ESCOLA SUPERIOR DE TECNOLOGIA DA SAÚDE DE COIMBRA

Polytechnic Institute of Coimbra
Coimbra Health School

Selective Internal Radiation Therapy

Review of the Standard Operating Procedure for Selective Internal Radiation Therapy using SIR-Spheres microspheres labelled with Yttrium 90

Ana Rita Catarino

Master Degree in Nuclear Sciences Applied to Health

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Dissertation

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Coimbra, October, 2016

“Knowledge is a treasure but practice is the key to it”

Thomas Fuller

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Abstract

Aim: Selective Internal Radiation Therapy (SIRT), also known as radioembolization, is a liver-directed therapy for inoperable primary and secondary liver tumours. The aim of this study is to review the Standard Operating Procedure (SOP) used in the Radiopharmacy Department of the Oxford University Hospital NHS Foundation Trust to prepare ^{90}Y labelled SIR-Spheres microspheres, in order to improve the dispensing procedure for delivering the intended patient treatment doses. The specification is: the activity prescribed ±10%. **Methods:** Eleven tests were carried out according to the current SOP. Radioactivity was diluted in up to 3 or 5 ml of water for injection and inserted into a V-vial. Following this, the used syringes and needles were measured using a Capintec Radionuclide Calibrator to check for any remaining activity. **Results:** One of the doses dispensed (11th) was below the specification. This, is in, turn triggered the review of the SOP. The operator must dilute the dose up to 3 ml with water for injection and inject it in the V-vial. According to the new procedure, using the same syringe and needle the operator must draw up an additional 1 ml of water for injection and inject this volume again into the V-vial. This washes the syringe and needle and removes any remaining activity. **Conclusions:** The reviewed SOP to prepare ^{90}Y labelled SIR-spheres microspheres has shown to improve the dispensing procedure in terms of dose delivered to the patient. The collected data has been accepted and the reviewed SOP implemented in the Radiopharmacy Department at Oxford University Hospitals NHS Foundation Trust.

Contents

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List of Abbreviations

A

Abs. - absolute

ACoP - Approved Code of Practice

ALARP - as low as reasonable practicable

C

CR - complete response

CT - computed tomography

E

EA - Environmental Agency

EU- European Union

EMA - European Medicines Agency

F

^{18}F-FDG - [^{18}F]-fluorodeoxyglucose

G

g - Gauge

GMP - Good Manufacturing Practice

H

HCC - hepatocellular carcinoma

HEPA - High-efficiency particulate air

I

IAEA - International Atomic Energy Agency

ICRP - International Commission on Radiological Protection

IRR99- Ionizing Radiation Regulation 1999

M

MA - Marketing Authorisation

MHRA - Medicines and Healthcare products Regulatory Authority

N

NHS- National Health Service

N/Z - neutrons/protons ratio

P

PR - partial response

PVC - Polyvinyl chloride

PET - positron emission tomography

Q

QA - Quality Assurance

QC - Quality Control

R

RPS - Radiation Protection Supervisor

RSO - Radiation Safety Office

RSA93 - Radiation Substances Act 1993

S

SD - standard deviation

SIR - Selective Internal Radiation

SIRT - Selective Internal Radiation Therapy

SOP - Standard Operating Procedure

SPC - Summary of Product Characteristics

T

TDS - Technetium Dispensing Suite

TLD - Thermoluminescent dosimeter

V

VPS - volatile dispensing suite

Z

Z - Atomic number

1. Introduction

Radioactive nuclides have been used for cancer therapy since the 1940's. Traditionally, the therapeutic nuclide used was ^{131}I, but "newer" isotopes with particularly favourable nuclear properties have emerged. Of those, ^{90}Y is a very interesting nuclide. It has a higher maximum beta energy than ^{131}I (2.27 MeV vs 0.81 MeV) that confers better tissue penetration and a shorter half-life (2.67 days vs 8.06 days) that allows it to clear the radioactivity from the patient in a timely fashion. (1)

SIRT, also known as radioembolisation is an innovative therapy that has been developed for the treatment of unresectable primary and secondary liver tumours. There are two types of products available in SIRT therapy: the SIR-Spheres and the Theraspheres, both using ^{90}Y-labelled beads.

The therapy with SIR-Spheres microspheres labelled with yttrium 90 consists in the delivery of extremely small biodegradable resin beads, ranging in size between 20-60µ in diameter (Figure 1), directly into the liver tumour via the hepatic artery (Figure 2). Because of their small size and weight, they are taken by the blood flow to the small blood vessels surrounding the tumour where they lodge with a dose of internal radiation up to forty times higher than conventional radiotherapy, while sparing the healthy tissue (Figure 3). The microspheres do not distribute uniformly in the liver due to the physiology of hepatic arterial flow, the tumour to normal liver ratio of the tissue vascularity and the tumour size. The margins of the tumour gets higher density per unit distribution of microspheres than the normal liver. The microspheres implanted into the liver are not metabolised or excreted and they stay permanently in the liver where their radiation is released in order to destroy the tumour cells. (2)

Figure 1 - SIRTEX vial. (3)

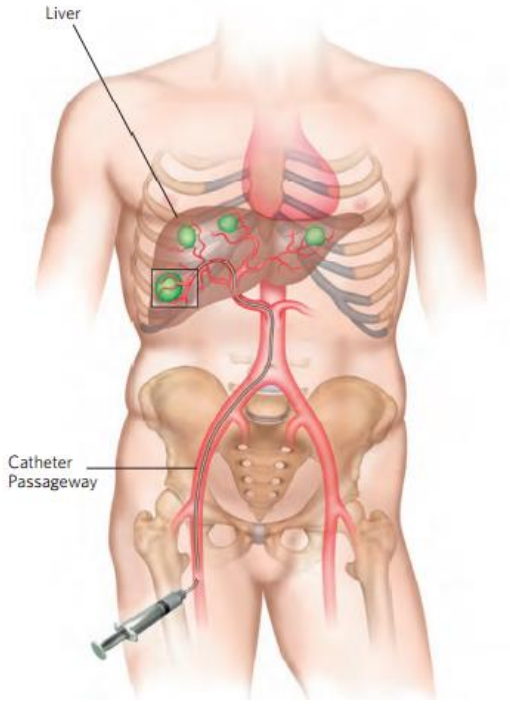

Figure 2 - Administration of SIR-Spheres microspheres. (4)

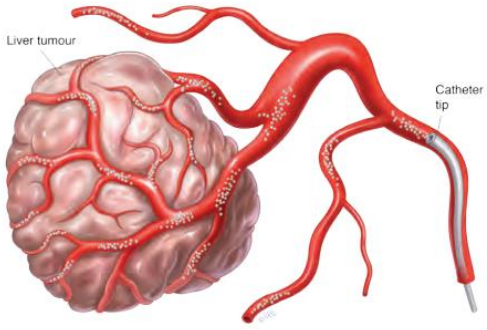

Figure 3 - Microspheres labelled with ^{90}Y being delivered to the tumor. (4)

The treatment of liver tumours with SIR-Spheres microspheres is possible because the liver tumours receive their blood supply almost entirely from the hepatic artery whereas the normal liver is supplied mainly from the portal vein. This means that infusion of labelled microspheres into the arterial system results in delivery of effective doses of radiation to the tumour without causing intolerable toxicity to the normal liver. (5)

Candidates for radioembolization are initially examined by hepatic angiogram to identify and map the hepatic arterial system, and at that time, a mixture of albumin particles is

delivered via the hepatic artery to simulate microspheres. After that, single-photon emission computed tomography gamma imaging is used to detect possible shunting of the albumin particles into gastrointestinal or pulmonary vasculature. (6)

Several studies have already demonstrated the efficacy of this technique in the treatment of primary and secondary liver tumours, as a single treatment or associated to chemotherapy. Randomised controlled studies in patients with liver metastases from colorectal cancer have demonstrated that SIRT using ^{90}Y labelled with microspheres significantly increases the tumour response and improves the control of the disease.

A study of 23 patients with unresectable liver tumours, hepatic metastases or HCC not responding to polychemotherapy and/or other local treatment has shown only minor side-effects with all patients still alive in the end of the study. Three-month follow-up investigations were available in 13 of 23 patients, which, so far, were showing a marked decrease of ^{18}F-FDG uptake, a drop in the level of tumour markers and unchanged or slightly decreasing lesion size (as measured by CT) in 10 of 13 patients. Two patients showed stable findings, while another patient showed progressive disease. Long-term follow-up investigations were available in 2 of 23 patients, showing hepatic and extrahepatic progression 6 and 9 months after SIRT with SIR-Spheres confirming that this treatment is a promising local therapeutic approach in patients with unresectable liver tumours which is feasible and has an acceptable toxicity profile. (7)

A study was conducted using SIRT for unresectable HCC with intra-arterial infusion of ^{90}Y labelled microspheres. The 71 participating patients did not demonstrate any extrahepatic disease. After the treatment, in 19 patients (26.7%) a 50% reduction in tumour volume was observed after the first treatment. However, the overall objective response in terms of changes in alpha-fetoprotein (tumour marker) level was 89% [PR 67%, CR 22%] among the 46 patients with raised pre-treatment levels. The study had shown that SIRT using ^{90}Y microspheres is effective for selected cases of unresectable HCC and is well tolerated. The objective response rate in terms of drop in tumour marker levels is higher than that based on reduction in tumour volume shown by CT. The non-tumorous liver appears more tolerant to internal radiation than external beam radiation. (8)

SIRT may convert unresectable tumours to resectable ones. This implies that previously inoperable liver tumours are now amenable to potentially curative resection or ablation. This

treatment increases time to progression of the tumours, extend overall survival and provide palliation of symptoms and can also be used allied to chemotherapy. (9) (10)
In order to provide this treatment effectively, the cooperation between different departments such as Radiopharmacy, Nuclear Medicine and Radiology is of crucial importance.

2. Hospital Radiopharmacy

A Radiopharmacy is a facility for manufacturing and dispensing of radioactive drugs, such as radiopharmaceuticals for diagnosis and therapy. It also needs to store radioactive materials, inventory records and prescriptions of radioactive substances. The Radiopharmacy is usually the collection point for radioactive waste and the unit responsible for waste storage and disposal. The unit can also be a centre for clinical investigations using radioactive tracers. It may also be a centre for research and for training of students and residents in radiology or nuclear medicine. (11)

The planning of a Radiopharmacy has to take several factors into consideration, namely the present and future needs of the department and compliance with all regulatory requirements. The concerns regarding facility design should be the safe production of radiopharmaceuticals in terms of good manufacturing and radiation protection practices, so the aims of the Radiopharmacy design is based on product protection and operator protection. Relatively to product protection, it must be protected from environment and operator contaminants as well as cross contamination from other products. Regarding operator protection, the operator must be protected from the radiation hazards as a consequence of handling radioactive materials and the biohazard present when radiolabelling blood components. Also of great importance is the protection of the surrounding environment as radioactive and microbial contamination must be prevented from escaping or being accidentally spread to other equipment, personal or general equipment. (12)

The two basic functions of a Radiopharmacy are the manipulation of unsealed radioactive materials and the preparation of these in a pharmaceutical form suitable for intravenous administration. In the United Kingdom the preparation of diagnostic and therapeutic radiopharmaceuticals is undertaken under the legislative control of the Medicines Act 1968. Commercial organisations must have a full manufacturing license with the MHRA or the EMEA, however organisations working with NHS have two options, to be licensed by the MHRA with a Manufacturer`s `Special´ License or working under a Section 10 exemption of the Medicines Act 1968, where medicinal products are dispensed under the direct supervision of a pharmacist. When manufacturing the guidelines provided in Rules and Guidance for Pharmaceutical Manufacturers and Distributors (GMP) (MHRA 2007) must be followed. (13) (14)

Diagnostic or therapeutic radiopharmaceuticals do not normally have any pharmacological effect and their administration is not associated with major clinical side effects. Their clinical use, however, is associated with a risk deriving from radiation exposure and possible contamination during radiopharmaceutical formulation by chemical, biological and microbiological impurities. This is particularly important since the majority of radiopharmaceuticals are administered intravenously. A thorough QA programme should, therefore, being in place and responsibilities clearly assigned.

Radiopharmaceuticals tend to differ from normal medicines in that they have a relatively "short" shelf-life. When manufactured in house, because of their rapid decay, they must be prepared shortly before their clinical use and comprehensive QC of the final product is not always possible: sterility testing, for instance, cannot be performed before patient administration because of time constrains. Safe and effective preparation and use of radiopharmaceuticals is, therefore, vital for the protection of the operator and the final user, the patient. Radiopharmaceuticals that contain radionuclides with longer half-lives as ^{90}Y SIR-Spheres microspheres are normally obtained as market-authorised finished products from commercial suppliers and dispensed in the Hospital Radiopharmacy. (15)

2.1. Radiopharmacy Facility - Cleanroom

The dispensing of the ^{90}Y SIR-Spheres microspheres is carried out in the Hospital Radiopharmacy constituted for cleanroom dedicated for manufacturing and dispensing of radiopharmaceuticals. In Oxford University Hospitals NHS Foundation Trust there are two different spaces connected with the cleanroom: the preparation room and the packing area. The preparation room is the area where the sundries, kits and radiopharmaceuticals used during the daily production are stored and is connected with the cleanroom through a changing room and one hatch. The packing area is connected with the cleanroom through one hatch and in this area the radiopharmaceuticals are not just packed and sent to the costumers as well as their radiochemical purity is tested in order to ensure they can be safely injected into patients. As part of the Radiopharmacy there is also a store room to keep the stock of material, the delivery radioactive store, the radioactive waste store and the reception area.

The main focus is the cleanroom, essential to carry out the dispensing of the radiopharmaceuticals. The cleanroom is a separate, dedicated and secure area. The operational area is always kept in good condition, and hygiene must always be ensured. The area meet local and national safety codes, including fire safety codes. The space is specifically designed and maintained to handle unsealed radionuclides so as to meet the required radiation safety standards. All work surfaces are smooth and impermeable, permitting easy cleaning and decontamination. Pipe work and cables are encased and properly laid to facilitate cleaning and decontamination. The space is sufficient to accommodate all essential equipment and accessories such as two isolators and radionuclide calibrators with adequate lead shielding around, L-shaped lead shields for handling radiopharmaceuticals, and shielded sharps waste storage containers (one for short lived radionuclides and the other for long lived radionuclides) and allow for at least two staff members to operate simultaneously. There are a sufficient number of long handle forceps, tongs, syringe shields, vial shields, shielded syringe carriers for gamma or positron emitting radionuclides and suitable shielding devices for handling beta emitting radionuclides. The work areas maintain satisfactory lighting, temperature and humidity to ensure the operator comfort, optimum equipment performance and expected radiopharmaceutical stability.

Each isolator, TDS and VPS (where the ^{90}Y SIR-Spheres microspheres are dispensed) presents a HEPA-filtered air supply. As the isolators are contained workstations providing the necessary environment conditions for aseptically producing and dispensing radiopharmaceuticals and radiotherapies such as SIRT they must comply with GMP Grade A and is recommended that isolators operating with negative pressure with respect to the background environment be used and the environment background is a minimum of GMP Grade D. (12) (16)

In terms of Grade, a cleanroom is defined as a room where the concentration of particles is controlled, constructed and operated in a manner that minimises the introduction, generation or retention of particles inside the room, and where parameters such as temperature, humidity and air pressure are also controlled. There are a number of systems used to classify cleanrooms but in this report will be presented the Good Manufacturing Practice (GMP) definition. (12)

Table 1 - EU GMP 2008, cleanroom air particle classification system for the manufacture of sterile products. (17)

GMP Grade	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		Operational	
	0.5µm	5µm	0.5µm	5µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

Regarding the properties of the cleanroom, in terms of air purity, the air is supplied by an air conditioning plant through diffusers in the ceiling that insure 20 to 60 total air changes per hour to dilute to an acceptable concentration any possible airborne contaminants produced in the room. Relatively to the air supply, the air enters into the cleanroom via HEPA filters capable of filtering 99.97% of all particles greater than 0.3µm. These filters are placed at the point of discharge of air into the room. In terms of room pressurisation, the cleanroom is positively pressurised to ensure air does not pass from the adjacent dirty areas, this is achieved by extracting slightly less air than the air supplied; to achieve this and to ensure air moves from areas of highest cleanliness to less clean in the cleanroom suite, it passes through grilles or extract ducts located at low levels in walls and doors. (12)

Table 2 - Recommended limits for microbial contamination. (17)

(a) these are average values.

(b) individual settle plates may be exposed for less than 4 hours.

(cfu) colony forming units.

Grade	Recommended limits for microbial contamination **(a)**			
	Air sample cfu/m^3	Settle plates (diameter 90mm) cfu/4h **(b)**	Contact plates (diameter 5mm) cfu/plate	Glove Print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

2.2. Operational Levels

The procedures performed in the field of a Hospital Radiopharmacy can vary considerably in different parts of the world. However, for clarity, these differences can be classified into three broad categories: operational levels 1, 2 and 3. Each category can be further subdivided to provide essential advice on staff qualifications, training, facilities, equipment, types of procedures, record keeping, QA and QC are essential at that level. The operational level 1 and 2 are subdivided in **a** and **b** and the operational level 3 is subdivided in **a**, **b** and **C**.

The operational level **1a** applies to the dispensing of radiopharmaceuticals purchased or supplied in their final form from recognized and/or authorised manufacturers or centralized radiopharmacies. This includes unit doses or multiple doses of prepared radiopharmaceuticals for which no compounding is required. The dispensing of ^{90}Y SIR-Spheres microspheres should be undertaken under **1b** which applies to the dispensing of radioiodine and other ready to use radiopharmaceuticals for radionuclide therapy or palliation. This includes ready to use injections of strontium and samarium for pain palliation.

Operational level **2a** is the preparation of radiopharmaceuticals from prepared and approved reagent kits, generators and radionuclides (closed procedure). This is the most common activity in nuclear medicine departments, with routine use of a technetium generator and reconstitution of pre-sterilized radiopharmaceutical cold kits. The operational level **2b** is the radiolabelling of autologous blood cells. This includes radiolabelling of red blood cells, platelets and white cells commonly used for infection or inflammation imaging.

The operational level **3a** is applicable for the compounding of radiopharmaceuticals from ingredients and radionuclides for diagnostic application (including open procedure); modification to existing commercial kits; in-house production of reagent kits from ingredients, including freeze dried operation; related research and development. Operational level **3b** applies to the compounding of radiopharmaceuticals from ingredients and radionuclides for therapeutic application (including open procedure) together with related research and development. The operational level **3c** is the synthesis of PET radiopharmaceuticals. This includes the increasingly popular ^{18}F-FDG injections among others. The compounding of radiopharmaceuticals produced from unauthorized or long lived generators such as ^{68}Ga or ^{188}Re - mostly related research and development - also falls under operational level 3c. (15)

2.3. Operating personnel and training

The practice of Radiopharmacy combines the expertise of manufacturing and dispensing pharmaceuticals or therapies and the skills needed to handle radioactive substances. To work in a Radiopharmacy the qualifications required for personnel should be in accordance with local regulations. When, however, these do not cover the qualifications needed for Radiopharmacy staff, it is suggested that the preparation and dispensing of radiopharmaceuticals is carried out by one of the following professionals: a nuclear technologist, medical doctor, pharmacist, chemist, biologist or nurse after completion of a basic training programme in radiation physics and instrumentation; mathematics of radioactivity use and measurement; radiation protection and regulations; radiation biology; radiopharmaceutical chemistry; and the clinical use of radiopharmaceuticals.(15)

All personnel should also receive practical training (hands on experience) in preparation, QC and analytical techniques, transport, laboratory cleaning and maintenance, equipment calibration and maintenance, preparation of individual doses and documentation as described in detail by the IAEA. Training should include a session on how to comply with aseptic procedure as part of GMP that must be in operation throughout the whole process. According to the level of operation, individual staff members should receive specific training which are described under each specific operational level. Any compounding as described in operational level 3 requires a qualified professional with certified training. (15) (16)

GMP is the minimum standard that manufacturers of medicinal products must meet in their production processes with a consistent high quality, to be appropriate to their intended use and meet the requirements of the MA and other relevant specifications. (14)

2.4. Standard Operating Procedure

All the procedures in the Radiopharmacy are described in SOPs. A SOP is a set of detailed written instructions that document a routine or repetitive activity followed by an organization. The development and use of SOPs are an integral part of a successful quality system as it provides individuals with the information to perform a job properly, and facilitates consistency in the quality and integrity of a product or end-result. They document the way activities are to be performed to facilitate consistent conformance to technical and

quality system requirements and to support data quality. They may describe, for example, fundamental programmatic actions and technical actions such as analytical processes, and processes for maintaining, calibrating, and using equipment. SOPs are intended to be specific to the organization or facility whose activities are described and assist that organization to maintain their QC and QA processes and ensure compliance with local, national and international regulations. (17)

If not written correctly, SOPs are of limited value. In addition, the best written SOPs will fail if they are not followed. Therefore, the use of SOPs need to be reviewed and re-enforced by management, preferably the direct supervisor. Current copies of the SOPs also need to be readily accessible for reference in the work areas of those individuals actually performing the activity, either in hard copy or electronic format, otherwise SOPs serve little purpose.

The development and use of SOPs minimize variation and promotes quality through consistent implementation of a process or procedure within the organization, even if there are temporary or permanent personnel changes. SOPs can indicate compliance with organizational and governmental requirements and can be used as a part of a personnel training program, since they should provide detailed work instructions. It minimizes opportunities for miscommunication and can address safety concerns. When historical data are being evaluated for current use, SOPs can also be valuable for reconstructing project activities when no other references are available. In addition, SOPs are frequently used as check lists by inspectors when auditing procedures. Ultimately, the benefits of a valid SOP is to reduced work effort, along with improved comparability, credibility, and legal defensibility. (16) (19)

3. Radiation Protection

In order to work safely with radioactive materials, there are radiation protection measures that must be taken into account. These measures are described in the ICRP and they are applicable not just in the United Kingdom but also in other countries around the world.
A fundamental principle of ICRP is to keep the activity ALARP. Radiation dose is received by irradiation from an external or internal source and directly absorbed into the body. In order to reduce the exposure we need the correct application of the three well-known dose-saving factors: time, distance and shielding. Time, means that the shorter the exposure to a radiation source the less dose is received. Shielding means that all radioactive sources should be returned to their container as soon as possible. Bins full of hot waste should be removed and placed away from staff members whenever possible. Distance, refers to the intensity and hence the absorbed dose from a radioactive source. It varies inversely as the square of the distance from the source (the "inverse square law"). So by doubling the distance, the dose rate drops to 1/4. The effects of radiation can be even worse at close distances, if for example the fingers are touching the external surface of the gamma emitting glass vial the dose may be one hundred times higher than that experienced by using tongs of reasonable length. Making a 10-fold increase in distance between source and finger means a 100-fold reduction in absorbed dose. In terms of shielding, the shield equipment should be adequate to the kind of isotope to be handling. (20) (21)
The electrons from beta emitters, as ^{90}Y, can be completely absorbed by with 1cm of Perspex. In comparison, gamma emitter show an exponential absorption with any absorber but this absorption depends on the energy of the gamma radiation and the atomic number and density of absorber. For low gamma energies the absorption varies as the cube of the atomic number and density of absorber, for higher energies it is independent of the atomic number. (21)

3.1. Beta emitters

Beta emission occurs through one of three processes of radioactive disintegration by which some unstable atomic nuclei spontaneously dissipate excess energy and undergo a change of one unit of positive charge without any change in mass number. The three processes are

electron capture, positron emission and electron emission. β decay was named (1899) by Ernest Rutherford when he observed that radioactivity was not a simple phenomenon. He called the less penetrating α- rays and the more penetrating β-rays. Most β particles are ejected at speeds approaching that of light. (22)

^{90}Y decays by electron emission, also called negative β decay (symbolized β^- decay). This process occurs when a nucleus is "neutron rich." So that means it has a higher N/Z ratio compared to a stable nucleus. Thus, it decays by β^- particle emission along with an antineutrino ($\bar{\upsilon}$). An antineutrino is an entity almost without mass and zero charge and is primarily needed to conserve energy in the decay. In β^- decay, a neutron (n) essentially decays into a proton (p) and a β^- particle according the example:

$$n \longrightarrow p + \beta^- + \bar{\upsilon}$$

The β^- is emitted with variable energy from zero up to the decay energy. The decay or transition energy is the difference in energy between the parent and daughter nuclides. The antineutrino carries away the difference between the β^- particle energy and the decay energy. The β^- particle decay can be followed by the emission of radiation gamma, if the daughter nuclide is in an exited state and the number of gamma rays emitted depends on the excitation energy. After β^- decay, the atomic number of the daughter nuclide is one more than that of the parent nuclide. However, the mass number remains the same for both nuclides. In comparison with other forms of radioactivity, such as γ or α-decay, β-decay is a relatively slow process. Half-lives for β decay are never shorter than a few milliseconds. (23)

^{90}Y is a high energy pure β^- emitting isotope that decays to stable ^{90}Zr with a physical half-life of 64.1 h. The emitted particle has a maximum energy of 2.27 MeV and a mean of 0.93MeV. The mean tissue penetration is 2.5 mm and the maximum is 10 mm. In therapeutic use, considering the isotope decay to infinity, 94% of the radiation is delivered in 11 days. The average number of particles implanted in the liver is 30 – 60 x 10^6. (2)

$$^{90}Y \longrightarrow {}^{90}Zr + \beta^- + \bar{\upsilon}$$

^{90}Y (Z= 39, N=51) decays to ^{90}Zr (Z=40, N=50) by emission of a beta particle and an antineutrino. ^{90}Zr is stable. (24) (25)

3.2. Controlled and Supervised areas

The designation of areas is an important part of radiation protection practice and must be adequately described in the Local Rules however it is an area which is often mismanaged either because of under-designation or over designation.

The cleanroom is designated as a Controlled Area**,** this is an area that when following a risk assessment indicates to be an area where it is necessary for a person who enters to follow special procedures designed to restrict exposure or prevent or limit the probability of a radiation accident or if the dose to an employee (aged 18 or over) working in the area is likely to exceed any of the values in column 2 of Table 3. Special procedures refer to more than 'generic safety procedures' which would ordinarily be applied in that area regardless. They are procedures specifically designed for the purpose of radiation protection. With respect to numerical limits, IRR99 does not go further than the above criteria. The ACoP does however include additional requirements for Controlled Area designation which are where:

- the average external dose rate exceeds 7.5μSv/h over a working day.
- the hands of an employee can enter an area and the 8 hour time averaged dose rate in that area is 75μSv/h;
- there is a significant risk of spreading radioactive contamination outside the working area;
- it is necessary to prevent (or closely supervise) access to the area by employees who are not directly connected to the radiation work.

The need to control access will also influence the decision as to whether an area needs to be designated. There are some management arguments for designating a Controlled Area in order to restrict access for reasons other than simply radiation protection – perhaps to enhance security. However, over designation should be avoided unless the area can meet all the requirements, particularly those in IRR99 outlined later.

In addition, caution should be given to designating on the basis of expected annual dose to employees alone. For example, if an area is occupied by an employee for 2000 hours a year (40 weeks, 5 days per week), then a continuous ambient dose rate of only 3 μSv/h would be enough to require designation on the basis of 6 mSv/year being reached.

The additional requirements designated for a Controlled Area are the physical demarcation of the area if reasonably practical and the displaying of suitable signs in suitable positions indicating the area designated and nature of the sources and risks, for example it is often useful to indicate if there is a contamination risk, a radiation risk or both. In the case of external radiation hazards it is also important to mention if this arises from radioactive sources or from x-rays.

Where a Controlled Area has been defined, entry is restricted to either classified workers, if the worker is likely to receive an effective dose in excess of 6mSv per year or an equivalent dose which exceeds 3/10 of any relevant limit; or a person entering under a written system of work which specifies how staff should carry out procedures to ensure the dose received will not exceed 3/10 of any limit and an assessment of any dose received must be undertaken. A written system of work will likely be acceptable where, for example, the employer has designated a whole room as "Controlled" but the work requiring designation is only carried out in a small part of it. It would also be appropriate where maintenance or service engineers, not normally working with ionising radiation, are required to enter the Controlled Area to perform their tasks. Adequacy of a system of work can be undertaken by examining appropriate personal dose assessments or recording the occupancy time where, for example, dose rates are known to be constant or do not exceed a particular level.

The employer who has designated an area as being Controlled must ensure that any outside workers are subject to arrangements for estimating dose. As soon as possible, an estimate of the dose received whilst in the Controlled Area must be entered into his/her radiation passbook. In most circumstances this should be undertaken on the day that entry is made into the area.

There are some additional matters in terms of Controlled Areas with radioactive materials, particularly in an unsealed form. As there is a significant risk of the spread of radioactive contamination from the Controlled Area, the employer must make adequate arrangements for its prevention such as, maintenance of washing and changing facilities, the prohibition of eating, drinking or similar activity and monitoring any person or goods leaving the area to avoid contamination trapping. Workplace monitoring should be undertaken routinely to assess the levels of removable contamination and airborne contamination. Airborne contamination can be assessed by measuring the level average over any 8 hours period, surface contamination may be assessed by wipe techniques on the basis 1/10 of removable

contamination has been transferred to the wipe and averaging over 1000 cm^2 for floor, walls, ceiling and 300 cm^2 for other areas. (26) (27)

A Supervised Area, packing area and waste decay store, is an area which, following a risk assessment, has been shown to be an area where is necessary to keep conditions under review to determine whether it should be Controlled or Supervised, in which a person is likely to receive an effective dose greater than 1mSv per year or an equivalent dose greater than 1/10 of any relevant dose limit referred in the column 3 of Table 3, or a combination of the two situations above mentioned.

It should be noted that many employers designate an area as Supervised even when assessments show that the doses in the third column of the Table 3 are unlikely to be reached. This can enhance good radiation protection practices and can be complemented by the appointment of a RPS and the adoption of local rules. (26)

Table 3 – Limits of annual exposure according the area designation. (26)

Area of Body	Controlled Area	Supervised Area
Whole body effective dose	6 mSv	1 mSv
Lens of eyes	45 mSv	15 mSv
Skin	150 mSv	50 mSv
Hands, forearms, feet and ankles	150 mSv	50 mSv

3.3. Personal Monitoring

Staff working in a Radiopharmacy may be designated as classified radiation workers, depending on the volume of work they are individually required to do. Staff in an averaged sized Radiopharmacy will probably not be designated as classified workers as they will be unlikely to exceed 3/10 of any relevant dose limit, however those in a very large Radiopharmacy may be classified workers. Additional classified or non-classified staff working with radioactive substances or patients should wear at least a personal dosimeter to give an estimate of effective dose and a dosimeter on an extremity (finger) to monitor their skin extremity dose. (28)

The body badges used at Oxford University Hospitals NHS Foundation Trust are Luxel Body Badges which contains a sheet of radiation-sensitive aluminium oxide sealed in a light and

moisture proof packet. When the atoms in the aluminium oxide sheet are exposed to radiation, electrons are trapped in an excited state until irradiated with a specific wavelength of laser light. The released energy of excitation, which is given off as visible light is measured to determine radiation dose. The packet contains a series of filters designed so that the energy and type of radiation can be determined. In order for the radiation type and energy to be determined, the dosimeter must be worn so that the front of the dosimeter faces towards the source of radiation. According the manufacturer the Luxel Body Dosimeters are among the most sensitive dosimeters available, the minimum detectable dose is 1 mrem for x-rays and gamma rays and 10 mrem for energetic beta radiation.

The ring dosimeter contains a small radiation-sensitive lithium fluoride crystal. When atoms in the crystal are exposed to radiation, electrons are trapped in an excited state until the crystal is heated to a very high temperature, the released energy of excitation, which is given off as visible light, is measured to determine radiation dose, calling this process thermoluminescence. The dosimeters that use this principle are often referred to as TLDs. TLD dosimeters are slightly less sensitive than Luxel dosimeters; the minimum detectable dose for TLD ring dosimeters is 30 mrem for x-rays and gamma rays and 40 mrem for energetic beta radiation. Both the body and ring badges do not detect radiation from beta emitters with energies less than 250 KeV.

The Guidelines to use dosimeters must be followed:

- badges must not be shared or worn by another person, each badge is intended to be worn by only the designated person;
- badges must not be intentionally exposed to radiation, intentional tampering with badges is a very serious matter;
- if it has been discovered that the badges are contaminated, the RSO must be promptly notified and replacement badges must be requested;
- badges must not be worn when receiving a medical x-ray or other medical radiation treatment. The badges are intended to document occupational dose, not medical dose. (29) (30)

3.4. Waste Management

There is a legal obligation for users of radioactive materials in the United Kingdom to comply with the RSA93, unless they are working under an exemption order, which is very unlikely to apply to a Hospital Radiopharmacy. This act ensures control over the use of radioactive material and its resulting waste. As the waste is potentially harmful, it is important to store and dispose it safely. Furthermore, it needs to be taken into account that waste is not produced in unnecessary quantities. Thus, control is necessary over the use and storage of radioactive materials, as well as to have an efficient waste management system in place.

The EA provides a regulatory system of registration and authorisation for the use, accumulation and disposal of radioactive materials. They inspect premises and departments whether or not they are fit for purpose and if satisfied, issue the appropriate permits. (31)

At the Radiopharmacy at Oxford University Hospitals NHS Foundation Trust, short lived isotopes, such as ^{99m}Tc, which has a half-life of 6 hours, can be disposed once it has decayed below background level. Long lived isotopes are disposed according the decay-in-store method, which safeguards the operator as well as members of the public from exposing unnecessarily from high radiation. Furthermore, it allows precise monitoring of the decay of long lived isotopes. The Radiopharmacy maintains a lead shielded long lived sharps bin as well as a safe, depending on the level of remaining activity in the vials. The lead shielded long lived sharps bin, will only contain vials, which have a remaining activity of below 20MBq. Anything above this level, needs to be stored into the lead lined safe, due to its safety aspects. An electronic and paper spreadsheet system is maintained for both the long lived sharps bin as well as the safe, which records the type of isotope, batch number of vial, activity (MBq) and the date of storage. The electronic spreadsheet system works under the decay calculation formulae, which then automatically calculates and notifies the operator, once the long lived isotope is safe for disposal. A waste database exists, which runs along the electronic spreadsheet system and calculates for the operator when the isotopes have decayed safely and the bin can be disposed. The database generates also a unique number to each long lived isotope bin. When dispensing ^{90}Y SIR-Spheres microspheres, a new radioactive bin is used for each dispensing process. According to IAEA recommendations it is crucial to record the estimated 10% of the waste from the dispensed patient dose, which is usually retained in syringes, needles and Lacto tubing.

4. Review of SOP to prepare Yttrium 90 labelled with SIR-Spheres microspheres in the Hospital Radiopharmacy

4.1. SOP to prepare Yttrium 90 labelled SIR-spheres microspheres (SOP NM-L3-155)

To prepare ^{90}Y yttrium labelled SIR-spheres microspheres for injection into the hepatic artery to produce therapeutic radioembolisation these working instructions must be followed and carried out by a competent person.

1. SIR-Spheres microspheres are intended for use on the day of calibration. At the date and time of calibration, the activity in the vial matches the activity printed on the label (3GBq ±10%). The microspheres may be used for up to 24 hours after calibration. Do not use beyond 24 hours of calibration time.
2. Please note that the dose may be divided into two, one dose for the left lobe of the liver and one for the right lobe of the liver. This will be indicated on the prescription.
3. The SIR-Spheres microspheres should be drawn up in the VPS. **NB:** This procedure MUST be observed and checked by a second competent member of staff
4. Materials required:
    - Tongs
    - Forceps
    - Alcohol wipes
    - V-vial*
    - Acrylic V-vial holder *
    - 2 x 25g needle (orange) **
    - 5ml syringe*
    - 5ml syringe shield (Perspex)
    - 21g needle 70mm long *
    - Perspex shield
    - Water for injection *
    - 50cm Lacto Tubing**
    - 0.2µm filter**

- Marker pen

* 2 will be required if the dose is split into 2 parts

** 3 will be required if the dose is split into 2 parts

5. Invert the lead pot several times before opening.
6. Set the calibrator to measure the Yttrium-labelled microspheres.
7. Quickly open the pot and remove the inner vial (containing the microspheres) with tongs and determine the total activity using the calibrator.

NOTE: Accurate measurement requires fully suspended microspheres, so it is important to make all measurements quickly.

8. Return the inner vial to the lead delivery pot and place it in the shielded work area replace the lid on the lead delivery pot.
9. Prepare the V-vial as follows. Completely remove centre of aluminium crimp seal from sterile V-vial with forceps to expose septum. Use the marker pen to put two dots on either side of septum (at 180º from each other) trace a line from each dot vertically down the side of the vial top. Swab the septum with an alcohol wipe.
10. Place sterile V-vial in the dedicated acrylic V-vial holder and screw on lid. This provides stability and shielding for the sterile V-vial. Place the V-vial holder near the lead pot in the shielded working area.
11. Connect a 25 g needle to one end of the Lacto Tubing and a 0.2 µm filter to the other end.
12. Insert the 25 g needle through the septum of the V-vial piercing the septum through one of the dots, to create a vent; do not push the needle too far down. The V-vial is now ready to receive microspheres.
13. Prepare the syringe for use by placing it in the Perspex syringe shield and attaching the long needle (70 mm).
14. Determine the volume of SIR-Spheres microspheres to be withdrawn from the vial to provide the required patient radiation dose. Please note if the volume is less than 3ml it will be necessary to dilute the SIR-spheres with water for injection. The spheres must be diluted in the syringe before they are added to the V-vial.

15. Re-suspend the microspheres by inverting the lead pot.
16. Remove lid from the lead delivery pot to expose microspheres inner vial.
17. Partially remove centre of aluminium crimp seal from the microspheres vial with forceps to expose septum and swab septum with an alcohol wipe held in forceps. Do not fully remove crimp seal.
18. Repeat stage 11 and then pierce the SIR-sphere vial septum ensuring that the needle tip is well clear of the SIR-spheres.
19. Use the shielded 5ml syringe with long needle to puncture the septum of the SIR-sphere vial.
20. Re-suspend microspheres with vigorous mixing by quickly drawing up and expelling the microspheres in the shielded 5ml syringe at least six times.
21. Quickly draw up the volume of SIR-Spheres microspheres containing the calculated dose into the shielded 5mL syringe. Carefully remove the 21g needle from the inner microspheres vial, recap the needle using forceps and set the dose aside.
22. To check the dose activity of the V-vial contents (patient specific dose), return the inner vial to the calibrator to measure the activity that is left.
23. If additional activity is required, repeat steps 12 to 14 above to obtain the correct patient dose.
24. If the total volume in the shielded syringe is less than 3ml, draw up enough sterile water for injection to make up to a total volume between 3 and 5ml. The water must be added whilst the spheres are in the syringe.
25. Insert the lubricated 21g hypodermic needle into swabbed septum of sterile V-vial through the second dot opposite the venting needle and deliver the microspheres from the shielded syringe into the V-vial ensuring the spacing between any punctured holes in the V-vial is at least 2mm apart and careful not to scrape the V-vial's sidewalls. **Note:** This step should be done ONCE only.
26. Remove the vent needle from the V-vial; use the marker pen to clearly write the activity and if the dose is split write L for left lobe dose and R for the right lobe dose. Ensure lid of the V-vial holder is secure and the plug is in place.
27. For split doses repeat steps 9 onwards for the second dose.
28. Remove the vent needle from the shipping vial and replace the lid of the lead delivery pot.

29. Remove the V-vial and lead pot from the isolator.
30. Complete the form for ^{90}Y labelled SIR-spheres microspheres
31. Expiry time for labelled ^{90}Y SIR-Spheres is 24 hours post the calibration time. (32)

Figure 4 - Material used to dispense SIR-spheres microspheres. (33)

4.2. Material and Methods

After dispensing each SIRT dose prescribed according SPC and SOP, the residue in the syringes and needles used to dispense are measured.

1. The 5ml syringe with the needle is removed from the beta syringe shield and measured in the Capintec Radionuclide Calibrator - CRC®-15R (SN 510215).
2. The syringe and needle are placed in the Acrylic (clear) liner PVC using the calibration setting 27*10 for measurements of the isotope ^{90}Y in 5 ml syringes.
3. The radioactivity (MBq) of each syringe and needle measurement is recorded once the readings on the calibrator have settled down.

4. The residue in the syringe and needle is subtracted from the activity dispensed. The activity dispensed is determined by the subtraction of the final activity measured in the ^{90}Y inner vial (after dispensing) from the initial activity measured in the ^{90}Y inner vial (before dispensing).

5. The subtraction of the activity in the syringe and needle from the activity dispensed gives the activity effectively dispensed.

5. Results

The collection of data resulted initially from the interest of verifying the level of precision of radioactivity effectively deliver to the patients.

The information collected revealed to be important when the patient`s doses started to be measured not just in Radiopharmacy but also by the Medical Physics before doses were sent for injection. The measurements taken have shown some discrepancies, which needed to be further investigated.

The SIR-Spheres microspheres are labelled with ^{90}Y suspended in an aqueous solution. The dense viscosity of microspheres is contributing for the loss of activity when using the subtraction method described in the SPC and SOP.

In order to understand the following tables it is important to note that the activity delivered to the patients is the activity effectively dispensed. This activity is obtained by the subtraction of the residue in the inner vial and the residue in the syringes and needles from the initial activity in the inner vial according the following formulae:

Activity Effectively Dispensed = Activity Delivered to the patient

Activity Effectively Dispensed =

Initial Activity in the Inner Vial – (Residue in the Inner Vial + Residue in the syringes and needles)

The results of the measurements during the dispensing procedure, following SOP NM-L3-155 are demonstrated in the following tables and charts:

Table 4 - Measurements of the residues in the syringe and needle when dispensing SIRT according SOP NM-L3-155.

SIRT N.	Activity prescribed (MBq)	Initial activity in the inner vial (MBq)	Required splits (%)	Drawn up split activity (MBq)	Residual activity in syringes/ needles (MBq)	Total residual activity (MBq)	Residual activity in the inner vial (MBq)	Activity dispensed into V-vial (MBq)	Activity effectively dispensed (MBq)	Error (abs. %)
1	1500 ± 10%	3810	30%	450	19.40	55.1	2320	1490	1434.90	4.34
			70%	1040	35.70					
2	1000 ± 10%	3640	30%	300	25.80	68.6	2600	1040	971.40	2.86
			70%	700	42.80					
3	1500 ± 10%	3600	100%	1630	45.20	45.2	1970	1630	1584.80	5.65
4	2100 ± 10%	3870	20%	450	48.50	168.5	1606	2264	2095.50	0.21
			80%	1814	120.00					
5	1100 ± 10%	3590	20%	200	3.50	24.94	2520	1070	1045.06	4.99
			40%	470	14.76					
			40%	400	6.68					
6	1200 ± 10%	3590	16.67%	190	7.34	42.96	2370	1220	1177.04	1,91
			41.67%	520	18.42					
			41.67%	510	17.20					
7	2000 ± 10%	2000	100%	2023	44.30	44.3	1647	2023	1978.70	1.06
8	900 ± 10%	3800	30%	270	12.99	44.39	2920	880	835.61	7.15
			70%	610	31.40					
9	800 ± 10%	3660	100%	860	64.70	64.7	2800	860	795.3	0.59
10	1800 ± 10%	3700	30%	540	32.80	43.8	1938	1762	1718.2	4.54
			70%	1260	11.00					
11	2100 ± 10%	3750	100%	1940	121	121	1810	1940	**1819**	13.38
							Average Error (% ± SD)			4.25 ± 3.76

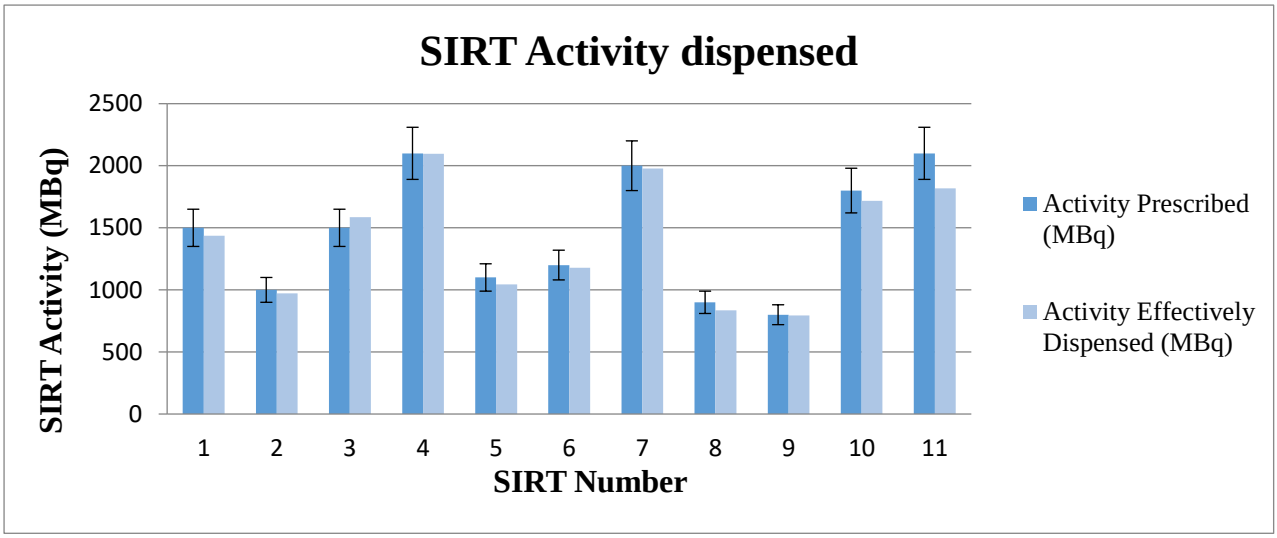

Figure 5 - Bar chart demonstrating the relationship between activity prescribed and activity effectively dispensed according to SOP NM-L3-155. Error bars represent accepted interval of ± 10% prescribed dose.

The results of the measurements during the dispensing procedure after changes in the SOP NM-L3-155 are revealed in the following tables and charts:

Table 5 - Measurements of the residues in the syringe and needle when dispensing SIRT after the changes in the SOP NM-L3-155.

SIRT N.	Activity prescribed (MBq)	Required splits (%)	Initial activity in the inner vial (MBq)	Residual activity in syringes/ needles (MBq)	Total residual activity (MBq)	Residual activity in the inner vial (MBq)	Activity dispensed into V-vial (MBq)	Activity effectively dispensed (MBq)	Error (abs. %)
12	1500 ±10%	50	3760	27	46	2180	1580	1534	2.27
		50		19					
13	1400 ±10%	30	3730	50	101.6	2220	1510	1408.4	0.6
		70		51.6					
14	900 ±10%	30	3570	22.8	44.9	2800	950	905.1	0.57
		70		22.1					
15	1400 ±10%	20	3710	10.65	24.65	2300	1410	1385.35	1.05
		80		14					
16	2100	60	3880	51	89.5	1672	2208	2118.5	0.88
		20		14.5					
		20		24					
17	1300	75	3740	14	28	2400	1340	1312	0.92
		25		14					
						Average Error (%± SD)			1.05 ± 0.63

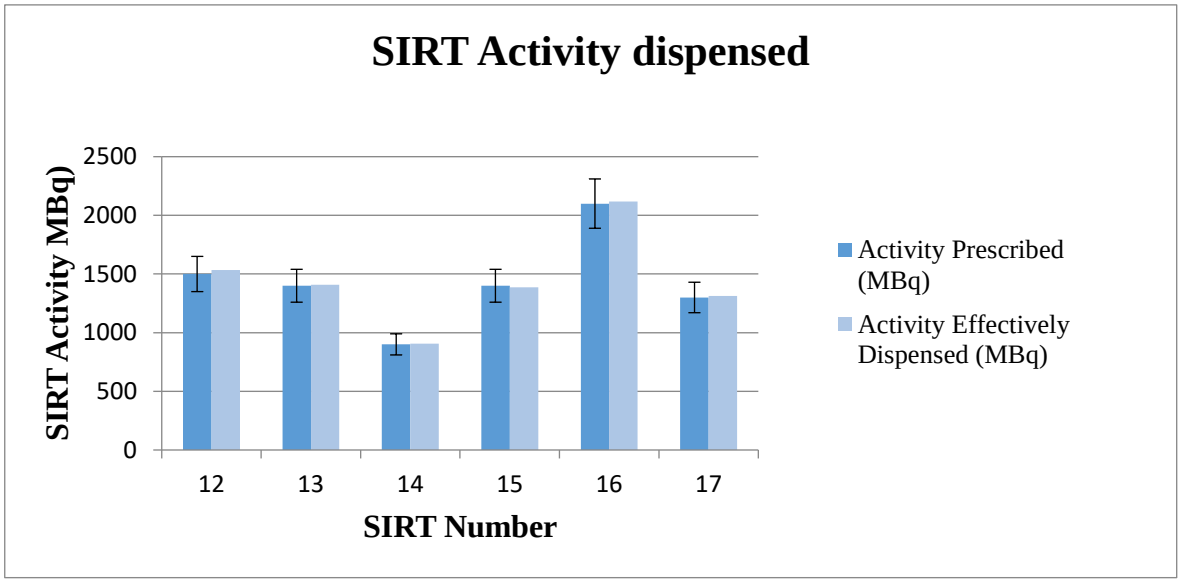

Figure 6 - Bar chart demonstrating the relation between activity prescribed and activity effectively dispensed after the changes in the SOP NM-L3-155. Error bars represent accepted interval of ± 10% prescribed dose.

6. Discussion

At Oxford University Hospitals NHS Foundation Trust around 100 patients are treated with SIR-Spheres microspheres per year. In previous studies I observed that after the dispensing procedure large quantities of ^{90}Y labelled SIR-Spheres microspheres have been found in the syringes and needles. The department of Medical Physics also confirmed that one of the doses dispensed were less than the prescribed activity (<10%). It is crucial for the effective treatment of unresectable primary or secondary liver tumours to deliver sufficient and accurate amount of microspheres into the hepatic artery. Despite drawing up ^{90}Y labelled SIR-Spheres microspheres according to SOP NM-L3-155 a large amount of microspheres have been lost in syringes and needles, which have been used to manipulate the dose.

These findings were confirmed in a series of 11 patients who have undergone this treatment and sufficient data was collected to realise that immediate changes in the SOP were required. The Radiopharmacy department receives the prescription for a ^{90}Y labelled SIR-Spheres microspheres study on the day of the procedure. The prescription will state the required total activity but will also direct (if applicable) the operator to split the activity ('required splits'), which refers to the percentage of dose to be drawn up for each liver lobe. According to SOP NM-L3-155 and manufacturers guidelines, the required activity of ^{90}Y labelled SIR-Spheres microspheres will be drawn up in a 5ml syringe and made up to a final volume between 3ml and 5 ml. Locally was set by Radiopharmacy and Medical Physics Experts that the radioactivity to be delivered to the patients must be ±10% of the prescribed dose.

Table 4 shows the eleven SIRT dispensing procedures evaluated and the activity effectively delivered to the patients. Procedures were carried out according to SOP NM-L3-155. The bar chart in Figure 5 indicates the acceptable ±10% dose activity interval with error bars. In nine dispensing procedures (SIRT number: 1, 2, 4, 5, 6, 7, 8, 9, 10) the effective activity dispensed and delivered to the patient was below the prescribed activity but within the ±10% range. On the other hand, in SIRT number 3, the activity was above the prescribed dose but also within the ±10% dose range. In contrast, in SIRT number 11 the delivered activity was 13.38% lower than the prescribed activity and therefore, outside the ±10% dose range.

The poor results can be explained due to the high viscosity of the ^{90}Y labelled SIR-Spheres microspheres, which are difficult to inject in a sufficient and accurate amount into the V-vial containing the patient`s dose.

The inaccuracy of the dose delivered to the patients can interfere with the efficiency of the treatment. Therefore, it was suggested that in order to dispense the prescribed activity accurately and to improve the radiation safety of the operator SOP NM-L3-155 needed to be amended. The "SOP to prepare Yttrium 90 labelled SIR-spheres microspheres" stated that the microspheres need to be drawn up in one session with sterile water for injection to a final volume between 3 and 5 ml. Retrospectively looking at the data, a large amount of microspheres have been lost in the syringes and needles. In order to obtain the remaining ^{90}Y labelled SIR-Spheres microspheres, the operator must draw up initially the required radioactivity with sterile water for injection up to a total volume of 3 ml and inject the volume into the V-vial. Following this using the same syringe and needle, the operator must wash with sterile water for injection up to a total volume of 1ml and inject the residual microspheres into the V-vial.

After introducing the reviewed SOP, another 6 procedures were carried out and results are considered very promising (Table 5 and Figure 6). The data demonstrates that the new procedure improved the dose effectively dispensed. In SIRT number 12, 13, 14, 16 and 17 the activity effectively dispensed is slightly higher than the activity prescribed and in procedure 15, is slightly lower. However, it is now always within the range of ±10%.

The improvements of the reviewed SOP can be justified as well by the percentage of average error ± SD of the activity effectively dispensed and delivered to the patients. Before implementing any changes in the SOP NM-L3-155 the average error was 4.25 ± 3.76. After implementing the reviewed SOP we have got an average error of 1.05 ± 0.63. To conclude, the results prior amending the SOP has shown a greater average error than the amended SOP. In comparison the reviewed SOP has shown a minor average error shifting the standard deviation towards the average, which proves that a change in SOP has led to more reliable doses being drawn up.

7. Conclusion

The changes made in the SOP to prepare ^{90}Y labelled SIR-spheres microspheres (Annex I) has shown to improve the dispensing procedure in terms of the dose effectively dispensed and delivered to the patient. Furthermore, the new procedure also helps in terms of radiation protection, as no more measurements are needed to insure that the correct activity has been dispensed.

The second flush of the V-vial with water for injection allows the operators to wash and remove the residues of microspheres labelled with ^{90}Y from the syringe and needle into the V-vial, increasing the dose in the V-vial.

The reviewed SOP permits the operators to be confident about the activity effectively delivered to the patient as it provides a significant reduction of the dispensing error.

It is important to mention that the changes in the SOP, also help the Operators involved in the process (dispensing and calculations) to predict the exact dose that will be dispensed for each split based on previous results and, therefore, make any necessary adjustments as needed. This process associated to the changes in the SOP will give a high degree of certainty regarding the efficiency of the dispensed procedure and the dose delivered to the patient.

The data collected was approved and used as reference by the Radiopharmacy department at Oxford University Hospitals NHS Foundation Trust and has been used since then as well as the reviewed SOP.

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32. Standard Operating Procedure NM-L3-155 at Oxford University Hospitals NHS Foundation Trust

9. Annex I

The described method to dispense ^{90}Y labelled with SIR-Spheres microspheres must be used in addition to SOP NM-L3-155 and was implemented from 26/08/2015.

- Once the V-vial is assembled into the V-vial holder, with lacto tubing ready for ventilation and syringes are in the syringe shields:
    - measure the activity of the inner vial using the "P6 vial calibration factor" (calibration factor set at Oxford University Hospitals);
    - through the calculations done, draw up the required volume;
    - verify the dose drawn up by measuring of residual activity in the inner vial using the "P6 vial calibration factor";
    - adjust the dose if necessary;
    - with the syringe and needle containing the drawn up dose, draw up sterile water for injection up to a total volume of 3ml and inject the volume in the V-vial;
    - with the same syringe and needle draw up sterile water for injection up to a total volume of 1ml to remove any residual activity from the syringe and needle and inject the volume in the V-vial.