a substantial portion of this time could be lost before arrival at the destination hospital. Extended shelf-lives can be validated but the responsibility in the event of an adverse incident then rests with the radiopharmacy rather than the kit manufacturer.

h *Limit in transport radius* Logistics (including the above factors) will limit how far it is feasible to transport products.

i *Delays in obtaining extra doses* The transport time will have to be taken into account when extra or urgent doses are required. This may not be possible for all sites.

j *Greater impact of equipment failure at central radiopharmacy* If there is no local back up, a failure in air handling would affect a large number of hospitals. Microbiological contamination or a radiation spill could have a similar effect.

k *Loss of radiopharmaceutical expertise in the wider community* Although consultant radiopharmaceutical scientists would be available in the central radiopharmacy there would be less access to local expertise. This can also be a limitation for training programmes in nuclear medicine technology, medical physics, and specialist medical registrars in nuclear medicine and radiology.

l *Fewer alternatives for back-up supply* This is less catastrophic than the unit failure mentioned above, but could include shortages of a particular product or occasional failure of a generator.

m *Limitations on weekend supply* Individual hospitals would have to negotiate with the central radiopharmacy for weekend or extended hours' supply.

n *Low priority* Specialist centres with their own radiopharmacy may be restricted in their operations if larger central radiopharmacies are given priority for supply of generators.

o *Access to procedures* Services that require direct radiopharmacy involvement as part of the procedure (e.g. gastric emptying, blood labelling or denatured red cells) may be limited at remote sites due to the unavailability of trained staff and a lack of specialised facilities. However, arrangements can be made for provision of some of these services, such as sending trained staff to remote sites or transporting blood to the radiopharmacy for radiolabelling.

Review of current UK situation

3.19 There are currently approximately 200 nuclear medicine departments in the UK. There are about 100 radiopharmacies, comprising 50 licensed and 50 unlicensed units. Therefore, 50 hospitals have their own unlicensed radiopharmacies (which tend only to supply internally) and 150 hospitals obtain their radiopharmaceuticals from centralised radiopharmacies at their own or distant locations. From these figures, it appears that three-quarters of UK hospitals already receive their radiopharmaceutical supply from a central radiopharmacy. However, the degree of 'centralisation' can differ from one unit to another; a radiopharmacy which supplies only one other nuclear medicine department with a single gamma camera would still be defined as a 'central' radiopharmacy. This should be contrasted with the small number of very large radiopharmacies in the UK which supply several nuclear medicine departments with multiple gamma cameras in each. The economies of scale and resilience in times of ^{99}Mo shortages will be markedly different between these two types of 'central' radiopharmacy.

3.20 Preliminary analysis has shown a variation in the degree of centralisation of radiopharmacies across the UK. Within Scotland, Wales and Northern Ireland there are large central radiopharmacies supplying multiple sites and very few 'single-centre' radiopharmacies. Within England, however, the picture is very different where nearly half of all central radiopharmacies supply themselves and only one additional site. In England there are very few radiopharmacies that supply more than five additional sites. Approximate figures for the whole of the UK are shown in Table 3.1 below.

Table 3.1 Central radiopharmacies in the UK

Central radiopharmacy supplying	Percentage (%)
<5 sites	74
5–9 sites	18
10 sites or more	8

3.21 Within England there may be scope for further centralisation of radiopharmacy services. A network of super central radiopharmacies could supply radiopharmaceuticals to the whole of the UK. The advantages and disadvantages of central radiopharmacies have already been considered. If the total number of radiopharmacies in England was to be reduced, then the time taken to transport prepared radiopharmaceuticals to nuclear medicine departments will inevitably increase in some cases. This has implications for radiopharmaceuticals with a short shelf-life – for some products this can be less than one hour. This could be overcome by co-locating the radiopharmacy within central NHS facilities with large clinical nuclear medicine departments. In addition, there may be a requirement for some centralisation of nuclear medicine services for the delivery of some investigations that require direct radiopharmacy involvement.

Previous experience with pharmacy centralisation in the NHS

3.22 As well as the advantages and disadvantages listed, previous experience of centralisation of pharmacy services should be taken into account. Following years with a lack of investment in many pharmacy licensed 'Specials' units in the NHS the Department of Health undertook a risk assessment exercise to quantify the unlicensed medicinal products manufactured in the NHS in 2002. As a result, a further £42 million (£4 milion had already been invested) was to be made available in England to modernise 'traditional' manufacturing within the NHS. This process was implemented by a national board, working in association with several multidisciplinary local groups. The capital was allocated to improve facilities and equipment for pharmacy production and associated quality control. Radiopharmacy departments were excluded from bidding for this funding as they were not considered 'traditional'.

3.23 The aim of the Modernisation of Pharmacy Manufacturing initiative was to provide a national, coordinated network of licensed hospital manufacturing lead and support units [24]. This would provide a 'joined up' hospital pharmacy manufacturing service based on an up-to-date product profile, clinical governance principles and assessment of patient needs.

3.24 The rebuilding and/or re-engineering of units that achieved successful bids was much slower and less coordinated than expected. Between the financial years 2004/5 and 2005/6, 40 units had spent allocations ranging from £20,000 to £3,020,000. With the introduction of Foundation NHS Trusts in the intervening period between bids being announced and building work actually commencing, new Foundation NHS Trust Boards identified differing priorities both financially and strategically. This led to the closure of a number of brand new and modernised facilities in 2008/9.

3.25 The success of the modernisation initiative is mixed in that the objectives were only partially met and rationalisation of manufacture of medicinal products across the sector has not been fully achieved.

Summary

3.26 Within the UK there are a number of different models of radiopharmaceutical production and supply. The majority of nuclear medicine departments in the UK receive their radiopharmaceuticals from small 'central' radiopharmacies. These are generally received as multidose vials or unit dose vials or syringes.

3.27 In order to make more efficient use of the ^{99}Mo available, different radiopharmaceutical production models may have to be considered, e.g. a second elution and production run per day. These changes will have staffing cost implications, which are considered in further detail in Chapter 5.

3.28 Based on current working practices, the generator delivery schedules offered by manufacturers in the UK do not support optimal use of ^{99}Mo and ^{99m}Tc.

Chapter 4

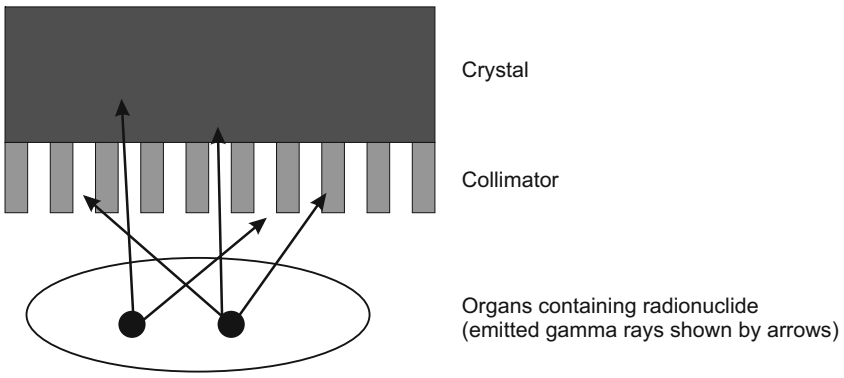
Making the Best Use of Available Activity within a Nuclear Medicine Department – Technology Issues

Introduction

4.1 Nuclear medicine imaging follows the administration of a radiopharmaceutical to the patient. Imaging may start at the same time as the administration, or after a period of time to allow for adequate uptake in the organ of interest. The gamma rays emitted by the radionuclide are detected by a crystal within the gamma camera and an image of the distribution of the radioactivity is built up.

4.2 Because the gamma rays are emitted from the patient in all directions a collimator is used to acquire an accurate image of their distribution. In gamma cameras, the collimator is generally made of lead or tungsten with a honeycomb of holes which allow the desirable gamma rays to pass through. Gamma rays which are not coming orthogonally from the patient are absorbed by the collimator and eliminated from the final image. This is illustrated in Figure 4.1. The type of collimator selected may vary depending on the imaging technique and the radioisotope administered to the patient. A collimator with small holes will provide better resolution but has lower sensitivity as it absorbs more of the emitted gamma rays. A collimator with larger holes is more sensitive (as it allows more gamma rays to be detected) but has poorer resolution. The exact characteristics of each collimator will vary depending upon how it has been manufactured. In nuclear medicine there is always a trade off between resolution and sensitivity. When imaging with ^{99m}Tc, most gamma cameras will use one of two types of collimators; low energy high resolution (LEHR) and Low energy all purpose (LEAP) (also referred to as low energy general purpose or LEGP). A range of other collimators does exist for use with ^{99m}Tc (e.g. low energy high sensitivity) but these are less commonly purchased.

Figure 4.1 Schematic of a gamma camera



4.3 A key challenge for nuclear medicine is to detect an adequate number of gamma rays in order to acquire an image that contains enough information for accurate diagnosis while keeping the radiation dose to the patient as low as reasonably practicable. This can be achieved as follows.

a *Imaging for a longer time* For procedures where the distribution is fixed, this is possible within the limits of the patient's ability to lie completely still (typically imaging times which exceed 30 minutes are prone to patient motion). This is not possible for some procedures where the distribution within the organ may be changing during image acquisition (showing the changing distribution of radionuclide within an organ is a key component of some studies).

b *Administering more radioactivity to the patient* This is not desirable as it results in an increased radiation dose to the patient. This also requires additional activity which may not be possible in times of shortages.

c *Changing the collimator to one with a higher sensitivity* Unfortunately this reduces the resolution of the image. For some procedures this is more critical than for others. In practice, the collimator choice depends upon the organ being imaged and the type of imaging.

4.4 In the UK, the administered activities in general use are lower than those in most other countries. Aided by guidance from ARSAC and complying with the Ionising Radiation (Medical Exposures) Regulations 2000 (IR(ME)R) [25] , nuclear medicine departments have always strived to optimise the dose to patients. The ARSAC Notes for Guidance [26] provide diagnostic reference levels (DRLs) for nuclear medicine studies consistent with the principle of administering the lowest amounts of ^{99m}Tc to obtain a diagnostic quality image. With conventional hardware and software there has been little scope to further reduce administered activities.

4.5 Throughout the recent shortages of ^{99}Mo/^{99m}Tc, nuclear medicine departments are facing the challenge of continuing to offer a service which provides the same good quality images with less available ^{99m}Tc. Where conventional imaging systems are used, it has not always been possible to offer all patients appropriate procedures and these have been delayed or postponed, or other imaging procedures substituted.

4.6 New software and hardware options are now available which offer potential solutions to these problems. In the past five years, manufacturers have developed a range of hardware and software products which can change the current balance between image quality, administered activity and scan time. Before the problems of ^{99m}Tc supply emerged, most manufacturers developed and marketed these products with the intention that image quality would be maintained or improved, administered activities would remain unchanged and scan times would be reduced. This would improve the efficiency and cost effectiveness of the nuclear medicine service by allowing more patients to be imaged within the working day. These products may, however, offer the potential to maintain image quality and scan times while reducing the administered activity to the patient. This has a positive impact on patient radiation dose but may also help nuclear medicine services use the available ^{99m}Tc more effectively, ensuring that costs are reduced and procedures undertaken as required.

Software solutions – resolution recovery technique

4.7 Resolution recovery software was developed to improve image quality in single photon emission computed tomography (SPECT) nuclear medicine studies. To acquire SPECT images the gamma camera rotates around the patient acquiring a series of images at a number of angles. Typically a 360° rotation is used with angular steps of 3–6°. The acquired images are reconstructed into a series of transaxial slices which are combined to produce a three-dimensional dataset showing the distribution of radioactivity throughout the patient's body. Additional cross-sectional images can be generated from the reconstructed three-dimensional dataset.

4.8 There are three different methods routinely used to reconstruct SPECT images: filtered back-projection (FBP) and two- and three-dimensional iterative reconstruction (2D-IR and 3D-IR). A detailed description of each reconstruction method is not discussed in this report but can be found elsewhere [27].

4.9 FBP was the standard reconstruction method used across the UK for many years. Image reconstruction is fast and processing times reduce significantly with increasing computing power. However, the amplification of noise is inherent in the FBP reconstruction method and artefacts can be introduced (apparent reduced radionuclide concentration in objects adjacent to those with high tracer concentration). The type of image filter used must be chosen carefully.

4.10 Both iterative reconstruction methods have longer image reconstruction times than FBP, with 2D-IR faster than 3D-IR. Image quality is improved and the method deals well with image noise. 2D-IR is widely used in the UK and 3D-IR is now available. The reconstruction algorithms used in iterative reconstruction model the acquisition process which allows the user to accurately correct for the effects of attenuation and scatter. Using 3D-IR an additional correction can be made for the variation in resolution with depth, this is known as resolution recovery.

4.11 Resolution recovery uses known collimator characteristics to identify which gamma rays are likely to have been absorbed or scattered and replace these in the final image, thus improving image resolution. While maintaining image quality, resolution recovery can be used either to reduce image acquisition times or to reduce the administered activity to the patient. The majority of resolution recovery software packages were developed to produce a good quality image in a shorter time. The concept of reducing activity administered was initially thought to be lower priority but in the context of a limited supply of ^{99m}Tc, it is of more interest.

4.12 In theory, the combination of resolution recovery software and a higher sensitivity collimator such as LEAP could give the resolution of a higher resolution collimator (increasing the number detected counts by a factor of approximately 1.6). Some manufacturers/papers have looked at the use of resolution recovery with high resolution collimators and suggested resolution recovery can also be used with these collimators to improve image quality, reduce imaging time or reduce the administered activity [28–32].

4.13 All major manufacturers have resolution recovery packages.

a Some are linked to specific camera/collimator combinations. These have potential advantages in terms of factory programmed collimator characteristics and minimal user set-up. However, multi-camera departments with different manufacturers' cameras would need a resolution recovery package for each system which is more costly.

b Some are marketed for specific studies, e.g. bone. These systems are set up for a specific acquisition and have been tailored to maximise results and have been formally evaluated and validated for this purpose. The disadvantage is that users need a different resolution recovery package for each procedure, which leads to increased costs. Use on a wider range of studies is not known or validated.

c Some resolution recovery options are independent 'generic' packages which can be used with any gamma camera. These have the advantage of being able to take data from different manufacturers' gamma cameras (as long as the collimator characteristics are specified by the gamma camera manufacturer). For multi-camera departments one single generic package may be used for all applications. As with the camera-specific packages, some generic resolution recovery options are tailored to particular procedures, others are validated for widespread use. Older versions of resolution recovery software require scientific input (including measurements within the department) to establish collimator parameters and tailor the package to a specific department's equipment and procedures. More recent versions take information provided by the gamma camera manufacturer.

d For all packages, there are a number of parameters that can be modified by the user and, without a rigorous and scientific approach to implementation, results could be poor.

e All resolution recovery packages have been validated for use by the manufacturers, and a number of publications have been written showing benefits in a clinical setting [28–32]. Many departments have seen the technique as a useful tool for improving quality but few have used it to implement a reduction in imaging time or administered activity (other than in difficult clinical situations where patients are unable to comply with the scan). The routine use of resolution recovery as a tool to allow reduced acquisition time or administered activity has not gained widespread acceptance within the UK.

4.14 There are a number of concerns and unknowns about the routine use of resolution recovery software, as follows.

- **a** The software packages may operate in different ways (some more akin to filters than actual resolution recovery).
- **b** Are the results from generic packages as good as those system-specific packages?
- **c** Are results from resolution recovery (following reduced dose or time) comparable with standard images?
- **d** Does resolution recovery introduce any artefacts?
- **e** The savings in terms of imaging time or administered activity have not been quantified.

4.15 To address these, ARSAC set up a subgroup in collaboration with the Institute of Physics and Engineering in Medicine (IPEM) Nuclear Medicine Software Quality Group (NMSQG) and Software Validation Working Party. The aims of this group were:

- **a** To establish what products are available in the UK, how they work, what is required in order to use them and what costs are associated with each product.
- **b** To evaluate at least one of the available products, as a pilot study, to establish whether resolution recovery can maintain or improve image quality, and hence image interpretation, and compensate for a reduction in administered activity, when compared to conventional imaging protocols. Details of the pilot study are given in paragraph 4.25. The results from the pilot study will allow an assessment of the value of a more comprehensive UK study.

4.16 A UK-wide study would provide evaluation of the full range of products and also allow a range of nuclear medicine departments across the UK to participate, providing widespread participation which will encourage departments to gain experience with resolution recovery and to adopt reduced activity techniques.

Resolution recovery products available

4.17 The subgroup contacted the applications specialist within each of the companies known to supply resolution recovery software in the UK to establish:

- **a** The range of software available and whether it is generic or manufacturer specific.
- **b** The range of studies that the software can be used on.
- **c** Hardware and software requirements including minimum system specifications.
- **d** Limitations on acquisition parameters (e.g. camera or collimator choice, radionuclide).
- **e** Limitations on image processing (e.g. attenuation correction(AC), use of normal databases).
- **f** Details of the resolution recovery algorithm used.
- **g** Performance of the system (processing time).
- **h** Whether the software is designed to reduce acquisition time or counts, reduce administered activity or change the collimator required.

4.18 A full summary of the information provided by the applications specialists is given in an annex to this chapter. Generic products are available from three companies: Hermes Medical, Scivis and UltraSpect. Camera-specific products are available from the three main gamma camera manufacturers that market equipment within the UK: Siemens, GE Healthcare and Philips.

4.19 Hermes Medical, Philips and Scivis offer a single resolution recovery software package that can be used on a variety of clinical studies. UltraSpect, Siemens and GE Healthcare offer multiple resolution recovery software packages which have been validated for use on specific types of clinical studies. It may be possible to use these packages on other types of clinical studies but this would need prior validation.

4.20 None of the resolution recovery software packages requires the user to make any practical measurements prior to implementation, although a knowledge of some gamma camera and collimator characteristics is required for the generic products.

4.21 The resolution recovery software provided by GE Healthcare can only be used on clinical studies with ^{99m}Tc and LEHR collimators. In contrast, all the other resolution recovery software packages can be used with a range of isotopes and at least one alternative type of collimator.

4.22 Each manufacturer offers at least one resolution recovery software package that allows the use of attenuation correction (AC). However, in most cases, this is limited to AC using CT rather than transmission sources such as gadolinium-153 (^{153}Gd).

4.23 Hermes Medical, Philips and Scivis resolution recovery software packages are designed to improve image quality, reduce projections, reduce time per projection, reduce administered activity or allow a change of collimator. Siemens software is designed to improve image quality, reduce projections, reduce time per projection or reduce administered activity but not to facilitate a change of collimator. The UltraSpect software is designed to improve image quality, reduce time per projection or reduce administered activity but not to reduce the number of projections or change the collimator required. GE Healthcare software is designed to improve image quality and to reduce the time per projection.

4.24 It is interesting to note that four of the available resolution recovery software packages can be used with planar imaging. Of these Scivis HiScan, UltraSpect Xact.bone and Siemens Oncoflash are aimed at improving image quality, reducing acquisition time or reducing administered activity, but are not aimed at improving resolution of a lower resolution collimator (e.g. LEAP) and allowing it to be used in place of a higher resolution collimator. By comparison, the Philips Astonish is designed to improve image quality or allow a change of collimator. It is not entirely clear how the software is applied to planar images.

Validation of the products available: pilot study

4.25 All manufacturers have software that can be applied to myocardial perfusion imaging (MPI). The diagnostic reference level (DRL) for MPI with ^{99m}Tc is 1600 MBq (for patients who have both stress and rest components of the study) and cardiac imaging is the second most common nuclear medicine investigation carried out in the UK [33]. Cardiac imaging contributes significantly to the use of ^{99m}Tc in the UK. If the activity administered for MPI could be reduced (halved) while maintaining image quality, it could offer significant savings of available ^{99m}Tc. A pilot research protocol was developed to validate the use of half-activity MPI using resolution recovery software.

4.26 The aim of the project was to validate the use of manufacturer's resolution recovery software for processing MPI obtained with half the standard counts to see whether it could replace the standard method.

4.27 The principal objectives of the pilot study were:

a To determine whether the interpretation of images obtained with half the normal administered activity and processed with resolution recovery software can be the same as the interpretation from that obtained with normal activity and processed in the standard way.

b To determine whether objective quantitative parameters calculated from gated images obtained with half the normal administered activity and processed with resolution recovery software are the same as those obtained with normal activity and processed in the standard way.

Method

4.28 The pilot study was carried out using GE Evolution for Cardiac resolution recovery software in the Central Manchester Nuclear Medicine Centre.

Patient study group

4.29 Stress and rest myocardial perfusion scans from 44 patients (15 male, 29 female) were performed on patients referred to the Nuclear Medicine Centre as part of their routine clinical investigation. The age range was 38 to 76 years (mean 63.1) in males and 40 to 80 years (mean 59.7) in females. The body mass index (BMI) range was 27.4 to 42.0 kg/m^2 (mean 33.6 kg/m^2) in males and 20.6 to 47.5 kg/m^2 (mean 35.0 kg/m^2) in females.

4.30 All patients were administered ^{99m}Tc-tetrofosmin with the prescribed activity scaled according to patient BMI in accordance with the department's normal policy. This scale increases the prescribed activity from 400 MBq in 20 MBq increments for every BMI point above 25 kg/m^2 to a maximum of 920 MBq for a BMI of 51 kg/m^2. Imaging was performed approximately 60 minutes post-injection.

Imaging protocol

4.31 Images were acquired on a GE Infinia Hawkeye 4 gamma camera using LEHR collimators. The standard SPECT acquisition was a 180° arc from the right-anterior oblique to left-posterior oblique (RAO to LPO) position with 60 projections, 30 seconds per stop (total scanning time: 16 min, 30 sec), 140 keV ± 10% energy window, 64 × 64 matrix with a zoom of 1.3 (6.8 mm pixel size). CT-based attenuation correction was performed using the Hawkeye CT in 32 of the 44 studies. All images were ECG gated with 16 time bins per cardiac cycle.

Image manipulation and reconstruction

4.32 Full-count and half-count data were derived from the 16-bin gated data. A full-count gated dataset with 8 time bins per cardiac cycle was produced by summing every pair of the 16 bins and the half-count images were produced by taking every other time bin from the 16-bin dataset and creating a half-count gated dataset with 8 time bins, which simulates halving the time per projection.

4.33 Raw projection data from the full-count acquisitions were transferred to GE Xeleris workstations for reconstruction with the standard reconstruction by the OSEM algorithm used in routine clinical service. The parameters were 2 iterations, 10 subsets and a Butterworth post-filter with a critical frequency of 0.3 cycles/cm and power 5. Reconstruction of the half-count images was performed using GE Evolution for Cardiac with 12 iterations, 10 subsets and a Butterworth post-filter of critical frequency of 0.35 cycles/cm and power 10.

Image comparison

Double reports

4.34 The half-count studies were anonymised and reported by the same clinician who reported the full-count study as part of the clinical service. The reports from the half-count images were compared with those of the full-count images. The comparison was scored as shown in Table 4.1.

Table 4.1 Scoring system used to compare reports

0	No difference
1	Minor difference; no enough to make a clinical difference
2	Clinically relevant difference that could affect patient management
3	Quality of half-count data is too poor to give a meaningful report

Quantitative left ventricular (LV) function analysis

4.35 Quantitative analysis of gated data was performed using the QGS software package. End diastolic volume (EDV), end systolic volume (ESV) and left ventricular ejection fraction (LVEF) were calculated for full-count and half-count data. Paired t-test and Bland-Altman analyses were performed.

Results

Double reports

4.36 For the 44 reports that were compared the scores are shown in Table 4.2.

Table 4.2 Double report comparison

Score	Number of reports
0	37
1	5
2	2
3	0

4.37 The two cases showing a clinically relevant difference between the two reports were examined in detail.

4.38 The first case showed significant breast attenuation visible on the raw projection images but no attenuation correction data were available for this study. The report of the full-count data decided that the antero-lateral reduction in counts could be explained by breast attenuation and concluded that the study was normal. The breast attenuation was less obvious on the raw projection data of the half-count study because of the reduced counts. The report described the same reduction in antero-lateral counts but was not convinced that this was completely explained by breast attenuation and therefore concluded that the study was probably abnormal. However, the extent was only 2 out of 20 segments, which would not have been sufficient to change patient management.

4.39 The second case showed a mild to moderate reduction in perfusion in the inferior wall at stress which partially normalised at rest on the full-count data. This was reported as ischaemia in 3 out of 20 segments with a superimposed attenuation artefact. However, on the half-count data there did not appear to be any difference between stress and rest and the perfusion defect was put down entirely to an attenuation artefact, therefore concluding that the study was normal. This represents a real difference in the two reports and the patient is being followed up to determine the ultimate outcome.

4.40 Therefore 1 out of 44 studies gave a report where the half-count data processed with resolution recovery would have led to a different patient management to the report from the full-count data processed in the normal way. This gives an average discrepancy rate of 2.3%. Using the binomial distribution the 95% confidence limits can be calculated as 0.1% to 11%.

Quantitative LV function analysis

4.41 Paired t-test results are shown in Table 4.3.

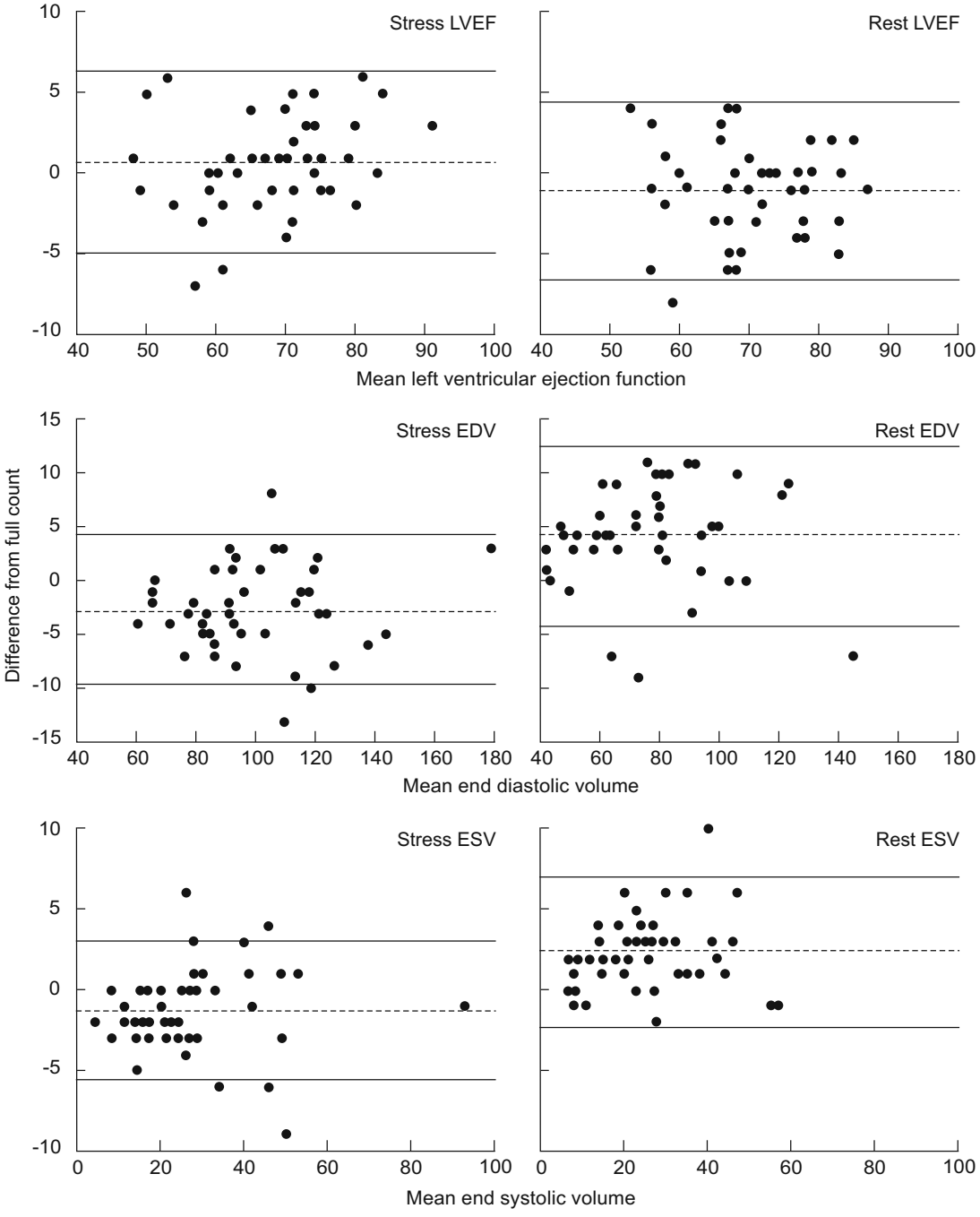
4.42 The data in Table 4.3 show that there is no significant difference in the LVEF values calculated from the full-count and half-count data at both stress and rest. However, the stress EDV and ESV calculated from the half-count data are significantly lower than those from the full-count data. The rest EDV from the half-count data is significantly higher than that from the full-count data.

4.43 Figure 4.2 shows the Bland-Altman plots for the data. The dashed line shows the mean difference and the solid lines show the 95% confidence limits.

Table 4.3 Paired t-test results

	Full count	Half count	p-value
Mean stress LVEF (%)	67.7	68.3	0.162
Mean rest LVEF (%)	70.3	69.2	0.016
Mean stress EDV (ml)	80.6	77.9	<0.001
Mean rest EDV (ml)	75.1	79.3	<0.001
Mean stress ESV (ml)	27.9	26.6	0.003
Mean rest ESV (ml)	24.0	26.3	<0.001

Figure 4.2 Bland-Altman plots



Conclusion

4.44 The results of the pilot study demonstrate that resolution recovery software solutions can play a significant role in making the best use of available ^{99m}Tc by producing images of accepted image quality from half the administered activity.

4.45 Similar results are required from other software packages before half-activity imaging protocols can be adopted as routine clinical practice. The methodology established in the pilot study could be developed to form a multicentre evaluation including data from multiple centres and comparing the software available from all manufacturers. A proposal for this work is outlined in Appendix A.

Traditional gamma camera technology

4.46 A variety of gamma cameras are available within the UK from a number of different suppliers. The British Nuclear Medicine Society (BNMS) Survey [33] provides data on the type and age of gamma cameras in nuclear medicine departments within the UK. In total during the reporting period (2009–10) 216 gamma cameras were identified from 109 sites (51% response rate). Age data were only specified for 203 of the gamma cameras identified. A full breakdown including camera age is given in Table 4.4.

Table 4.4 Gamma cameras reported within the BNMS Survey

		Age		
	Number	**<5 years**	**5–10 years**	**>10 years**
Gamma camera planar only	14	2	2	9
SPECT	152	44	63	36
SPECT CT	50	36	9	2

4.47 The age of the gamma camera is important in relation to the possible replacement with more efficient equipment and the upgrading of the system with resolution recovery software. It is understood that resolution recovery software can be applied to most cameras less than five years old. The upper replacement age of a gamma camera is considered to be ten years. Of the gamma cameras where the age was specified, 47 were ten years or older (23% of the gamma cameras where age was specified and 22% of the total cameras identified). The detection technology within most gamma camera systems has remained largely unchanged for the past 20 years.

Single head cameras

4.48 These cameras have a single detector, they can usually perform a range of planar and SPECT studies (some may be limited in terms of whole body imaging). Some have benefits in terms of a small footprint and flexibility of head movement and are useful for studies where only one head is required, e.g. MUGA studies. However, for departments performing whole body studies or SPECT, a single headed camera is much less efficient. Single headed cameras would be most likely to benefit large departments that already have other cameras but may use a small single headed camera for specific elements of the workload or benefit very small departments performing a very limited range of studies.

Dual headed cameras

4.49 These cameras are commonly used within nuclear medicine departments. They have two detectors which can usually be configured at 180° (opposite each other) or at 90° (at right angles to each other). This choice of configuration allows the user to achieve the most efficient use during imaging. For

example the 180° configuration would be used for whole body planar imaging and also for SPECT studies where a full 360° rotation is required (such as bone SPECT). The 90° configuration may sometimes be used for planar oblique views but is mainly advantageous for SPECT MPI where the SPECT is only performed over 180°.

Triple headed cameras

4.50 These cameras have three heads fixed in a triangular orientation. This means that the aperture is fixed. Because it is essential for the detectors to remain close to the patient in order to obtain good quality images, the detector size in such cameras tends to be small and triple headed cameras are limited to use for brain imaging.

Cardiac cameras

4.51 There are a number of models of cardiac cameras on the market in the UK. The detectors are fixed in the 90° orientation but are half the height of standard detectors. These cameras vary in terms of the ergonomics of the detectors in relation to the bed (upright, semi-upright or supine). The advantages of dedicated cardiac cameras are: they have a smaller footprint than a standard camera and are cheaper (approximately £200,000 [34]). Patients frequently find the couch position more comfortable and the semi-upright patient position helps reduce problems with gut uptake obscuring the myocardium. The disadvantages are that the smaller detector size can result in truncation problems with large patients and that they can only be used for this examination. In a department performing only cardiac nuclear medicine or a large department with other gamma cameras these cameras are useful. In a smaller department performing mixed procedures a cardiac camera may be too limiting in terms of the flexibility required. In addition, given that the upper replacement age of a gamma camera is around ten years, departments purchasing new equipment need to be sure that the referral patterns for cardiac imaging are not likely to change.

Gamma camera technology developments

4.52 Recently new gamma camera designs have emerged for limited applications. As departments renew their equipment, it may be useful to consider how new advances in hardware and software could provide a benefit in terms of efficient use of ^{99m}Tc or the throughput of patients.

Solid state detectors

4.53 For cardiac nuclear medicine, technological advances have meant that cameras with new types of detectors are also becoming available in the UK. Standard gamma cameras use sodium iodide (NaI) scintillation crystals to convert gamma rays into light photons. These light photons are then guided towards a photomultiplier tube which converts the light into electrical signal to form the basis of the image. New detector technology uses cadmium zinc telluride (CZT) crystals to convert gamma rays directly into electrical signals. This has significant advantages over conventional NaI detectors, giving improved spatial resolution and energy resolution. In the past, the development of CZT gamma cameras was hindered by the ability to produce large-area CZT crystals. This problem has been tackled by two camera manufacturers by using a novel camera design to approach SPECT imaging in a completely different way.

4.54 The D-SPECT cardiac camera from Spectrum Dynamics uses ten CZT detector columns with tungsten collimators with large holes and a wide angle of acceptance (in place of the standard parallel hole collimator). The columns rotate and focus on the object of interest. This technology promised significantly improved sensitivity along with increased resolution (a ‘holy grail’ in nuclear medicine

where, with standard gamma cameras, increased resolution is obtained at the price of decreased sensitivity or vice versa). A number of publications have evaluated this technology and confirmed significant improvements in sensitivity along with two-fold increases in resolution [35].

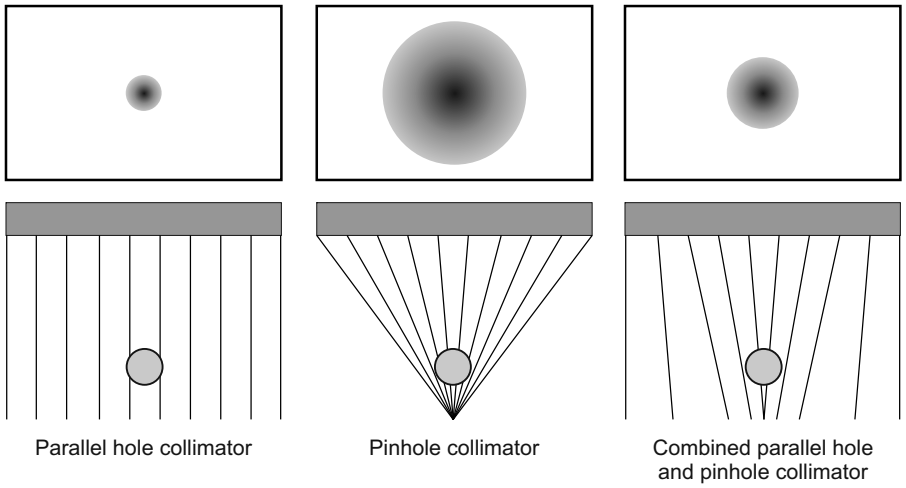
4.55 The GE Healthcare Alcyone camera uses a bank of nine CZT detectors in fixed positions. A collimator with a series of pinholes allows the detectors to focus on the heart. Neither the detectors nor collimators move during image acquisition – a significant advantage for some patients. The combination of CZT detection efficiency and pinhole collimator resolution can be used to reduce image acquisition time significantly.

4.56 Both these cameras offer significant advantages in terms of reducing patient dose and/or increasing patient throughput for MPI. They offer no advantage to departments that do not have a significant cardiac workload. However, as MPI is 16% [33] of the nuclear medicine imaging performed within the UK and requires one of the largest DRLs of any nuclear medicine procedure, the introduction of this technology could have a significant impact on the use of available ^{99m}Tc.

Focussed collimators

4.57 When using standard parallel-hole collimators to image objects smaller than the camera field of view, the full detector area is not used. By altering the collimator design, to focus at a single point, a high resolution, magnified image can be acquired. This design is known as a pinhole collimator. Such collimators are not used for SPECT imaging as it is difficult to position the gamma camera so that the organ of interest is always in the field of view as the camera rotates. Truncation artefacts are created if the organ of interest is outside the field of view at some camera angles. By combining a parallel hole and pinhole design, the benefits of focussed collimation can be gained while also minimising truncation artefacts. These effects are demonstrated in Figure 4.3.

Figure 4.3 Collimation effects



4.58 Siemens IQ SPECT collimators can be fitted to Siemens Symbia S and T series dual headed gamma cameras. The collimator is designed so that the centre of the field of view magnifies the heart, while the edges sample the entire body to avoid truncation artefacts. As the detectors rotate around the patient, their positions are adjusted to ensure that the heart remains within the centre of the field of view. This system has advantages as the collimators may be fitted to standard gamma camera which can also be used for non-cardiac applications. Due to the gain in counts acquired from the cardiac region the acquisition time may be reduced to a few minutes. Theoretically, this could also be used to reduce the amount of activity administered while keeping the acquisition time the same. The cost of the

collimators is significant, and departments may need to justify the investment with 'guaranteed' MPI throughput. The actual imaging characteristics have not been established and are yet to be used in routine practice in the UK.

Scientific support and staff training

4.59 With all new systems education and training are required for all members of the multidisciplinary team operating within nuclear medicine departments. Successful implementation can only take place with the support of scientists with the underpinning knowledge and understanding of the technology. Operators need to be trained to use the equipment/software and clinicians need to understand the technology and gain experience of images which might appear different and where different artefacts may be possible. There will also be an impact on any standard databases that are in used and clinicians will need to be aware of this.

Summary

4.60 Nuclear medicine imaging uses an established technology which has remained largely unchanged for the past 20 years. New developments in hardware and software could potentially alleviate some of the problems associated with shortages of ^{99m}Tc.

4.61 Resolution recovery software is widely available and results from a pilot study suggest that it has a role to play in allowing nuclear medicine departments to reduce the activity administered to patients. However, further work is required to evaluate this for the range of software routinely available in the UK.

4.62 New hardware solutions also offer potential benefits to users but few sites in the UK currently have this equipment and the real impact on administered activity has not been established. Nuclear medicine departments will have the opportunity to consider new technologies when replacing existing equipment.

Annex to Chapter 4

Resolution Recovery Software Products

Software packages available for use in the UK

Manufacturer	Resolution recovery product name	Generic/specific
Hermes Medical	Hybrid Recon	Generic
Scivis	ReSPECT HiScan	Generic
UltraSpect	Xpress/Xpress3.Cardiac Xpress/Xact.Bone	Generic
Siemens	Flash3D OncoFlash CardioFlash	Specific
GE Healthcare	Evolution for Bone Evolution for Cardiac	Specific
Philips Healthcare	Astonish	Specific

Summary of design characteristics on SPECT images

	Improve image quality	Reduce projections	Reduce time per projection	Reduce activity	Change the collimator
Hybrid Recon	Yes	Yes	Yes	Yes	Yes
ReSPECT	Yes	Yes	Yes	Yes	Yes
Xpress3.Cardiac	Yes	No	Yes	Yes	No
Xact.Bone	Yes	No	Yes	Yes	No
Flash 3D	Yes	Yes	Yes	Yes	No
OncoFlash	Yes	Yes	Yes	Yes	No
CardioFlash	Yes	Yes	Yes	Yes	No
Evolution for Bone	Yes	–	Yes	–	–
Evolution for Cardiac	Yes	–	Yes	–	–
Astonish	Yes	Yes	Yes	Yes	Yes

Summary of design characteristics for resolution recovery on planar images

	Improve image quality	Reduce acquisition time	Reduce activity	Change the collimator
HiScan	Yes	Yes	Yes	No
Xact.Bone	Yes	Yes	Yes	No
OncoFlash	Yes	Yes	Yes	No
Astonish	Yes	No	No	Yes

Hermes Medical

Product	Hybrid Recon
Range of studies that the software can be used on	SPECT MPI, Bone, Oncology, RNV/MUGA, Parathyroid, Brain ^{99m}Tc, ^{123}I, ^{111}In, ^{201}Tl, ^{131}I, ^{67}Ga Dual isotope studies using ^{99m}Tc/^{201}Tl, ^{99m}Tc/^{123}I All standard parallel hole collimators and fan-beam collimators Not suitable for planar imaging
Hardware and software requirements including minimum system specifications	Hybrid Recon requires a standard PC running Windows OS New users can have a locally installed solution which would require hardware and software New and existing users can purchase access to the software via the on-line TeleHERMES hosted service which requires no software Existing users may only need to purchase the software but may also require a hardware upgrade up depending on the age of the HERMES systems
Limitations on acquisition parameters (e.g. camera or collimator choice, radionuclide)	Certain gamma camera and collimator characteristics must be known (hole diameter, hole length, detector resolution and energy resolution) The radius of rotation for each projection angle when performing non-circular orbit acquisitions is required The upper limit for matrix sizes is 128 x 128
Limitations on image processing (e.g. attenuation correction, use of normal databases) and artefacts	Attenuation correction with SPECT CT, CT, sealed sources and uniform attenuation map for brain studies A normal database would need to be repopulated to be valid for resolution recovery images Induced artefacts have been identified in previous software versions (Gibbs ringing artefacts if standard OSEM is used), but these artefacts can be removed with the Bayesian reconstruction method which is added as an optional method
Details of the resolution recovery algorithm used	Incremental Gaussian diffusion algorithm
Performance of the system (processing time)	20–46 seconds

Scivis

Product	ReSPECT 3.1	HiScan
Range of studies that the software can be used on	Any SPECT application ^{99m}Tc, ^{57}Co, ^{67}Cu, ^{67}Ga, ^{123}I, ^{131}I, ^{111}In, ^{177}Lu, ^{201}Tl Bremsstrahlung-SPECT using ^{90}Y, ^{188}Re Any dual and triple isotope studies Any parallel-hole collimators or fanbeam collimators	Any planar studies
Hardware and software requirements including minimum system specifications	Hardware: PC platform with CUDA capable NVidia GPU, 2 GB RAM, CPU Pentium IV Platforms: Windows, Linux, Macintosh	
	For 256 x 256 SPECT studies a 64 bit operation system and 8 GB RAM are required	–
Limitations on acquisition parameters (e.g. camera or collimator choice, radionuclide)	Geometrical parameters of camera/collimator/nuclide combinations are generated during installation process, for exotic combinations calibration measurements are mandatory Data need to be DICOM or Interfile 3.3 For automatic reconstruction: (a) collimator ID, (b) camera ID (or equivalent), (c) radius of rotation (for each projection angle for non-circular orbits), and (d) radionuclide or energy window(s) are required If parameters are missing, user input is possible, missing radius can be estimated either for circular or non-circular scans There is no limitation on or requirement for the number of acquired counts Maximum number of bins for gated studies is 16	No limitations
Limitations on image processing (e.g. attenuation correction, use of normal databases) and artefacts	Attenuation correction using CT or sealed sources or homogeneous attenuation within automatically computed body contour is supported Local scatter compensation using data from three-energy-window acquisition protocols during iteration procedure No need to adjust number of iterations User control to change the degree of noise reduction No induced artefacts	No user interaction necessary No induced artefacts
Details of the resolution recovery algorithm used	Bayesian iterative reconstruction algorithm accounting for depth-dependent point spread function and proprietary noise reduction strategy	Bayesian iterative algorithm for simultaneous resolution recovery and noise reduction. The noise reduction algorithm takes Poissonian noise behaviour explicitly into account
Performance of the system (processing time)	1–2 minutes (128 x 128 matrix, 120 angles)	1–2 minutes (256 x 1024 matrix)

UltraSpect

Product	Xpress/Xpress3.Cardiac	Xpress/Xact.Bone
Range of studies that the software can be used on	Validated for use on myocardial perfusion images (MPI) using ^{99m}Tc or ^{201}Tl with either LEAP or LEHR collimators only Use with other isotopes requires validation Not suitable for planar imaging	Validated for SPECT Bone, Oncology, Parathyroid and Renal studies with ^{201}Tl and ^{99m}Tc using LEAP and LEHR collimators only Validated for planar bone studies using ^{99m}Tc Can be used for other planar studies (renal, lung and MUGA) and with other radionuclides (^{123}I, ^{111}In, ^{131}I and ^{67}Ga) but this use has not been validated to date
Hardware and software requirements including minimum system specifications	Both packages run on a PC platform with a Linux operating system New customer – purchases the product based on WBR software loaded on UltraSPECT.gate computer Existing customers – purchase additional licences for the connection of new devices (cameras or workstations) and new versions of the software	
Limitations on acquisition parameters (e.g. camera or collimator choice, radionuclide)	Both packages use a database of geometrical parameters of the collimator The radius of rotation is required from the acquisition data but can be calculated if missing Data need to be in DICOM or ADAC format	
	Limited to 64 x 64 matrix size and 8 time bins	Xpress/Xact.Bone is limited to a maximum 128 x 128 matrix with a minimum angular step of 3° over 360° for SPECT and a matrix size of 256 x 256 with a pixel size of ~2 mm for planar images
Limitations on image processing (e.g. attenuation correction, use of normal databases) and artefacts	For both packages, the user defines the processing parameters which control resolution and noise in the reconstructed image No induced artefacts have been demonstrated	
	MPI functional parameters (EDV, ESV and EF) calculated from Xpress/Xpress3.Cardiac differ slightly from FBP/OSEM values Attenuation correction with CT and SPECT CT only	No attenuation correction for Xpress/Xact.Bone
Details of the resolution recovery algorithm used	Proprietary wide beam iterative reconstruction algorithm, adaptive to input data count density	
Performance of the system (processing time)	10 seconds – 2.5 minutes Total processing time and data transfer Time might vary depending on network performance	

Siemens

Product	Flash3D	OncoFlash	CardioFlash
Range of studies that the software can be used on	Any SPECT application Not suitable for planar imaging.	Any SPECT application Any whole body or planar application	MPI SPECT imaging only Not suitable for planar imaging
	^{99m}Tc, ^{123}I, ^{111}In, ^{201}Tl, ^{131}I, ^{67}Ga Any parallel-hole collimator		
Hardware and software requirements including minimum system specifications	Windows XP operating system with the Syngo user interface and MI applications platform (version 3.5 and above)		
Limitations on acquisition parameters (e.g. camera or collimator choice, radionuclide)	Cameras: Siemens e.cam, Symbia SPECT or SPECT CT with Syngo MI applications acquisition and processing workplaces Radius of rotation and collimator model are required from the header file Adequate count density is required for each acquisition type		
Limitations on image processing (e.g. attenuation correction, use of normal databases) and artefacts	Certain parameters can be modified by the user: Siemens provides recommended parameters for use Cardiac attenuation correction using SPECT CT from hybrid system only Attenuation correction for other clinical applications with SPECT CT and CT		
	Induced artefacts for Flash3D and OncoFlash were present in previous software versions (image degradation when combining multiple bed positions during SPECT studies) but have been resolved in the recent software upgrade		For CadioFlash the software would invalidate normal databases in standard packages but new databases exist in Corridor 4DM SPECT Cardiac package
Details of the resolution recovery algorithm used	All packages use the same Siemens Flash 3D algorithm based on maximum likelihood reconstruction using ordered subsets (OSEM) Flash3D uses the distances of the collimator to centre of rotation for each view, as well as characteristic parameters of the collimator for the balanced beam modelling in both forward- and back-projection		
	–	OncoFlash planar processing uses the patented Pixon® method	–
Performance of the system (processing time)	1–2 minutes		

GE Healthcare

Product	Evolution for Bone	Evolution for Cardiac
Range of studies that the software can be used on	Validated for Bone SPECT using ^{99m}Tc with LEHR collimator Can be used on Parathyroid and Oncology SPECT studies but not validated	Validated for MPI SPECT using ^{99m}Tc with LEHR collimator Can be used on Bone, Parathyroid, RNV/MUGA and Oncology SPECT studies but not validated
	Not suitable for planar imaging ^{99m}Tc only; LEHR collimators only	
Hardware and software requirements including minimum system specifications	Xeleris hardware platform supporting Xeleris1.13+	Xeleris hardware platform supporting Xeleris2.0523+
	A floating licence is also available for both packages (XFL version)	
Limitations on acquisition parameters (e.g. camera or collimator choice, radionuclide)	Cameras: Discovery NM/CT 670 (any release), Infinia (Version 2.004.004.2+)	Cameras: Discovery NM/CT 670 (any release), Infinia (Version 2.004.004.2+), Ventri (any)
	Both packages require details of the collimator and detector type and the radius of rotation from the header file.	
Limitations on image processing (e.g. attenuation correction, use of normal databases) and artefacts	No attenuation correction Some induced artefacts are known relating to lower than expected counts next to high count regions	Attenuation correction using CT or hybrid SPECT CT only Third-party normal databases would be affected by the implementation of resolution recovery No known artefacts are induced when using the software
	Reconstruction parameters can be set by the user for both packages	
Details of the resolution recovery algorithm used	Incorporating a 3D physical model of the imaging process into an OSEM iterative image reconstruction algorithm. This 3D modelling of the collimator-detector response function includes intrinsic system response and collimator-specific geometric response	
Performance of the system (processing time)	30 seconds – 4 minutes	

Philips Healthcare

Product	Astonish
Range of studies that the software can be used on	SPECT MPI, Bone, Oncology, MUGA and Parathyroid studies ^{99m}Tc, ^{123}I, ^{111}In, ^{201}Tl, ^{131}I, ^{67}Ga, ^{177}Lu Any parallel-hole collimator or Philips cardiac collimator Suitable for planar bone, renal, lung and MUGA studies
Hardware and software requirements including minimum system specifications	Hardware: Philips JETStream Workspace (HP 3500) and EBW NM (Dell T7400) workstations Platforms: JETStream Workspace 3.0 + later version and EBW NM 1.0 + later versions AutoSPECT 3.0 SPECT processing software required
Limitations on acquisition parameters (e.g. camera or collimator choice, radionuclide)	Cameras: Forte JETStream, SKYLight, BrightView, BrightView XCT, CardioMD and Precedence Collimator ID and radial distance from the camera required
Limitations on image processing (e.g. attenuation correction, use of normal databases) and artefacts	Users can modify the number of iterations, subsets and filter cut off Attenuation correction with SPECT CT, CT and sealed sources New normal databases are needed for any third-party packages No known induced artefacts
Details of the resolution recovery algorithm used	OSEM with resolution recovery using measured collimator response function and measured radial distance A matched filter is applied within the iterative process
Performance of the system (processing time)	JETStream: add 2 or 3 minutes to the reconstruction with attenuation correction EBW NM: add 30 seconds to the reconstruction

Chapter 5

Making the Best Use of Available Activity within a Nuclear Medicine Department – Human Resource Issues

Introduction

5.1 Within the UK nuclear medicine services are provided by a range of different staff groups. The main tasks performed by individuals will vary from one department to another but can be broadly split into the following categories:

a Radiopharmacy functions.

b Imaging functions.

c Medical physics functions.

d Medical functions.

5.2 Radiopharmacy functions are undertaken by radiopharmacists, pharmacists, chemists, physicists, radiographers and clinical technologists. These staff are involved in all aspects of the aseptic preparation of radiopharmaceuticals. This work starts at the beginning of the working day, normally around 8 am (or even earlier depending on the department). These staff elute the generator, manufacture radiopharmaceutical kits and dispense individual patient injections all within an aseptic environment. They may also carry out blood labelling and other complex preparations of radiopharmaceuticals, package radiopharmaceutical kits for transport and perform quality control testing of products.

5.3 Imaging functions are undertaken by radiographers and clinical technologists. These staff will carry out administrations of radiopharmaceuticals to patients (which may include infusions and involvement in cardiac stress testing) and perform patient imaging procedures using a gamma camera. They will often also carry out image processing using computer systems and provide images, data analysis and patient information to the clinician for interpretation. They may also carry out equipment quality control and analyse biological specimens in the laboratory.

5.4 Medical physics functions are undertaken by physicists and clinical technologists. These staff will carry out a range of scientific and technical roles, including equipment management, calibration and quality assurance tests, and patient dosimetry including advice on diagnostic reference levels, radiation protection, waste management, risk assessment and advice on transport of radioactive materials. Physicists may also be involved in the implementation of new procedures, the evaluation of current procedures, complex and novel image processing and IT support. Physics support may be on-site at larger facilities, or remote for smaller centres.

5.5 Medical functions are undertaken by nuclear medicine specialists, cardiologists and other medical staff. These staff are involved in the justification of medical exposures, setting of diagnostic reference levels, development of protocols and procedures, provision of immediate care of patient, supervision of the investigations including cardiac stress testing, and provision of a clinical evaluation of the outcome of the nuclear medicine investigation. Medical staff may also attend multidisciplinary meetings for both cancer and non-cancer patient groups, which are often held before/at the beginning of the working day or at the end of the day.

5.6 There may be other staff involved in specific roles within the nuclear medicine department, e.g. some nursing staff undertake injections and ECG technicians may be involved in cardiac stress testing. The use of lower band staff such as imaging assistants and assistant technical officers is becoming more common in many areas of nuclear medicine.

5.7 The team will be supported by secretarial and clerical staff who may be specific to the department (if it is geographically self-contained) or shared if co-located with another diagnostic department.

5.8 In general, nuclear medicine services are provided by a relatively small number of highly specialised staff from a range of disciplines, compared with other imaging services. This is particularly true in small departments – a department with one gamma camera may rely upon four members of staff to provide all routine aspects of the service. In these cases staff training is often expanded to overlap the different roles required within a department. The exact nature of the tasks performed by each group will vary from site to site as will the degree of overlap.

5.9 In addition to investigations using ^{99m}Tc, some departments will use non-^{99m}Tc products and carry out therapy procedures.

Working patterns

5.10 Most nuclear medicine departments have not routinely operated imaging services out of working hours as few, if any, of the procedures offered are generally required in urgent situations. In the last three years however, with increased pressures on equipment and the introduction of waiting list targets for diagnostics, more departments are adopting alternative working hour patterns. This could include longer working days or weekend working. Whilst this seems a logical use of the limited equipment resource, there are significant logistical issues that need to be resolved to ensure delivery of safe patient care. The extent of this will depend on whether weekday extended hours or weekend services are offered throughout the hospital as a whole. If the staff either are already providing extended day working in other areas, or are part of the imaging on-call team, this would also limit their availability to provide extended hours working for nuclear medicine.

5.11 Alternative working patterns can be adopted to make the most efficient use of a reduced supply of activity during short-term periods. In these cases, the working pattern can be designed to maximise the availability of activity from the generator. Currently this would include weekend working. This may not be practicable for long periods. If the total working hours remain the same, then the nuclear medicine services will not be available in the working week when other hospital services are operating routinely. Maintaining a limited traditional weekday working patterns and adding weekend working will make the best use of the available activity and preserve access to nuclear medicine services, but will increase costs and may test staff acceptability.

5.12 Achieving an appropriate work/life balance is difficult in small departments if extended working is to become normal practice. It is made more so if the need for extended working is only required on an intermittent and unpredictable basis and at short notice, as has been the case during the recent reduction in ^{99m}Tc availability. The erratic nature of the supply problems has meant that it has not been possible or sensible for many departments to introduce formal changes to working patterns. The human resource processes surrounding contract changes can be prohibitive unless there is a real long-term need. It is difficult to make a robust business case for extra staff based on the shortage of ^{99m}Tc. It is unlikely that the response provided by nuclear medicine services over the past two years will be sustainable in the medium term.

5.13 If a department were to adapt and extend current working patterns, the implications can be summarised as follows.

Advantages

a Does not require radiopharmacy staff to work extra days. However, extended days or shift working may be required.

b Some products can be made in a first production session, while some will require a second (or third) session, depending on amount of activity available and the shelf-life of the product.

Disadvantages

a Requires the radiopharmacy to be staffed all day, although some departments could work with multidose vials.

b Still 'wastes' activity over the weekend.

c Less cost efficient use of kits.

d Late re-elution affects next day's yield.

e Requires shift patterns or extra working hours for imaging staff.

f Medical cover may need to be shared with other departments and it may make the nuclear medicine specialist's participation in multidisciplinary meetings difficult.

g Reception functions may have to be carried out by other staff or staff from other departments; alternatively reception staff will have to agree to an extended working week.

h Extra transport from central radiopharmacies.

5.14 Weekend working offers more significant advantages. Due to the unhelpful delivery schedules for some ^{99m}Tc generators, without weekend working, the period when the highest amounts of activity are available is when the nuclear medicine department is closed. Even when generators are available during the working week, weekend working will give more efficient use. If weekend working is to be implemented, existing working patterns may have to be more extensively modified. Nuclear medicine services vary greatly throughout the country and different models will have to be adopted. The staffing required will vary according to the site of the department within the hospital and the out-of-hours activity of neighbouring departments which will govern the amount of cross-cover medical and nursing support available to help in the event of a medical emergency or staff illness. For weekend working, the implications can be summarised as follows.

Advantages

a Makes use of ^{99m}Tc (and camera time) which would otherwise be wasted.

b No extra cost for ^{99m}Tc.

c Convenience of outpatients.

d Timeliness of care, particularly for inpatients.

Disadvantages

a Specialised radiopharmacy staff coverage is difficult; while imaging can be performed with limited numbers of staff, virtually full radiopharmacy staffing is required.

b Small number of imaging staff will not be able or willing to sustain weekend working.

c Increasing pressure on already stretched medical cover.

d Reception functions will have to be carried out by secretarial staff or staff from other departments.

e Delivery problems if ^{99m}Tc supplied from a more distant radiopharmacy.

f Staff recruitment and retention issues for regular unsocial hours.

g Staff training time is reduced as available staff are spread over a longer overall working time.

h Limitations in other support services.

i Some Private Finance Initiative hospitals may not allow weekend work.

j Not achievable without more staff – especially for radiology departments that have to provide multiple imaging modalities and on-call support.

5.15 Both extended hours and weekend working make it difficult to get staff together for training and meetings. Sessions may have to be duplicated which puts further pressure on resources.

5.16 Running a nuclear medicine service is not possible in isolation, however, and a range of generic hospital support services is required if alternative working patterns are to be provided. These include patient transport, portering, catering, cleaning and interpretation services. Restrictions on these will have a significant impact on alternative working patterns for nuclear medicine services and, traditionally, costs associated with these services have not been made available for nuclear medicine.

5.17 The implementation of the European Working Time Directive [36] has had the effect of reducing the maximum hours worked from an average of 56 hours per week to 48. This must be taken into account when considering any changes to working patterns.

5.18 The additional financial resources required to provide alternative working patterns are not trivial and cannot be ignored, particularly when all public spending is under review. Costs can be reduced by batching procedures together within one extended period, but will vary depending on other hospital services. Any change in working patterns, however, is a response to the need to maximise ^{99m}Tc availability and increased costs will have to be accepted to achieve this.

Service delivery

5.19 Reconfiguring nuclear medicine services resulting in fewer but larger departments holds the promise of economies of scale and staff flexibility. Additional benefits include the facility to provide a comprehensive, high quality range of procedures, offered by a specialist workforce. However, this option will reduce patient choice, remove local services and may be unachievable given the formation of Foundation NHS Trusts which may consider consolidation to conflict with their established business models and given some recent investment by these Foundation NHS Trusts to repatriate services traditionally provided centrally.

Summary

5.20 Local services have responded well to shortages of ^{99m}Tc but the solutions involving extended hours and weekend working are unlikely to be sustainable in the medium term with the current configuration of services. This is particularly true for small nuclear medicine departments or small radiopharmacies. The best solution may rest in a radical reassessment of traditional working patterns and staffing levels. If the delivery schedules for some ^{99m}Tc generators can be changed to provide maximum activity within the traditional working week the changes could be more limited.

Chapter 6

Alternative Products, Imaging Techniques and Pathways

Introduction

6.1 While nuclear medicine is an established diagnostic imaging modality, recent shortages of ^{99}Mo/^{99m}Tc have promoted discussion of potential alternative imaging techniques and pathways which could be employed during periods when the supply of ^{99m}Tc is extremely restricted or disrupted. The total range of nuclear medicine procedures used in the UK is extensive but the number of procedures undertaken on a regular basis is somewhat smaller and it is estimated that most nuclear medicine departments use ^{99m}Tc in about 50 procedures, the most common of which are used to investigate bone, cardiac, renal and pulmonary conditions.

6.2 A number of bodies have considered the impact of the recent ^{99}Mo/^{99m}Tc shortages on clinical imaging services. The European Medicines Agency (EMA) held a workshop in 2010 to discuss alternative imaging techniques. The workshop conclusions [37] indicate that a shortage of ^{99}Mo/^{99m}Tc would affect nuclear medicine services across Europe. Some nuclear medicine investigations using ^{99m}Tc were highlighted as there was no identified alternative investigation. These conclusions may not be directly applicable to UK practice and demonstrate the variability of nuclear medicine services across Europe.

Alternative imaging pathways

6.3 Alternative imaging pathways may substitute for other radiological investigations (plain radiography, ultrasonography, multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), non-^{99m}Tc-based nuclear medicine investigations (including PET CT), or a combination of these. Although emerging MRI techniques might be able to replace some nuclear medicine procedures, these have not been assessed in large populations. Within the UK, the expertise to perform and interpret these investigations is not widely available, acquisition procedures are frequently more time consuming and resource dependent than conventional MRI examinations, and these studies have not been fully costed under governmental tariff systems and would add further to existing waiting lists for MRI. Given their complexity, it is unlikely that it would be possible to outsource these investigations to commercial providers.

Radiology workforce issues

6.4 Transferring radionuclide imaging studies to other modalities has both scanner capacity and workforce issues and the workforce which is currently providing a radionuclide imaging service cannot simply ‘follow’ this work.

6.5 The UK already has fewer radiologists per million of population than other developed countries (38 per million in the UK, 67 per million in Australasia and 100 per million in the USA) [38] and transferring radionuclide investigations onto this workforce will stretch it further. In addition, whilst some investigations (for example, computerised tomographic pulmonary angiography or CTPA) are within the core competency of most radiologists, specialist MRI may not be and radiologists taking this on would require a further period of training. Similarly, any nuclear medicine radiographers would need additional training to transfer to specialist MRI.

Comparative costs

6.6 Historically, the production of medical radioisotopes has been a byproduct of the main output from research nuclear reactors and previous costings have been below the commercial production cost. As these readjust, the relative cost of any investigation involving radioisotopes will increase. However, even at current tariffs, the cost of most nuclear medicine procedures will be greater than those for ultrasound and CT examinations, partly because of their much higher throughput, reducing overhead costs per examination. The cost of MRI examinations depends upon the costing regime and the number of sequences used. More specialised and time consuming MRI examinations have not been fully costed and are likely to remain more expensive than nuclear medicine investigations.

Alternative imaging pathways: bone

Bone scintigraphy

6.7 Bone scans using ^{99m}Tc-labelled diphosphonates are the most commonly performed nuclear medicine investigation in the UK. They use a relatively high activity of ^{99m}Tc (ARSAC DRL of 600–800 MBq). Bone scans assess bone vascularity and osteoblastic activity and can detect early changes before plain radiographs show an anatomical abnormality. The vast majority of bone scans are performed for the evaluation of skeletal metastases (particularly arising from breast, prostate and lung cancer). Other indications include investigation of bone pain, suspected bone infection (osteomyelitis) or infection of joint prostheses, suspected trauma and characterisation of indeterminate abnormalities detected by plain radiography. Image acquisition is usually undertaken three to four hours post-injection and takes 40–60 minutes. The effective dose is 3 mSv (following administration of 600 MBq).

6.8 The skeleton is the most common site of metastasis in breast cancer. Bone scanning is routinely used in suspected stage 3 and 4 disease. Bone scanning has an important role in differentiating between benign and malignant bone pain within the breast cancer population [39].

6.9 The incidence of prostate cancer is rising, partly as the result of prostate-specific antigen screening. Bone scanning is routinely used in suspected stage 3 and 4 disease. For most patients, the disease has a benign course, with 90% of patients aged 50–59 years living five years [40]. Thus bone scanning is also useful to investigate benign bone pain within an ageing population of men with prostate cancer [39].

6.10 Within the UK, 75% of all bone scintigraphy studies are acquired as planar whole body images [33]. Approximately 5% of these studies include SPECT imaging. The use of SPECT greatly increases the diagnostic accuracy of bone imaging [41] and the addition of CT to SPECT further improves specificity by allowing anatomical characterisation of equivocal lesions [42,43]. SPECT imaging does, however, require a higher administered activity (typically 800 MBq ^{99m}Tc, compared with 600 MBq for planar imaging).

Positron emission tomography CT (PET CT) with either ^{18}F-FDG or ^{18}F-fluoride

6.11 The mechanism of accumulation of ^{18}F-FDG in bone is different from that of ^{99m}Tc-diphosphonate and ^{18}F-fluoride.

6.12 PET CT performed with ^{18}F-FDG is more sensitive than ^{99m}Tc-diphosphonate bone scintigraphy in detecting bone marrow abnormalities but less sensitive in demonstrating sclerotic bone lesions. It is the imaging agent of choice for assessing skeletal involvement by lymphoma and has largely replaced ^{99m}Tc-diphosphonate bone scans in lymphoma patients. ^{18}F-FDG PET CT and ^{99m}Tc-diphosphonate bone scans may demonstrate different skeletal lesions in the same patient and are therefore considered complementary. Bone metastases arising from some cancers, e.g. renal cell and prostate carcinoma, are rarely ^{18}F-FDG avid and ^{99m}Tc-diphosphonate bone scans remain the investigation of choice for these patients. The effective dose to the patient is much higher with ^{18}F-FDG PET CT than a conventional ^{99m}Tc bone scan (8 mSv from 400 MBq ^{18}F-FDG + 5 mSv for CT).

6.13 Fluoride is rapidly taken up into bone (90% injected dose at one hour) and was used for skeletal imaging prior to the development of ^{99m}Tc-diphosphonate. Until recently, limited tracer availability and the lack of PET scanners precluded widespread use. Image resolution is significantly higher than that of gamma camera scintigraphy [44]. Several studies report superior skeletal lesion detection using ^{18}F-fluoride compared with ^{99m}Tc-diphosphonate bone scintigraphy. The effective dose to the patient is much higher than that from a ^{99m}Tc-diphosphonate bone scan (6 mSv from 250 MBq ^{18}F-fluoride + 5 mSv for CT).

6.14 The sensitivity and specificity of SPECT CT, MRI and ^{18}F-fluoride PET bone scanning are comparably high. Service shortfalls arising from a severe ^{99m}Tc shortage could, therefore, be filled by either PET studies or by MRI depending on local circumstances. A cost–benefit analysis is needed to determine future strategy.

6.15 These other radiopharmaceuticals can only be used in departments having access to PET scanners. Currently a large percentage of PET CT services in England are provided through time-limited independent sector contracts. This has made PET scanners more widely available geographically but not on a daily basis. In addition, during the period when these services are being established, they may not be working to full capacity for logistical or financial reasons. Both ^{18}F-fluoride and ^{18}F-FDG are routinely available from three independent sector commercial cyclotron manufacturers as well as the two PET centres currently operating within the NHS. Only ^{18}F-FDG has a product licence. Each tracer costs approximately £200 per patient dose, which is more than the national tariff for a traditional ^{99m}Tc-diphosphonate bone scan.

Multidetector computed tomography (MDCT)

6.16 Plain radiographs can only detect bone destruction after 50% of bone density has been lost. CT is more sensitive than both plain radiography and MRI in demonstrating cortical and trabecular bone destruction. Current MDCT scanners with ultrathin collimation can visualise bone abnormalities with high resolution but cannot distinguish reliably between benign osteopaenia and marrow infiltration unless there is bone destruction as well. As some patients with cancer already undergo a staging CT assessment of the torso, it has been proposed that this should replace bone scintigraphy for the assessment of bone metastases [45]. This approach would, however, exclude clinically important skeletal metastatic sites such as the skull and peripheries. Imaging the whole skeleton with CT is unrealistically time consuming and results in high absorbed radiation dose.

6.17 MDCT is likely to have a higher false negative rate (i.e. miss more bone lesions) than other modalities. Image interpretation errors are higher for CT than for any other modality. A recent study [46] showed that CT reporting errors accounted for 62% of all recorded radiological errors, the majority of these being false negative interpretations. Missing a clinically important bone lesion was one of the commonest errors. MDCT studies comprise a huge dataset of images per patient and modern scanners can produce these datasets very rapidly. CT departments are under pressure to increase patient throughput and report turnaround times, which are precisely the factors which have been shown to increase reporting error rates. Double reporting reduces reporting error rates but double reporting of every CT study undertaken in the UK would require a huge expansion in the radiological workforce.

Magnetic resonance imaging (MRI)

6.18 Imaging for marrow metastases with MRI relies upon T1 weighted and STIR sequences. Several papers report that MRI is more sensitive and specific than planar bone scintigraphy. Whole body MRI marrow imaging is not practicable using existing MRI machines which are unable to survey the whole body at a single sweep, such that whole body studies would take at least an hour per patient [47]. Multichannel MRI scanners, using multiple phased array coils, and moving table feeds will accelerate whole body scanning in the future but are not widely available at present.

6.19 It has been proposed that limited marrow MRI scans (torso only) in patients with breast cancer could replace bone scintigraphy as only 2% patients have peripheral metastases and those usually present with pain [48]. This approach would not be suitable for other cancers. Existing MRI workload pressures limit the feasibility of this approach in routine practice. When comparing lesion by lesion detection of bone metastases, the sensitivities of planar bone scans and torso MRI scans in breast cancer were 71–72% and 82–97%, respectively [49,50]. MRI is more sensitive than planar bone scintigraphy in detecting vertebral lesions (and can assess potential spinal cord compression at the same time), but is less reliable in demonstrating lesions in the skull and ribs [50]. MRI is the most accurate method of distinguishing benign from malignant vertebral collapse, which is a common clinical scenario [39].

6.20 Contraindications to MRI include patient claustrophobia, recent surgery and some metallic implants.

6.21 Anatomy-based imaging modalities such as CT and MRI are of limited value in assessing skeletal treatment response by comparison with functional imaging. A recent survey by the European Association of Nuclear Medicine [2] predicted an increase in the use of SPECT CT in the next ten years.

6.22 Further research is required to compare the accuracy of MDCT, MRI and SPECT CT.

Alternative imaging pathways: cardiac

6.23 Department of Health statistics regarding the effects of coronary artery disease in the UK show that 2,000,000 people suffer from angina, approximately 110,000 patients have myocardial infarctions per year and 70,000 patients die per year [51].

6.24 Within nuclear medicine imaging, the two most common types of cardiac imaging tests performed are myocardial perfusion imaging (MPI) and radionuclide ventriculography (RNV).

Myocardial perfusion imaging (MPI)

6.25 Myocardial perfusion imaging is used to detect, localise and measure areas of reversible myocardial ischaemia and hibernating myocardium, to assess the functional significance of coronary artery stenoses demonstrated by coronary angiography (or CT angiography, CTA) and document the extent of myocardial infarction. ^{99m}Tc-labelled tetrofosmin or MIBI are the most commonly used radiopharmaceuticals for MPI in the UK [33].

6.26 MPI is normally composed of two studies; one at stress and another at rest. The cardiovascular stress may be treadmill or bicycle exercise or pharmacological stress. SPECT imaging is acquired and cross-sectional images of the heart at stress and rest are compared. Changes between stress and rest images demonstrate changes in perfusion and uptake dependent on the degree of ischaemia.

6.27 Thallium-201 (^{201}Tl) may be used as an alternative to the ^{99m}Tc products. Thallium-201 is cyclotron produced and is the forerunner of the ^{99m}Tc agents of today. It was replaced several years ago as the agent of choice because of less favourable imaging characteristics (large patients can cause increased artefacts in certain views) and an increased radiation dose to the patient. However, with newer imaging equipment and more sophisticated software programs, image quality has improved.

6.28 The costs of ^{201}Tl are directly comparable to those of the ^{99m}Tc imaging agents (approximately £90 per patient study) and it is available throughout the working week. However, it should be noted that ^{201}Tl makes less efficient use of camera time, so its use will affect patient throughput. Many nuclear medicine departments have now reintroduced this tracer routinely as an alternative for short-term interruptions to the supply of ^{99}Mo.

6.29 The National Institute for Health and Clinical Excellence (NICE) has produced recent guidance regarding the use of the varying imaging modalities in the investigation of patients with chest pain of recent onset [52] and have recommended that functional imaging should be the first-line diagnostic test in patients with an intermediate (30–60%) risk of coronary artery disease. Local circumstances will dictate whether patients are offered stress echocardiography, MPI or cardiac MRI. Historically there has been wide variability in the provision/availability of MPI and, because of this, many patients who are at intermediate risk go straight to coronary angiography. These guidelines mean that the need for functional imaging will rise significantly and this requires investment in equipment and staff and the development of multidisciplinary networks to ensure appropriate use of resources and imaging pathways.

Radionuclide ventriculography (RNV)

6.30 Radionuclide ventriculography is a well-established and validated technique. The blood is labelled with ^{99m}Tc and ECG-gated images of the ventricular blood pools are acquired. Quantitative analysis provides information on left ventricular function such as ejection fraction and regional function. RNV is often used to monitor function in patients receiving cardio-toxic chemotherapy. This technique is performed using ^{99m}Tc and there are no alternative radioisotopes which could replace the use of ^{99m}Tc.

Positron emission tomography CT (PET CT)

6.31 PET CT imaging using rubidium-82 (^{82}Rb) may be a possible alternative to MPI with ^{99m}Tc or ^{201}Tl. The perfusion study at rest and stress may be carried out with CT angiography in a single examination. It should be noted, however, that successful imaging of this type cannot be carried out on an ad hoc basis. Rubidium-82 is produced on site from a radionuclide generator using a long-lived parent radionuclide (strontium-82, ^{82}Sr). It is analogous to the ^{99}Mo/^{99m}Tc generator but has a shelf-life of four to eight weeks. Currently it is used in routine clinical practice in two PET centres in the UK and being actively explored in two others.

6.32 This generator is currently available from two manufacturers in North America only. Neither has a product licence. Each generator costs £20,000–30,000 and is sufficient for 10–20 patient studies each day throughout its shelf-life. The radiation dose to the patient from the radiopharmaceutical administration per completed study is much lower than either ^{99m}Tc or ^{201}Tl (1.8 mSv compared to 12 mSv and 14 mSv, respectively).

Echocardiography (ECHO)

6.33 Echocardiography uses ultrasound to examine the structure and function of the heart. Stress ECHO may also be carried out. Visualisation is poor in some patients with ‘poor echo windows’. The test is relatively cheap but the accuracy relies upon the availability of trained cardiac physiologists. There is currently a shortage of suitably skilled staff to carry out ECHO examinations.

Magnetic resonance imaging (MRI)

6.34 There are an estimated 50 centres in the UK which provide cardiac MRI [34] and it is best concentrated in high volume centres which offer a range of cardiac investigations and which can comply with quality standards. Therefore it is unlikely to be accessible to all patients at presentation. Contraindications to MRI include metallic implants (e.g. pacemakers, implantable defibrillators and intraocular implants) and impaired renal function (glomerular filtration rate (GFR) < 30 ml/min).

Computerised tomographic angiography (CTA)

6.35 CT and cardiac MRI require dedicated software and hardware in addition to a standard scanner.

6.36 Standards for delivery of a cardiac imaging service and the strategy for financing this has been detailed by the National Imaging Board [34].

Alternative imaging pathways: pulmonary thromboembolic disease

Lung scintigraphy

6.37 The vast majority of nuclear medicine lung scans are performed for the investigation of suspected pulmonary thromboembolism (PE). It is usual to perform two studies to demonstrate lung perfusion and lung ventilation, known as a V/Q scan. Perfusion-only imaging may be undertaken in pregnant patients. Perfusion imaging is performed using ^{99m}Tc-labelled macroaggregated human serum albumin (MAA).Ventilation imaging may be performed using either ^{99m}Tc-labelled aerosols or krypton-81m (^{81m}Kr).

6.38 The sensitivity and specificity of V/Q imaging is enhanced using SPECT CT and has been shown to be more accurate than CTPA alone in the investigation of PE [53].

6.39 Krypton-81m is produced from a radionuclide generator following the decay of its parent radionuclide rubidium-81 (^{81}Rb). The latter has a half-life of 4.7 hours which gives each generator a working life of one day. These generators are commercially available from two manufacturers on a daily basis in the UK. They cost £200–300 depending on size (activity) required and will provide sufficient activity for up to ten patients. The generator has to be ordered in advance and is therefore expensive if the workload is unpredictable.

Computerised tomographic pulmonary angiography (CTPA)

6.40 The only validated alternative investigation is computerised tomographic pulmonary angiography (CTPA). It is available as a core imaging technique in all radiology departments. However, it cannot be performed in every patient who has suspected PE as it requires patients to have good venous access, to be able to lie flat and hold their breath for approximately 20 seconds, and to be suitable for iodinated intravenous contrast administration. Contraindications to iodinated intravenous contrast include previous reaction to iodinated contrast and caution needs to be exercised in asthmatics, patients with impaired renal function, and diabetics on concurrent medication with metformin [54]. Approximately 25% of patients with suspected PE investigated in the Prospective Investigation of Pulmonary Embolism Diagnosis trials II [55] were deemed unsuitable for CTPA on the grounds of iodinated contrast contraindication or pregnancy.

6.41 British Thoracic Society (BTS) guidelines [56] already recommend CTPA as the first-line test for the investigation of acute PE but allow that where V/Q scanning is available, this can be performed first in patients with no underlying lung disease and a normal or near-normal chest radiograph (many of these are young patients). CTPA is the investigation of choice for patients with pre-existing pulmonary disease and/or abnormal chest radiographs, particularly post-operatively, in whom V/Q imaging is likely to be indeterminate.

6.42 V/Q lung scans and CTPA have similar sensitivities and specificities for demonstrating PE [57]. A normal V/Q scan has a higher negative predictive value (100%) than CTPA [58].

6.43 PE remains the commonest cause of maternal death directly attributable to pregnancy at 1.94 per 100,000 pregnancies [59] and therefore it is important to investigate suspected PE promptly. V/Q scanning has been shown to be more accurate than CTPA in pregnant patients [60]. Although the

foetal radiation dose resulting from radionuclide perfusion imaging is higher than that arising from CTPA, the level of increased risk in terms of cancer induction is considered negligible (1 : 100,000 and 1 : 250,000 for half-dose perfusion scan and CT, respectively). The risk to the mother from CTPA is potentially greater, as much of the 5 mSv whole body dose is delivered to the breast tissue, which is more sensitive to radiation in pregnant/post-partum patients. The significance of foetal thyroid exposure to iodinated contrast is unclear [54].

6.44 In the event of a ^{99m}Tc shortage, it would therefore only be appropriate to redirect a proportion of patients from V/Q imaging to CTPA. The latter would carry the penalty of a significantly larger radiation dose to patients, for many of whom it would be particularly desirable to minimise radiation dose. For the remaining patients who cannot undergo CTPA (many of whom are elderly), there is no alternative imaging technique.

Alternative imaging pathways: renal, adult patients

Renal scintigraphy

6.45 Renal imaging in nuclear medicine allows an assessment of relative renal function and clearance measurements. All the radiopharmaceuticals for renal imaging are labelled with ^{99m}Tc (^{99m}Tc-DTPA, ^{99m}Tc-MAG3 and ^{99m}Tc-DMSA). In the past ^{123}I-Hippuran has been used for renography but it has been withdrawn from the market by the manufacturer and is no longer available in the UK, giving no nuclear medicine alternatives.

Obstruction

6.46 Both CT and MRI urography (CTU and MRU) have replaced the conventional intravenous urography (IVU) as they provide superior anatomical information. However, in order to give the dynamic information about differential renal function and drainage that a nuclear medicine renogram provides, intravenous contrast needs to be administered and that is precluded in patients with reduced renal function. Both CTU and MRU require more scanner time than conventional CT and MRI studies and the expertise for MRU is not widely available. An integral part of assessing drainage from a kidney during a radionuclide renogram (^{99m}Tc-DTPA or ^{99m}Tc-MAG3) is the acquisition of post-micturition and/or images after a change of posture. This is difficult to achieve following MRU or CTU.

Divided renal function estimates

6.47 There is no alternative to the ^{99m}Tc-DMSA scan.

Assessment of renal artery stenosis

6.48 MRI angiography (MRA) has replaced captopril renography as the investigation of choice for patients with suspected renal artery stenosis. Renal Doppler ultrasound provides good results in expert hands, although this expertise is not universally available. Patients with impaired renal function (GFR < 30 ml/min) cannot have gadolinium or iodinated intravenous contrast. The development of 'fresh blood imaging' allows MRA without the administration of contrast. This technology is coming online in the UK but is not yet widely available.

Studies for which there is no alternative imaging pathway: sentinel lymph node imaging

6.49 Sentinel lymph node (SLN) lymphoscintigraphy to identify SLN for biopsy accounts for a small proportion of nuclear medicine imaging studies overall but is an important example of a radionuclide imaging technique for which there is no imaging alternative. SLN biopsy was introduced into the modern staging and management of patients with cancer in the early 1990s and its use has expanded since then. In the UK, SLN biopsy is the standard of care for the management of patients with breast cancer, malignant melanoma and penile cancer.

6.50 There were approximately 46,000 new diagnoses of breast cancer in the UK in 2007 [62] and 60% are eligible for SLN biopsy. Approximately 70% of these (19,000 patients) do not have nodal metastases and will not need axillary clearance. SLN biopsy is a less invasive procedure than axillary clearance, with a shorter patient stay in hospital and better patient well-being afterwards [61], so is a cheaper option for the NHS. Without it, patient management would have to revert to the previous standard of care, which was axillary dissection for all patients, with attendant morbidity and costs.

6.51 There were 10,600 new cases of malignant melanoma in the UK in 2007 [62], of which approximately 90% would have been eligible for SLN biopsy and approximately 1700 of these would have had SLN metastases. Prior to SLN biopsy, the standard of care in the UK for these patients was to excise the tumour alone and only do nodal dissection if clinically enlarged lymph nodes developed at a later stage. Although SLN biopsy itself does not affect five year survival, it does give patients prognostic information and allows early stratification for further treatment such as chemotherapy or radiotherapy.

6.52 There are around 400 new cases of penile cancer in the UK annually [63], of which approximately 50% are eligible for SLN biopsy. Without this technique, the standard of care is bilateral inguinal nodal dissections, with a 25–30% risk of lymphoedema per leg. This can be very difficult to manage clinically and can reduce a patient's mobility and increase dependency significantly.

6.53 Nuclear medicine departments undertaking SLN biopsy need to adhere to agreed standards and audit their results, e.g. the Newstart training scheme [64]. Alternative techniques (e.g. ultrasound microbubble contrast agents [65], MRI lymphangiography and near-infrared (NIR) lymphangiography) are either still experimental or have been investigated for technical feasibility studies but have not been validated across larger populations. SLN localisation using blue dye and ^{99m}Tc-labelled colloid is more successful than using blue dye alone. There is no alternative imaging method to replace ^{99m}Tc-labelled colloid. If the UK were unable to offer SLN biopsy it would not be able to offer patients the internationally accepted standard of care for cancer staging and would not be able to participate in trials extending the use of this technique to other cancers. The NHS costs per breast cancer patient would increase significantly.

6.54 SLN localisation does involve much lower administered activities than most other imaging investigations (typically 20–40 MBq). In practice it should be possible for nuclear medicine departments to prioritise stocks of available ^{99m}Tc for these patients. SLN biopsies for melanoma and penile cancers are only carried out in specialist centres and there may be scope to 'batch' patients together to conserve supplies of ^{99m}Tc.

Imaging pathways in paediatric patients

6.55 Imaging studies in children have two special considerations compared with adults, firstly their greater sensitivity to radiation and secondly their compliance with the investigation.

6.56 Children are approximately twice as sensitive to long-term adverse effects from radiation as adults, partly because their tissues are more sensitive and partly because they have longer to live to develop these adverse effects. The justification for any investigation involving ionising radiation exposure in children must be considered carefully. For example, a bone scan giving an effective dose of 3 mSv will

carry a higher risk of cancer induction in a child compared with an adult because a child's skeleton is composed of relatively more red marrow which is more radiation sensitive.

6.57 For this reason, high dose investigations such as CT are not a viable alternative to radionuclide investigations in children, MRI being the preferred alternative imaging option. Most children aged below seven or eight years of age will require general anaesthesia for an MRI investigation [66]. MRI under general anaesthesia requires paediatric anaesthetic support and this expertise is not available in every hospital [66]. These studies are time consuming and resource intensive. Because of this, facilities for paediatric MRI under general anaesthesia are already limited to specialist hospitals. Further expansion would require a significant increase in MRI facilities, paediatric radiologist and anaesthetic support. Young children have reduced lower glomerular filtration rate (GFR) than adults (for example, babies aged below one year have a GFR half that of an adult), which theoretically places them at greater risk of nephrogenic systemic fibrosis (NSF) following gadolinium contrast administration. Current European Society for Magnetic Resonance in Medicine and Biology guidelines [67] recommend that gadolinium contrast should be used with caution in babies aged below one year of age.

Renal scintigraphy in paediatric patients

6.58 In children, the most commonly performed radionuclide investigations are renal studies for the investigation of urinary tract infections and obstructive uropathies, with the aim of preventing renal impairment or failure.

6.59 The incidence of obstructive uropathy is 1 : 1000 live births and the majority of these are detected by antenatal ultrasonography. However, antenatal ultrasonography also detects many more patients (approximately 1 or 2 per 100) who do not ultimately have a surgically correctable anomaly but who will require post-natal follow up. There were 708,711 live births in the UK in 2008 [68] resulting in 3500– 3700 babies per year that require imaging follow up and many of these will need ^{99m}Tc-MAG3 and/or ^{99m}Tc-DMSA scanning.

6.60 Approximately 1 in 10 girls and 1 in 30 boys will have had a urinary tract infection by 16 years of age and, of these, approximately 32% girls and 59% boys will have had an episode of pyelonephritis [69], which may be an indicator of an underlying abnormality. The aims of investigation are to identify which patients are at risk of developing renal scars as a result of repeated urinary tract infections and to identify those with a surgically correctable anomaly that was not evident at antenatal ultrasonography. The NICE guidelines regarding the management of childhood urinary tract infection [69] seek to rationalise investigation to those clinically defined groups of patients who are likely to have an underlying abnormality which requires further investigation. The main two investigations recommended are ultrasonography and ^{99m}Tc-DMSA scanning.

6.61 The NICE guidelines specify ^{99m}Tc-DMSA scans as the 'gold standard' for assessing renal scars in children. Although ultrasonography with power Doppler analysis can demonstrate areas of acute infection and renal scars with good sensitivity and specificity, the technique is dependent on patient compliance and operator skill. It is unlikely that the high sensitivities and specificities for detecting renal scars obtained from individual expert centres using ultrasound equipment optimised for the paediatric population can be translated across the UK, where many children will have their renal ultrasound examinations performed by non-specialists using a general ultrasound machine. Furthermore, it is much harder to assess serial change with ultrasonography than with ^{99m}Tc-DMSA.

Magnetic resonance imaging (MRI)

6.62 MRI urography has been proposed as an alternative to ^{99m}Tc-MAG3 studies [70,71] and provides anatomical detail as well as functional data using similar mathematical calculations as are applied in ^{99m}Tc-MAG3 studies. However, in order to obtain these functional data (renal parenchymal transit time and differential renal function), the patient has to be given a gadolinium contrast agent. As mentioned

above, neonates and young children may be at increased risk of NSF because of their physiological reduced GFR and, in addition, the incidence of NSF increases in patients who undergo repeated studies and who have underlying renal disease – i.e. just this population. Most studies in young children would need to be performed under general anaesthesia and some authors advise that a urinary catheter is placed in all children [70]. Therefore, this is a significantly more invasive test than a ^{99m}Tc-MAG3 study and, whilst it is indicated in select cases requiring better anatomical resolution than ultrasonography can provide, it is neither a reasonable nor a practical replacement for ^{99m}Tc-MAG3 studies for most neonates/infants.

Summary

6.63 Technetium-99m studies are proven to be the procedure of choice in a range of diagnostic investigations. Alternative imaging techniques may provide inferior clinical information and a lack of ^{99m}Tc will affect the imaging pathways in a number of critical conditions. In some cases there are no alternative options to ^{99m}Tc-based nuclear medicine studies. Where alternative nuclear medicine investigations are possible using non-^{99m}Tc radioisotopes there may be issues regarding availability, patient dose and staff training. There is little available capacity in other imaging modalities even where these can be used. Any transfer to PET services, CT or MRI would require substantial further investment in personnel and equipment. Transferring paediatric studies to other modalities incurs the additional risk and costs of a general anaesthetic in many patients.

Chapter 7

Legislative Issues – Obstacles to Change

Legislative framework and inspectorates/regulators

7.1 The administration of radiopharmaceuticals for medical diagnosis, therapy and research is subject to strict control. The transport, receipt, storage, manufacture and dispensing of these materials is covered by a range of regulatory articles with the intent of ensuring their safe and effective use.

International regulation

7.2 The EURATOM Basic Safety Standards Directive [72] defines the European legal framework for radiation protection of workers and the general public and is based on the following main principles.

a *Justification* of all new types of practices resulting in exposure to ionising radiation before being first adopted giving due regard to their economic, social or other benefits in relation to the health detriment they may cause.

b *Optimisation* of protection to ensure that the radiation exposures of workers, members of the public and the population as a whole are kept as low as reasonably achievable, economic and social factors being taken into account.

c *Limitation* of the exposure to ensure that the sum of the radiation doses from all relevant practices will not exceed the legal dose limits for workers or members of the public.

7.3 The Basic Safety Standards Directive establishes a system of national reporting and regulatory authorisation of activities resulting in exposure to ionising radiation. It also requires a system of inspection to enforce the legal requirements to be established in Member States.

7.4 The Medical Exposure Directive [73] supplements the Basic Safety Standards Directive by providing specific requirements for health protection of patients and other medically exposed individuals against the dangers from ionising radiation. The Medical Exposure Directive provides a legal framework based on the basic radiation protection principles of justification and optimisation taking into account the specificity of medical exposure as deliberate exposure of people for their own health benefit. Dose limits do not apply to patients and other medically exposed individuals. The Basic Safety Standards Directive is currently being reviewed with four other radiation protection directives, including the Medical Exposure Directive, with the intention of making a single comprehensive directive.

UK regulation

7.5 Within the UK, the requirements set out in the various European directives are satisfied through a number of sets of regulations, some of which are described below.

7.6 The Ionising Radiations Regulations 1999 (IRR99) [74] were made under the Health and Safety at Work etc Act 1974 [75]. They require employers to establish a framework for ensuring that exposure from ionising radiation resulting from work activities, whether man-made or natural radiation and from external radiation or internal radiation is kept as low as reasonably practicable and does not exceed the dose limits specified in the regulation. These Regulations are enforced by the Health and Safety

Executive in Great Britain. In Northern Ireland, the Ionising Radiations Regulations (Northern Ireland) 2000 [76] were made under the Health and Safety at Work (Northern Ireland) Order 1978 [77]. These Regulations are enforced by the Health and Safety Executive for Northern Ireland.

7.7 The Ionising Radiations (Medical Exposures) Regulations 2000 [25] and the Amendment 2006 [78] (IR(ME)R) identify a number of duty holders with responsibilities associated with medical exposures. These Regulations also include the principles of justification and optimisation which apply to all types of procedures resulting in a medical exposure. These Regulations are enforced by the Care Quality Commission in England, Health Inspectorate Wales in Wales and the Scottish Executive in Scotland. In Northern Ireland the Ionising Radiations (Medical Exposures) Regulations (Northern Ireland) 2000 [79] and the Amendment 2010 [80] (IR(ME)R(NI)) are enforced by the Regulation and Quality Improvement Authority.

7.8 The Environmental Permitting Regulations (England and Wales) 2010 (EPR2010) [81] were introduced on 6 April 2010 and replaced the provisions of the Radioactive Substances Act 1993 (RSA93) [82] in England and Wales. RSA93 still applies in Scotland and Northern Ireland. The purpose of both sets of legislation is to control radioactive waste in order to provide radiation protection to members of the public. Hospitals wishing to use radioactive materials or to accumulate, dispose or receive radioactive waste need to apply for a permit under EPR2010 or for registration and/or authorisation under RSA93. These Regulations are enforced by the Environment Agency (EA) in England and Wales, the Scottish Environment Protection Agency (SEPA) in Scotland and the Northern Ireland Environment Agency (NIEA) in Northern Ireland.

7.9 The provisions of the Medicines Act 1968 [83] and the Medicines for Human Use (Marketing Authorisations etc) Regulations 1994 [84] apply to the sale, supply and manufacture of all radiopharmaceuticals. The Regulations allow the manufacture of licensed and unlicensed radiopharmaceuticals at sites holding a Manufacturer's (Specials) Licence. A person preparing licensed and unlicensed radiopharmaceuticals in a hospital under the supervision of a pharmacist is exempt from the requirement to hold a Manufacturer's Licence under Section 10 of the Act. These Regulations are enforced by the Medicines and Healthcare products Regulatory Agency (MHRA) in Great Britain and the Department of Health, Social Services and Public Safety (DHSSPS) in Northern Ireland.

7.10 The Medicines (Administration of Radioactive Substances) Regulations 1978 [85] and the Amendments 1995 [86] and 2006 [87] (MARS) provide a system of prior authorisation for doctors or dentists wishing to administer radioactive medicinal products. The MARS Regulations established the Administration of Radioactive Substances Advisory Committee (ARSAC) to advise ministers on matters relevant to issuing certificates of authorisation. These Regulations are enforced by the MHRA in Great Britain and the DHSSPS in Northern Ireland.

7.11 The transportation of radiopharmaceuticals is subject to restriction under the Carriage of Dangerous Goods and Use of Transportable Pressure Equipment Regulations 2009 [88] (CDG2009), which require appropriate consignment and documentation when any materials are transported on a public highway. These regulations are principally enforced by the Health and Safety Executive.

7.12 Responding to the ^{99}Mo shortages has been particularly challenging for a number of agencies that are involved with the enforcement of these regulations.

Environment Agency position on ^{99}Mo shortage

7.13 In order to assist hospitals minimise the impact on patient care the EA has taken a flexible approach to be applied when shortages are in place. It first published guidance on its enforcement position in 2008 and then updated this in May 2010 [89] following the introduction of EPR2010. The terminology from RSA93 is still used for familiarity when describing the enforcement position, which can be summarised as follows.

Registration

7.14 The EA has stated that it will not take enforcement action against registration holders who choose to respond to the $^{99}Mo/^{99m}Tc$ shortages by keeping increased amounts or a range of radioisotopes beyond that allowed by their current registrations. This includes the holding of larger generators incorporating depleted uranium shielding, the delivery of ^{99m}Tc (where the current registration only includes $^{99}Mo/^{99m}Tc$ generators) and the use of alternative isotopes such as ^{201}Tl. The EA requires registration holders to maintain suitable records of any temporary arrangements.

Authorisation

7.15 The EA has also stated that it will not take enforcement action against authorisation holders who respond to the $^{99}Mo/^{99m}Tc$ shortages by disposing to sewer an increased amount or range of radionuclides (beyond that allowed by their current authorisation) provided that the overall radiological impact of those disposals is not greater than that of the disposals allowed by their authorisation. The Radiation Protection Adviser (RPA) should review the hospital's radiological impact assessment. If this confirms that the revised disposals will not result in an increased radiological impact, a summary should be provided to the local regulator who will confirm the enforcement position in writing.

7.16 Substituting ^{99m}Tc with other isotopes may result in additional radioactive waste which may need to be stored for longer periods prior to disposal. The EA requires nuclear medicine departments to review their arrangements for waste storage to ensure that any additional waste can be handled safely and provide a summary to the local regulator. Where a department proposes to increase the solid waste consigned for off-site disposal, the EA requires the department to confirm its proposed approach with its local regulator.

7.17 This enforcement position is intended to apply only when temporary or ad hoc measures are in place. Permit holders are expected to resume their compliance with all the limits and conditions of their permits once the period of acute shortage is over. Where a permanent change in arrangements has resulted from the problems with the $^{99}Mo/^{99m}Tc$ supply, the EA require the department to apply for a variation to the registration or authorisation.

MHRA position on the ^{99}Mo shortage

7.18 During shortages of $^{99}Mo/^{99m}Tc$ the ability to distribute surplus ^{99m}Tc or ^{99}Mo generators to other NHS departments would be advantageous. However, concerns have been expressed whether this is legally possible under the control mechanisms that apply to radiopharmaceuticals. The MHRA has not published guidance on this topic and questions about liability remain unanswered.

7.19 It is unclear whether the Medicines Act would be contravened and where the liability rests in the following situations.

- **a** If an unlicensed hospital was to supply another hospital with multidose vials or unit doses following receipt of a signed order or prescription. In this case it is assumed that the liability rests with the unlicensed hospital supplying the radiopharmaceuticals.
- **b** If an unlicensed hospital was to supply another hospital with a vial of generator eluate in order the latter could compound its own licensed or unlicensed radiopharmaceuticals (assuming that signed orders or prescriptions were in place). In this case it is unclear if the liability is shared.
- **c** If a hospital with a wholesaler dealer licence sold a used $^{99}Mo/^{99m}Tc$ generator to another hospital in order that the latter could prepare kits within its own radiopharmacy. The 'second-hand' generator would be classed as an unlicensed product and MHRA Guidance Note No. 14 [90] would be applicable as no licensed product is available. The receiving hospital should treat the generator as an unlicensed product and test as given in guidance from the UK Radiopharmacy Group (UKRG) [91].

ARSAC position

7.20 ARSAC has put in place mechanisms to prioritise applications for non-^{99m}Tc procedures.

Transport regulations

International shipping

7.21 The production of ^{99}Mo/^{99m}Tc generators is an international business with the production process often involving transportation of radioactive materials across international borders on several occasions prior to shipping to the hospital user. These cross-border shipments are regulated by individual countries in accordance with the International Atomic Energy Agency's (IAEA) International Regulations for the Safe Transport of Radioactive Material [92]. Although these Regulations allow radioactive materials to be transported in commercial airliners, airline companies can refuse to carry these shipments and individual airline pilots can refuse to carry shipments even if company policies allow it. The IAEA has reported that it is becoming increasing difficult to ship radioactive materials by air [92].

7.22 The North American Council on Radionuclides and Radiopharmaceuticals (CORAR), with the support of the Nuclear Energy Agency (NEA/OECD) and the European Association of Imaging Producers and Equipment Suppliers (AIPES), has entered into discussion with the IAEA on how to better inform shippers of the medical nature of the shipment of ^{99}Mo, both in bulk and in generators. Possible options to be pursued include developing a new UN shipping classification for medical radionuclide shipments, providing more information for aircraft freight handling, or adding new labels on transport containers to provide additional information.

7.23 A continuing problem with the air shipment of radioactivity is that packages are often relatively small, but of high weight. It is frequently the case that aircraft are found to be overweight and these packages are removed immediately prior to take off. Since there is no current recognition that these materials are for medical use they are not regarded as high priority.

7.24 Operators and industrial participants will continue to supply information to the IAEA on different transport-related issues as they arise, including denial of shipments. It is recommended that systematic reporting of these issues is carried out by the process laid out in IAEA Denial Network Handbook [93].

7.25 Within Europe it is estimated that 2.5 million packages containing radioactive material are shipped each year [8]. Across Europe, there are a variety of different national and regional regulations which must be complied with, which can complicate transport by ground. Although the national deviations in the regulatory requirements can appear to be minor, the impact in terms of additional effort, time and resources can be significant. The European Commission has recognised this regulatory burden and is currently examining the possibility of a new Council regulation establishing a system for registration of carriers of radioactive material [8]. The intention is to harmonise and simplify administrative procedures.

Domestic transportation

7.26 The transport of any radioactive materials must be carried out in accordance with the requirements of the CDG2009 [88]. In many cases NHS staff (healthcare scientists) would be in a position to carry small amounts of activity in private vehicles to enable clinical investigations to take place; however, this is restricted due to exclusions on private insurance policies. There is anecdotal evidence to show widespread inconsistencies in the provision of insurance cover to carry small amounts of radioactive materials. Often, the decision from the insurance company varies depending upon the level of seniority of the person handling the query. It is unclear whether there is a mechanism to highlight this issue with insurance companies.

7.27 Hospitals and universities with multiple buildings separated by public roads have to ensure that transportation is carried out to the same standards even for a short journey. This has implications for transport packaging, vehicle costs and driver training (staffing).

7.28 Any nuclear medicine department sending more than two Type A packages per month is highly likely to need to appoint a dangerous goods safety adviser (DGSA).

Counterterrorism security requirements

7.29 Over recent years the security requirements for the use of radioactive materials have increased significantly. There may be some situations where these requirements could make it difficult to change working practices, in particular for out-of-hours deliveries (e.g. weekend or overnight generator deliveries).

Cost implications/impact

7.30 The costs associated with revising EA permissions or MHRA licence agreements are not prohibitive. It is likely that these costs would only be incurred if a permanent change is made.

Information and communication

7.31 It has been clear that during ^{99}Mo shortages one of the main issues for nuclear medicine departments has been advance warnings of planned delivery schedules and amounts of activity to be delivered. Commercial suppliers in the UK have responded by issuing bulletins and, with the support of the Department of Health, the British Nuclear Medicine Society has provided a comprehensive information service via its website, www.bnms.org.uk.

7.32 However, even when global information is available about likely periods of shortages it is difficult for nuclear medicine departments to plan until delivery confirmation is received from the generator supplier. This may be obtained at very short notice and often not until the week that the generator is due for delivery.

7.33 The evidence has shown that the provision of this information has been essential for nuclear medicine departments to maintain patient services and meet waiting list objectives with reduced amounts of ^{99}Mo/^{99m}Tc.

Summary

7.34 Within the UK, nuclear medicine services are governed by a range of regulatory controls and agencies. Most regulatory and professional bodies have been flexible in responding to the acute shortage of ^{99}Mo/^{99m}Tc but agreement needs to be reached on more permanent approaches. The transfer of radiopharmaceutical products and part-used generators between hospitals offers a partial solution to interruptions of supply but clear guidance on liability is needed in this specific scenario.

Chapter 8

Conclusions

8.1 Nuclear medicine provides an expanding and essential imaging modality with proven benefits in a wide range of clinical conditions. In contrast to other imaging modalities, nuclear medicine is dependent on a time-defined and external element, namely the radiopharmaceuticals administered to the patient, as well as the equipment and staff employed to produce images.

8.2 It is based largely on the use of ^{99m}Tc-labelled radiopharmaceuticals and services have evolved over a period of time to meet local needs. This model has relied upon a cheap and readily available source of ^{99}Mo. Recently, the cost of ^{99}Mo generators has increased to cover supply chain issues and will probably rise again to support new technologies. While a hub and spoke model for nuclear medicine provision has been discussed for many years, it has never been progressed in any planned or logical way. The worldwide shortage of ^{99}Mo has provided an opportunity to consider afresh this aspect of the nuclear medicine service.

8.3 The complexity of the ^{99}Mo target and generator production processes means that local solutions for sources are not currently practicable. There are no research reactors producing ^{99}Mo in the UK and it would not be financially viable to consider developing these. Nor is it sensible when considering supply alone, as long as European and international cooperation is established, supported and maintained. Future technological developments may offer more opportunities within the UK but these are for the long rather than medium term.

8.4 At local level, options now exist which may help to alleviate the shortages of ^{99}Mo. Different radiopharmaceutical production models can make more efficient use of the ^{99}Mo available. New gamma camera technology has led to the development of more efficient detection systems, allowing patient dose savings. Software solutions developed to decrease scan times may have application in dose reduction with benefits to the patient as well as providing a response to ^{99}Mo supply issues.

8.5 Alternatives to conventional nuclear medicine imaging are limited. PET services in the UK are not fully developed and, although PET may provide a suitable alternative, further capacity is required. Imaging modalities such as CT and MRI may be capable of providing diagnostic information for conditions where nuclear medicine is usually employed, but in many cases these modalities do not have the equivalent sensitivity and specificity. Nor is there spare capacity within CT and MRI services. Evidence suggests that a move away from nuclear medicine to increased application of CT and MRI would have an impact on the quality of patient care while incurring significant costs.

8.6 The current staffing profile and numbers within nuclear medicine are inappropriate to support flexible working for the medium and long term if approaches are based on addressing temporary situations. It may be more productive to consider alternative working arrangements with a view to long-term adoption, whether the ^{99}Mo shortage remains or not. It should be noted, however, that any model of service delivery designed to maximise the use of available ^{99}Mo under existing delivery schedules will have additional costs.

8.7 The importance of a flexible approach to regulation, the cooperation of nuclear medicine professionals and the provision of information through professional bodies such as the British Nuclear Medicine Society has become clear throughout the past two years and this multidisciplinary, multi-agency

approach needs to be maintained if nuclear medicine services are to continue to provide high quality, timely care for patients.

8.8 Finally, in considering this topic, we have reviewed the evidence available from a wide range of sources. The circumstances that have initiated this report have changed since it was originally commissioned and continue to do so on a frequent basis. As a consequence, reliable data on some aspects of the report are not as abundant as for others but this is to be expected.

Chapter 9

Recommendations

Recommendation 1

Nuclear medicine services are an integral part of healthcare and, despite the increased use of PET CT, for the near future, diagnostic nuclear medicine will continue to be based on ^{99m}Tc-labelled products. Security therefore of ^{99}Mo supply is essential. This can be achieved in the long term at international level by investment to upgrade existing reactors and to build new research reactors, to ensure provision of ^{99}Mo at a sufficient level to meet current and expanding demand during all foreseeable events. We recommend that the Department of Health and other government departments should continue to support European Commission initiatives to ensure a stable supply of ^{99}Mo for Europe. In addition, the Commission and other international agencies should be supported in their efforts to amend European legislation to facilitate the transport of irradiated targets across national borders to ensure timely supply to generator manufacturers.

Recommendation 2

While the existing model for ^{99}Mo production has proved effective for many years, the recent shortages have demonstrated that over-reliance on a few suppliers can prove problematic. We recommend that new technological solutions are monitored, including the potential long-term solution of UK-based production of ^{99m}Tc in medical cyclotrons.

Recommendation 3

Currently the three European companies that manufacture ^{99}Mo generators do so during the working week rather than during weekends. This is not the case in the USA. We recommend that the Department of Health should explore with generator suppliers the feasibility of weekend production and alternative delivery schedules to ensure that ^{99m}Tc availability matches the traditional, efficient service delivery model for healthcare.

Recommendation 4

During periods of ^{99}Mo shortages many hospitals have adapted traditional working practices, e.g. changing the radiopharmaceutical production model to provide a second elution and production run per day or working at weekends to make more efficient use of the available ^{99}Mo. We recommend that where practicable hospitals should consider adopting some of these strategies on a permanent basis, and that traditional employment contracts should be amended to introduce flexible working patterns, to include weekends and extended days within the current pay constraints.

Recommendation 5

Compared with Wales, Scotland and Northern Ireland, radiopharmaceutical production and supply within England is essentially local and is undertaken on a small scale. This is for historical rather than logistical reasons. While some larger central radiopharmacies exist, these are very much in the minority. The introduction of PET CT services in the UK using ^{18}F-FDG has demonstrated that for routine diagnostic nuclear medicine services, a production and supply service based on fewer centralised

facilities is viable. We recommend that the Department of Health undertakes a review of radiopharmacy services to explore whether the number of large central radiopharmacies, which are more resilient during shortages, should be increased to provide the majority of ^{99m}Tc-based radiopharmaceuticals for safe and patient-focussed nuclear medicine services within England.

Recommendation 6

Nuclear medicine imaging demonstrates functional information. It relies upon the administration of radiopharmaceuticals which in general are produced outside the UK. It has already been highlighted that ^{99}Mo production using traditional technology is not practicable at UK level. PET CT services, which can provide physiological information as an alternative to conventional nuclear medicine in some circumstances, rely upon local production of radiopharmaceuticals in cyclotrons. This is a robust supply chain; however, a large percentage of PET CT services in England are currently provided through time-limited independent sector contracts. We recommend that adequate PET CT services continue to be provided across the UK. Optimal coverage of these services should be ensured following the completion of the independent sector provision in England.

Recommendation 7

The UK has well-established regulatory frameworks designed to ensure the safe production, use and disposal of radioactive materials and radiopharmaceuticals. As a consequence of recent shortages, the Environment Agency in England and Wales has demonstrated a flexible approach regarding its own regulatory and enforcement policies to enable the most efficient use of available ^{99}Mo while maintaining overall safety strategies. We recommend that the Department of Health, with other government departments and agencies, addresses options regarding transfer of radioactivity, radiopharmaceuticals and generators between different hospitals, with a view to issuing clear guidance.

Recommendation 8

Technological developments in gamma camera hardware and software design have the potential for nuclear medicine investigations to be performed using less activity. This has benefits for the patient with regard to radiation dose but also for the nuclear medicine service in terms of costs and efficient use of available ^{99}Mo. We recommend that a multicentre, multivendor trial is undertaken in order that the viability of resolution recovery software with reduced activity is evaluated. If proved to be successful, we strongly recommend that nuclear medicine services purchase this software for new and existing gamma camera systems where applicable.

Chapter 10

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Appendix A

Proposal for a Multicentre Research Study to Validate a Reduced Activity Protocol using Resolution Recovery Software

Data collection

A1 All nuclear medicine departments in the UK will be invited to take part in the study. They will be eligible to take part if they regularly perform myocardial perfusion imaging (MPI) with ^{99m}Tc-tetrofosmin or ^{99m}Tc-sestamibi using any combination of the equipment given below. They should be imaging a minimum of 20 patients per week and these must be reported locally by someone who is experienced in reporting MPI studies. Each department will be expected to enter 50 routine MPI SPECT studies (50 stress and 50 rest scans) into the project. These should be chosen randomly from the range of pathologies and patient groups normally scanned by the department.

A2 For every MPI study a standard acquisition and a half-count acquisition will be used for both stress and rest scans, but this will be achieved without the need to repeat the acquisition on any patient. This is possible because most manufacturers have developed programs that can take produce a simulated half-count scan from an existing scan. Therefore the project can be carried out retrospectively using existing patient data. Alternatively, one manufacturer has acquisition software that can acquire full-time and half-time data simultaneously with some gamma camera models. If a department wished to use this method it would have to collect new data prospectively, but this would not affect the patient in any way. Both of these methods have the advantage that, apart from the number of counts, the two sets of images will be identical in terms of patient position, patient movement, activity distribution in the myocardium and presence of non-cardiac activity. This makes it much easier to detect any change due just to the number of counts acquired. Neither method requires any change to the routine clinical procedure for the patient, so both are classified as service evaluation rather than research. The National Research Ethics Service Enquiry Line has confirmed that this project is service evaluation and therefore it does not require ethical review by an NHS Research Ethics Committee.

A3 The way in which the half-count data are obtained and processed will depend on the equipment available in each nuclear medicine department. Since users may not have yet invested in installing resolution recovery software on their computer systems, some manufacturers have kindly agreed to process data on behalf of users for the purpose of this project. Any data sent to manufacturers for processing must have all possible patient identification removed beforehand, apart from a study number allocated by the local investigator.

a Departments using GE Healthcare gamma cameras (Infinia, Ventri or Discovery NM/CT 670) with LEHR collimators and GE Healthcare computers (Xeleris with version 2 software) can potentially make use of GE Healthcare's Evolution for Cardiac software for resolution recovery. Users should contact GE Healthcare (david.whalley@med.ge.com) to ascertain whether their hardware and software are suitable for participation in this project. If users do not already have Evolution software installed, then GE Healthcare may be able to provide it on a trial, basis. GE Healthcare may be able to provide users with a half-time simulation program so that they can generate the half-count data and process it themselves.

b Departments using Philips Healthcare gamma cameras (Forte JETStream, SKYLight, BrightView, BrightView XCT, CardioMD or Precedence) and Philips computers (JETStream workspace or EBW NM) can potentially make use of Phillips Astonish software for resolution recovery. Users should contact Philips (Joe.Glennan@philips.com) to ascertain whether their hardware and software are suitable for participation in this project. If users do not already have Astonish installed, then Philips may be able to provide a loan system. Philips software already includes a program that can be used to generate half-angle or half-count data from existing scans. Alternatively, since most new Philips cameras support concurrent acquisition, it is possible to acquire full-time and half-time data simultaneously. Therefore the department could choose to acquire its next 50 patient studies (50 stress and 50 rest scans) using acquisition parameters that give two sets of images for each acquisition – a full-count image with standard parameters and a half-count image with half the normal time per frame. Indeed some users may already be acquiring data this way by default. User will then be able to process the half-count images with Astonish.

c Departments using Siemens gamma cameras (Symbia, e-cam or c-cam) and Siemens computers (Syngo MI Applications version 3.5) can potentially make use of Siemens CardioFlash software for resolution recovery. However, Siemens does not yet have a validated method for generating half-count data and so it is not currently possible for this company to participate in this project.

d Departments using any gamma camera and Hermes computers can potentially make use of Hermes HybridRecon software for resolution recovery. Users should contact Hermes (steve@hermesmedical.com) to ascertain whether their hardware and software are suitable for participation in this project. Users may already have HybridRecon installed or they may be able to have access to it via the online TeleHERMES hosted service. Hermes does not have its own software for generating half-count scans but users may be able to generate half-count data using software from their gamma camera manufacturer as described above.

e Departments using any combination of gamma camera and computer system (including, but not limited to, those listed above) can potentially make use of Scivis ReSPECT software for resolution recovery. Users should contact Tilmann Prautzsch at Scivis (prautzsch@scivis.de) who will be able to make arrangements for users to send anonymised data to Scivis which will run it through a half-count simulation program, then process it with ReSPECT and return the processed images to the users.

f Departments using any combination of gamma camera and computer system (including, but not limited to, those listed above) can potentially make use of UltraSpect Xpress Cardiac software for resolution recovery. Users should contact Bob Kenny at Link Medical (bob@linkmed.org) who will be able to make arrangements for users to send anonymised data to UltraSpect which will run it through a half-count simulation program, then process it with Xpress Cardiac and return the processed images to the users.

A4 Once users have made suitable arrangements with the appropriate supplier as described above, they will select 50 patient studies (50 stress and 50 rest scans) from amongst the routine myocardial perfusion studies acquired during the preceding two months. Studies that were not considered to be of adequate technical quality at the time can be omitted, but apart from that studies should be selected randomly by taking consecutive patients. The selected studies will be copied and anonymised. All 100 anonymised scans will then be put through the manufacturer's special program to create additional half-count images out of the original full-count images. (Philips users who have chosen to acquire data prospectively will instead select the next 50 consecutive studies and acquire full-time and half-time datasets simultaneously. The half-count datasets will then be copied and anonymised.)

Data processing

A5 All standard (full-count) scans will be reconstructed using the department's normal processing protocol, including any processing of gated data to give cardiac function parameters, end diastolic volume (EDV), end systolic volume (ESV) and left ventricular ejection fraction (LVEF). These standard results will then be reported in the normal way, before anonymisation, as part of the routine clinical protocol. An anonymised copy of the standard report will then be saved for the purpose of this project.

A6 An initial selection of 10 patient studies (10 stress and 10 rest scans) will be used for familiarisation with the resolution recovery processing. The half-count images will be processed using the appropriate resolution recovery software (either installed locally or sent to the manufacturer as appropriate). Reconstruction parameters (e.g. filter settings and number of iterations) will be based on the manufacturer's recommendations, but the user may choose to adjust these if required to give a result as similar as possible to the standard processing method used by the department. The person who normally reports myocardial perfusion scans will be shown a selection of half-count images reconstructed using different resolution recovery reconstruction parameters and asked to select the ones with which they feel most comfortable. Because the resolution recovery software is designed to improve resolution, it is inevitable that the images will appear different to standard ones. Therefore the reporter will be given time to compare standard and resolution recovery images of the same anonymised patient and to familiarise themselves with the different image appearances. This is equivalent to what would happen in practice if the user decided to purchase the resolution recovery software and start acquiring half-count images routinely.

A7 Once the familiarisation stage is complete, the remaining 40 half-count studies (40 stress and 40 rest scans) will then be processed with the resolution recovery software, using the optimum parameters determined from the familiarisation stage. If appropriate, gated data will be further processed to give cardiac function parameters.

A8 If results show that the half-count studies processed with resolution recovery software give acceptable images then it will be necessary to determine whether the resolution recovery software was actually necessary or whether half-count studies without resolution recovery would also be acceptable. To do this all 50 half-count studies will finally be processed by the user's standard methods and reported for a third time.

Data reporting

A9 At a separate reporting session the person who reported the original studies will be shown the remaining 40 anonymised half-count studies reconstructed with resolution recovery software and asked to re-report these. They will be given any relevant clinical information from the original request that they would normally have had available at the time of reporting. This clinical information will be anonymised and any unusual details that might allow the reporter to remember the original case will be removed or changed. This is only necessary in order to stop the reporter from recalling their original report. The reporter should be made aware that they are looking at resolution recovery processed data and they will make any necessary allowances for this based on their experience during the familiarisation stage.

A10 The local investigator will then compare the new report with the original report and grade them on the following scale.

0	There is no difference between the original and new reports
1	There are only minor differences between the reports, not enough to make a clinical difference
2	There is a clinically relevant discrepancy between the reports which could affect patient management
3	The quality of the half-count images is too poor to give a meaningful report

A11 It should be noted that scans of poor technical quality should have been excluded from the study, so all of the original reports should have been based on images of adequate quality. If there is any doubt as to whether a difference between the reports is minor or clinically relevant, then the two reports should be reviewed by an independent clinician other than the person who created the reports. If any reports show a clinically relevant discrepancy, then this should be followed up as appropriate to determine the best outcome for the patient. This might include obtaining a second opinion on the images, discussing the case with the referring clinician or, if necessary, requesting further investigations. This follow up is necessary to resolve any discrepancies between the two results and hence to improve future reports. It is an important part of the service evaluation of this new software because it closes the audit loop.

A12 If results of this stage indicate that the half-count data reconstructed with resolution recovery software are likely to be acceptable, then the person who reported the original studies will be asked to re-report the 50 anonymised half-count studies reconstructed in the standard manner (without resolution recovery). These reports will be compared with the original report using the same grading scale as before.

Analysis of results

A13 The number of studies where there is a clinically significant discrepancy between the two reports will be determined. It is expected that there should be no more than 1% of cases showing significant differences. The actual number of discrepancies will be compared with the expected number using the binomial distribution. With a sample size of 50, any more than two clinically significant discrepancies would be statistically significant. The sample size of 50 gives a power of 58% for detecting 6% of clinically significant discrepancies and a power of 77% for detecting 8% of discrepancies.

A14 The percentage of studies where there is a minor difference between the two reports will be calculated. Since minor differences are not clinically relevant there is no critical value for this parameter.

A15 The null hypothesis that there is no difference between the cardiac parameters EDV, ESV and LVEF calculated from the two scans will be tested using the paired t-test. Any differences will be analysed using Bland-Altman plots.

Appendix B

Administration of Radioactive Substances Advisory Committee

Chairman

Dr T Nunan*

Present members

Dr J Ballinger
Dr L Biassoni
Dr K Bradley
Dr W Evans
Dr T Grüning
Dr S Hughes
Mr D Jones
Dr T Lynch
Mr P Maltby
Dr J MacDonald
Mr D McCool
Dr J B Neilly
Dr A Notghi
Prof M O'Doherty
Dr R Owen
Dr A-M Quigley
Dr J Rees
Mr J Thom
Dr W Thomson
Dr W L Wong

Former members who served during the preparation of this report

Dr R Allan
Dr J Bomanji
Dr B Ellis
Prof J Franklyn
Ms C Greaves
Dr A Hilson
Dr N Kennedy

Secretariat

Mr S Ebdon-Jackson
Mrs L Fraser
Ms K Stonell
Mrs C Strange

Strategic Report Subcommittee

Chairman

Mr P Maltby

Members

Dr R Allan
Dr J Ballinger
Ms C Greaves
Dr T Nunan
Dr M Prescott
Prof A Perkins

Secretariat

Mr S Ebdon-Jackson
Mrs L Fraser

* Following the retirement of Dr T Nunan in October 2010, Dr J Rees agreed to stand as Chairman on an interim basis, until a formal appointment can be made.

Appendix C

Declaration of Members' Interests

Code of practice

Introduction

1 This code of practice guides members of ARSAC as to the circumstances in which they should declare an interest in the course of the Committee's work.

2 To avoid any public concern that commercial interests of members might affect their advice to Government, Ministers have decided that information on significant and relevant interests of members of its advisory committees should be on the public record. The advice of the Committee predominantly relates to matters which are connected with the medical use of radioactive medicinal products and, less frequently, to commercial interests involving radioactivity and the radiation industry. It is therefore essential that members should comply with the code of practice which is set out below.

Scope and definitions

3 This code applies to members of ARSAC and its subcommittees, subgroups, working groups and working parties which may be formed.

4 For the purposes of this code of practice, the 'radiation industry' means:

(a) Companies, partnerships or individuals who are involved with the manufacture, sale or supply of products, processes or services which are the subject of the Committee's business. This will include isotope producing industries, and medical services industries.

(b) Trade associations representing companies involved with such products.

(c) Companies, partnerships or individuals who are directly concerned with research or development in related areas.

(d) Interest groups or environmental organisations with a known interest in radiation matters.

This excludes government departments, professional bodies, international organisations and agencies.

It is recognised that an interest in a particular company or group may, because of the course of the Committee's work, become relevant when the member had no prior expectation this would be the case. In such cases, the member should declare that interest to the Chairman of the meeting and thereafter to the Secretariat.

5 In this code, 'the Department' means the Department of Health, and 'the Secretariat' means the secretariat of ARSAC.

Different types of interest – definitions

6 The following is intended as a guide to the kinds of interests which should be declared. Where a member is uncertain as to whether an interest should be declared they should seek guidance from the Secretariat or, where it may concern a particular subject which is to be considered at a meeting, from the Chairman at that meeting. Members of the Committee and the Secretariat are under no obligation to search out links between

one company and another, for example where a company with which a member is connected has a relevant interest of which the member is not aware and could not be expected to be aware.

If members have interests not specified in these notes but which they believe could be regarded as influencing their advice they should declare them to the Secretariat in writing and to the Chairman at the time the issue arises at a meeting.

Personal interests

6.1 A personal interest involves current payment to the member personally. The main examples are:

(a) Consultancies and/or direct employment: any consultancy, directorship, position in or work for the radiation industries which attracts regular or occasional payments in cash or kind.

(b) Fee-paid work: any work commissioned by those industries for which the member is paid in cash or kind.

(c) Shareholdings: any shareholding in or other beneficial interest in shares of those industries. This does not include shareholdings through unit trusts or similar arrangements where the member has no influence on financial management.

(d) Membership or affiliation: any membership role or affiliation that the member or close family member has to clubs or organisations with an interest or involvement in the work of the Department. This will not include professional bodies, organisations and societies.

Non-personal interests

6.2 A non-personal interest involves current payment which benefits a department to which the member is responsible, but is not received by the member personally. The main examples are:

(a) Fellowships: the holding of a fellowship endowed by the radiation industry.

(b) Support by industry: any payment, other than support or sponsorship by the radiation industry which does not convey any pecuniary or material benefit to a member personally but which does benefit their position or department, e.g.

(i) a grant from a company for the running of a unit or department for which a member is responsible;

(ii) a grant or fellowship or other payment to sponsor a post or a member of staff in the unit for which a member is responsible. This does not include financial assistance for students, but does include work carried out by postgraduate students and non-scientific staff, including administrative and general support staff.

(iii) the commissioning of research or work by, or advice from, staff who work in a unit for which the member is responsible.

(c) Support by charities and charitable consortia: any payment, other support or sponsorship from these sources towards which the radiation industry has made a specific and readily identifiable contribution. This does not include unqualified support from the radiation industry towards the generality of the charitable resource.

(d) Trusteeships: where a member is trustee of a fund with investments in the radiation industry, the member may wish to consult the Secretariat about the form of declaration which would be appropriate.

Specific interests

6.3 A specific interest relates explicitly to the material, product, substance or application under consideration by the Committee.

6.4 A member must declare a personal, specific interest if they currently receive a payment, in any form, for any significant fundamental development work undertaken previously or at any time, on a material, product or substance or its application under consideration. This will include the production of radioactive substances and devices designed to use ionising or non-ionising radiation for diagnostic, treatment or other purposes.

A member must declare a non-personal, specific interest if they are aware that the department to which they are responsible currently receives payment for significant fundamental development work undertaken previously or at this time, on a material, product or substance or its application under consideration but they have not personally received payment for that work in any form. This will include the production of radioactive substances and devices designed to use ionising or non-ionising radiation for diagnostic, treatment or other purposes.

Non-specific interests

6.5 A non-specific interest relates to a company or associated material, product, substance or application, but not to the specific material, product, substance or application under consideration by the Committee.

6.6 A member must declare a personal, non-specific interest if they have a current personal interest with a material, product, substance or application from a particular company, which does not relate specifically to the material, product, substance or application from that company under consideration.

A member must declare a non-personal, non-specific interest if they are aware that the department to which they are responsible is currently receiving payment from the company concerned which does not relate specifically to a material, product, substance or application under discussion.

If a member is aware that a material, product, substance or application under consideration is or may become a competitor of a material, product, substance or application manufactured, sold or supplied by a company in which the member has a current personal interest, they should declare their interest in the company marketing the rival material, product, substance or application.

6.7 Members are under no obligation to seek out knowledge of such work done for or on behalf of the radiation industry within departments to which they are responsible if they would not reasonably expect to be informed. This applies to all non-personal, specific and non-specific interests.

Declaration of interests

7 Members should inform the Secretariat in writing when they are appointed of their current personal and non-personal interests and annually in response to a Secretariat request. Only the name of the company (or other body) and the nature of the interest is requires; the amount of any salary, fees, shareholding, grant, etc, need not be disclosed. An interest is current if the member has continuing financial involvement with the industry, e.g. if they hold shares in a radiation company, have a consultancy contract, or if the member or the department for which they are responsible is in the process of carrying out work for the radiation industry. Members are asked to inform the Secretariat at the time of any change in their personal interests, and may be invited to complete a form of declaration when required. It would be sufficient if changes in non-personal interests are

Declaration of interests to the Secretariat

reported at the next annual declaration following the change. (Non-personal interests involving less that £5000 from a particular company in the previous year need not be declared.)

The register of interests should be kept up to date and be open to the public.

Declaration of interests at meetings and participation by members

8 Members are required to declare relevant interests at Committee meetings and to state whether they are personal or non-personal interests. The declaration should include an indication of the nature of the interest.

(a) If a member has a current (personal or non-personal) interest in the business under discussion, they will not automatically be debarred from contributing to the discussion subject to the Chairman's discretion. The Chairman will consider the nature of the business under discussion and of the interest declared (including whether it is personal or non-personal) in deciding whether it would be appropriate for the relevant member to participate in the item.

(b) If a member has an interest which is not current in the business under discussion, this need not be declared unless not to do so might be seen as concealing a relevant interest. The intention should always be that the Chairman and other members of the Committee are fully aware of relevant circumstances.

9 A member, who is in any doubt as to whether they have an interest which should be declared, or whether to take part in the proceedings, should ask the Chairman for guidance. The Chairman has the power to determine whether or not a member with an interest shall take part in the proceedings.

10 If a member is aware that a matter under consideration is or may become a competitor of a product, process or service in which the member has a current personal interest, they should declare the interest in the company marketing the rival product. The member should seek the Chairman's guidance on whether to take part in the proceedings.

11 If the Chairman should declare a current interest of any kind, they should stand down for that item and the meeting should be conducted by the Deputy Chairman or other nominee if the Deputy Chairman is not there.

Member's declarations of interests 2010

Member	Company	Personal interest	Company	Non-personal interest
Dr J Ballinger		None	GE Healthcare Imaging Equip Ltd	Equipment for research Support of PhD student
Dr L Biassoni		None		None
Dr K Bradley		None		None
Dr W Evans		None		None
Dr T Grüning		None		None
Dr S Hughes		None		None
Mr D Jones		None		None
Dr T Lynch		None		None
Mr P Maltby		None		None
Dr J MacDonald		None		None
Mr D McCool		None		None
Dr J B Neilly		None		None
Dr A Notghi	GE Healthcare	Course fee paid	GE Healthcare	Grant for research
Dr T Nunan		None		None
Dr M O'Doherty		None	GE Healthcare	Grant for research
Dr R Owen		None		None
Dr A-M Quigley		None		None
Dr J Rees		None		None
Mr J Thom		None		None
Dr W Thomson		None	Physics and Nuclear Medicine Department, City Hospital, Birmingham	Provision of a krypton gas generator service to other NHS Trusts
Dr W L Wong	InHealth 4 Ways Healthcare	PET CT clinical lead PET CT auditor		None

Appendix D

Glossary

ANGIOGRAPHY	Imaging of the blood vessels, with intravenous contrast added to the blood to make visualisation possible.
ATTENUATION CORRECTION (AC)	Method used in computed image reconstruction to account for a loss of detected counts caused by attenuation of gamma rays.
BECQUEREL (Bq)	The international (SI) unit to measure radioactivity. One becquerel is equal to one nuclear decay per second. Within nuclear medicine, administered activities are typically in the megabecquerel (MBq) range.
CARDIAC GATING	Using an electrical signal from the contraction of the heart to trigger the imaging of separate phases of the cardiac cycle.
COLLIMATOR	Fitted to gamma cameras, the collimator is generally made of lead or tungsten with a honeycomb of holes which allow the desirable gamma rays to pass through. Gamma rays which are not coming orthogonally from the patient are absorbed by the collimator and eliminated from the final image.
COMPUTED TOMOGRAPHY (CT)	A radiographical technique that uses a computer to assimilate multiple X-ray images into a two-dimensional cross-sectional image.
CURIE (Ci)	A unit to measure radioactivity commonly used within the USA and Canada. One curie = 3.7×10^{10} becquerel (37 GBq)
CYCLOTRON	A compact particle accelerator. A cyclotron uses electric and magnetic fields to accelerate a charge, eventually emerging from the cyclotron at high speed. Cyclotrons are routinely used to produce radiopharmaceuticals for positron emission tomography (PET) in the UK.
DIAGNOSTIC REFERENCE LEVEL (DRL)	Standard dose levels or levels of radioactivity for nuclear medicine for typical diagnostic investigations using ionising radiation. ARSAC sets DRLs for the most commonly used nuclear medicine tests in its Notes for Guidance on the Clinical Administration of Radiopharmaceuticals and Use of Sealed Radioactive Sources (last issued in 2006)
EFFECTIVE DOSE	Effective dose is the sum of the weighted equivalent doses in all the tissues and organs of the body. It takes into account the biological effectiveness of different types of radiation and variation in the susceptibility of different organs and tissues to radiation damage. Thus it provides a common basis for comparing exposures from different sources. It has the unit of sievert (Sv)
ELUTION	Chromatographic system to extract one material from another. This is used within a $^{99}Mo/^{99m}Tc$ generator where the ^{99m}Tc is eluted from ^{99}Mo.
END DIASTOLIC VOLUME (EDV)	The volume of the left ventricle of the heart at peak filling (diastole).
END SYSTOLIC VOLUME (ESV)	The volume of the left ventricle of the heart at contraction (systole).
FISSION	A nuclear reaction in which the nucleus of the atom splits into smaller parts releasing large amounts of energy.

GAMMA CAMERA	Equipment used to image gamma radiation. Commonly used within nuclear medicine scintigraphy to image gamma radiation emitted from a patient previously administered with a radiopharmaceutical.
GENERATOR	A system used to produce a short-lived radionuclide from a relatively long-lived parent radionuclide for medical practice. Commonly used radionuclide generators in nuclear medicine include ^{99}Mo/^{99m}Tc and ^{81}Rb/^{81m}Kr.
HIGHLY ENRICHED URANIUM (HEU)	Uranium containing more than 20% ^{235}U. Natural uranium contains 0.7% ^{235}U. HEU containing more than 90% ^{235}U is used in some research nuclear reactors that produce ^{99}Mo.
INTRAVENOUS CONTRAST	A dye injected into the vein used to provide contrast between blood vessels and other tissues, or to enhance the visibility of tumours on an image.
IONISING RADIATION	Radiation that is sufficiently energetic to remove electrons from atoms in its path. In human or animal exposures ionising radiation can result in the formation of highly reactive particles in the body which can cause damage to individual components of living cells and tissues.
ISCHAEMIA	A low oxygen state usually due to obstruction of the arterial blood supply or inadequate blood flow leading to hypoxia in the tissue
LEFT VENTRICULAR EJECTION FRACTION (LVEF)	The fraction of blood ejected with each heart beat divided by the end diastolic volume, i.e. LVEF = (EDV – ESV) / EDV.
LOW ENRICHED URANIUM (LEU)	Uranium containing less than 20% ^{235}U. LEU is used as fuel in nuclear power reactors.
MAGNETIC RESONANCE IMAGING (MRI)	An imaging technique that uses a powerful magnetic field and radiofrequency fields to construct high resolution anatomical and functional images of the body. No ionising radiation is used in MRI.
METASTATIC DISEASE	A disease which is able to spread from the organ or tissue of origin to another part of the body.
MULTIDETECTOR COMPUTED TOMOGRAPHY (MDCT)	A form of CT technology used in diagnostic imaging, where a two-dimensional array of detector elements replaces the linear array typically used in conventional and helical CT scanners. This arrangement allows the acquisition of multiple slices or sections simultaneously and therefore greatly increases the speed of image acquisition.
MYOCARDIAL PERFUSION	Blood flow through the heart.
NUCLEAR RESEARCH REACTOR	A nuclear reactor used for research purposes rather than the generation of nuclear power.
PARTICLE ACCELERATOR	A device that uses electromagnetic waves to propel charged particles to high speeds. Linear particle accelerators (linac) are commonly used in radiotherapy to accelerate electrons into a target to produce a beam of high energy (MeV) X-rays.
POSITRON EMISSION TOMOGRAPHY (PET)	A diagnostic investigation involving the acquisition of physiological images based on the detection of radiation through the emission of positrons. The positrons are emitted from a short-lived radioactive isotope incorporated into a metabolically active substance administered to the patient prior to the examination.
PULMONARY EMBOLISM (PE)	A blockage of the main artery of the lung or one of its branches from a blood clot.
RADIATION PROTECTION ADVISER (RPA)	An individual or body that meets the criteria of competence specified by the Health and Safety Executive and, for ongoing consultation, is appointed in writing by a radiation employer.

RADIOPHARMACEUTICAL	A pharmaceutical or drug labelled with a radionuclide used in nuclear medicine imaging and therapy.
RECONSTRUCTION	The computerised creation of images from a series of X-ray projections in computed tomography.
REFERENCE DATE/DAY	The calibration date (and normally time) at which the radioactivity of a source is known. Reference dates and activities are always supplied with deliveries of radiopharmaceuticals.
SENSITIVITY	A measure for assessing the results of diagnostic tests. Sensitivity is the proportion of diseased persons who are identified as being diseased by the test. It is the probability of correctly diagnosing a condition in a person who has that disease.
SIEVERT (Sv)	The international (SI) unit of effective dose. Because the sievert is a large unit, effective dose is commonly expressed in millisievert (mSv), i.e. one-thousandth of one sievert.
SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)	A nuclear medicine imaging technique that uses images acquired from a gamma camera to reconstruct a series of transaxial slices which are combined to produce a three-dimensional dataset showing the distribution of radioactivity throughout the patient's body.
SPECIFICITY	A measure for assessing the results of diagnostic tests. Specificity is the proportion of normal individuals who are so identified by the screening test. It is the probability of correctly excluding a disease in a normal individual.
STAGE 3 OR 4 CANCER	Locally advanced or metastatic cancer.
STIR	STIR (Short T1 Inversion Recovery) is an inversion recovery pulse sequence used in MRI with specific timing so as to suppress the signal from fat.
T1 (WEIGHTED MRI)	T1 is a magnetic timing parameter that differs from one tissue to another. Image contrast can be changed by varying timing parameters used in magnetic resonance pulse sequences. In T1 weighted images fat appears bright and water appears dark.
TYPE A PACKAGE	Transport package designed to withstand minor accidents, and only release a small fraction of its contents in a more serious accident. Common contents are technetium generators and other medical isotopes.
ULTRASONOGRAPHY	A diagnostic imaging technique that uses sound waves to image soft tissues of the body and for assessing flow in blood vessels.
X-RAY IMAGE	An image obtained using high energy radiation with waves shorter than those of visible light. X-rays possess the properties of penetrating most substances (to varying extents), of acting on photographic film or plate (permitting radiography), and of causing a fluorescent screen to give off light (permitting fluoroscopy). In low doses X-rays are used for making images that help to diagnose disease, and in high doses to treat cancer.