QUEEN MARGARET UNIVERSITY

A RETROSPECTIVE CLINICAL AUDIT OF THE CLINICAL APPLICATION OF THE RAYPILOT REAL TIME MOTION MANAGEMENT SYSTEM AND THE FEASABILITY OF ITS USE FOR FURTHER DOSE ESCALATED STEREOTACTIC BODY RADIOTHERAPY FOR PROSTATE CANCER.

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ABSTRACT

Background and purpose

Prostate cancer is one of the most prevalent malignancies within oncology cases. Intrafraction motion is an important consideration in the clinical delivery of radiotherapy and indeed, long-term outcome and toxicity for patients. The purpose of this retrospective clinical audit was to review the efficacy of the RayPilot® real time motion management system and the impact that this has on planning target margins in prostate stereotactic body radiotherapy to assess if the RayPilot® system could be used clinically to allow for further dose escalation and fractionation reduction.

Materials and methods

Intrafraction motion was measured and recorded using the RayPilot® real time motion management system in seven patients. The RayPilot® system collated intrafraction data thirty times per second during treatment delivery for each patient. The collected data was then used to replan the patient in the Eclipse treatment planning software using reduced planning target margins to assess if this was a feasible method of dose escalation by reducing treatment fractionation.

Results

The RayPilot® recorded data resulted in 54175 intrafraction motion measurements in total. Mean displacement (following removal of outliers >0.3cm) was 0.1cm (SD± 0.1cm), 0.1cm (SD± 0.1cm) and 0.1cm (SD± 0.1cm) in the lateral, longitudinal and vertical directions respectively. The Van Herk Margin recipe was used to calculate the required clinical margins using the intrafraction motion data resulting in lateral, longitudinal and vertical margins of 0.7cm, 0.7cm and 0.7cm respectively. These margins allowed for dose escalation of 2400cGy in three fractions with no detrimental effects or increase in patient toxicity using dose volume histogram analysis.

Conclusion

RayPilot® is an efficient method of monitoring and recording prostate intrafraction motion and allowed for a reduction in target volume margins resulting in dose escalation in prostate stereotactic body radiotherapy. However, further analysis and research must be carried out to assess the feasibility of it being used as a stand-alone monitoring modality.

Keywords: RayPilot®, hypofractionation, intrafraction motion, prostate, motion management, margins, SBRT

LIST OF ABBREVIATIONS

2D – Two Dimensional

3D – Three Dimensional

ACCORD - The Academic and Clinical Central Office for Research and Development

ADT – Androgen Deprivation Therapy

AHP – Allied Health Professional

AP – Anterior/Posterior

ASTRO – American Society for Radiation Oncology

BBC – British Broadcasting Corporation

BFFS – Biochemical Failure Free Survival

CASP – Critical Appraisal Skills Programme

CBCT – Cone Beam Computed Tomography

cc – Cubic Centiliters

cGy – Centigray (unit of measurement of dose)

CHHiP – Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy in Prostate Cancer

CHI – Community Health Index

CI – Confidence Interval

CINAHL – The Cumulative Index to Nursing and Allied Health Literature

cm – Centimeters (unit of measurement)

CRUK – Cancer Research UK

CT – Computerised Tomography

CTV – Clinical Target Volume

DNA - Deoxyribonucleic acid

DPU – Data Processing Unit

DRR – Digitally Reconstructed Radiograph

DVH – Dose Volume Histogram

EBRT – External Beam Radiotherapy

ECCO – European Cancer Congress

ED – Erectile Dysfunction

EM – Electro Magnetic

EPIC-CP - Expanded Prostate Cancer Index Composite for Clinical Practice

EPIDS – Electronic Portal Imaging Devices

FFF – Flattening Filter Free

GC-IMS - Gas Chromatography, Ion Mobility Spectroscopy

GCP – Good Clinical Practice

GI - Gastrointestinal

GPS – Geographical Positioning System

GS – Gleason Score

GTV – Gross Target Volume

GU – Genitourinary

HDR – High Dose Rate

ICH GCP - International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice

ICRU – International Commission on Radiation Units and Measurements

IFM – Intrafraction Motion

IGRT – Image Guided Radiotherapy

IMRT – Intensity Modulated Radiotherapy

INJF – Introverted, Intuitive, Feeling and Judging

IPSS – International Prostate Symptom Score

IRAS - Integrated Research Application System

IRMER – Ionising Radiation Medical Exposure Regulations

IQR – Interquartile Range

KIM – Kilovoltage Intrafraction Monitoring

kV – Kilovoltage

LGR – Lead GU Radiographer

LR – Left/Right

LUTS – Lower Urinary Tract Symptoms

MBTI – Myers Brigg Type Indicator

MCO – Multiple Constraint Optimisation

MDM – Multidisciplinary Team Meeting

MG – Myasthenia Gravis

mls – Millilitres (unit of volume)

mm – Millimeter (unit of measurement)

ms - Millisecond

MRI – Magnetic Resonance Imaging

MSc – Master of Science

MV – Megavoltage

NCBI – National Centre for Biotechnology Information

ng/ml – Nanogram/Milliliter

NES – NHS Education for Scotland

NHS – National Health Service

NICE – National Institute for Clinical Excellence

OARs – Organs at Risk

OBI – On Board Imaging

OD – Organ Delineation

OM – Organ Motion

PgCAP – Post Graduate Certificate in Academic Practice

PIO – Population, Intervention and Outcomes

PIS – Participant Information Sheet

PRINToUT - Using Breath Analysis to Predict Normal Tissue and Tumour Response During Prostate Cancer SBRT

PRISMA – Preferred Reporting Items Systems for Systematic and Meta-analyses

PROMs – Patient Reported Outcome Measures

PSA – Prostate Specific Antigen

PTV – Planning Target Volume

QIT – Quality Improvement Team

QMAX – Maximum Urinary Flow

QOL – Quality of Life

RCR – The Royal College of Radiologists

ROI – Region of Interest

RP – Rapid Plan

RTMG - Radiotherapy Management Group

RTOG – Radiation Therapy Oncology Group

SBRT – Stereotactic Body Radiotherapy

SCQF – Scottish Credit and Qualifications Framework

SD – Standard Deviation

SI – Superior/Inferior

SOR – Society of Radiographers

SUE – Set Up Error

TURP – Trans Urethral Resection Prostate

UK – United Kingdom

UKIO – UK Imaging and Oncology Congress

US – Ultrasound

VDU – Visual Display Unit

VHMF – Van Herk Margin Formula

VMAT – Volumetric Arc Therapy

VOC – Volatile Organic Compound

WHO – World Health Organisation

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1 INTRODUCTION

In Scotland in 2017 prostate cancer was the most common male cancer accounting for 22.2% (n=3518) of all cancer registrations (Public Health Scotland, 2017). Prostate cancer is the 2nd most common cause of cancer-related deaths in males accounting for 11% of male cancer deaths (n=986) in 2017 and Cancer Research UK (2019) have reported that in the decade from 2006/2008-2016/2018, prostate cancer incidence has risen by 8%, a trend that is set to continue as illustrated in figure 1. This marked increase can be attributed to earlier diagnosis, increases public awareness of signs and symptoms of prostate cancer and routine age based prostate specific antigen (PSA) testing.

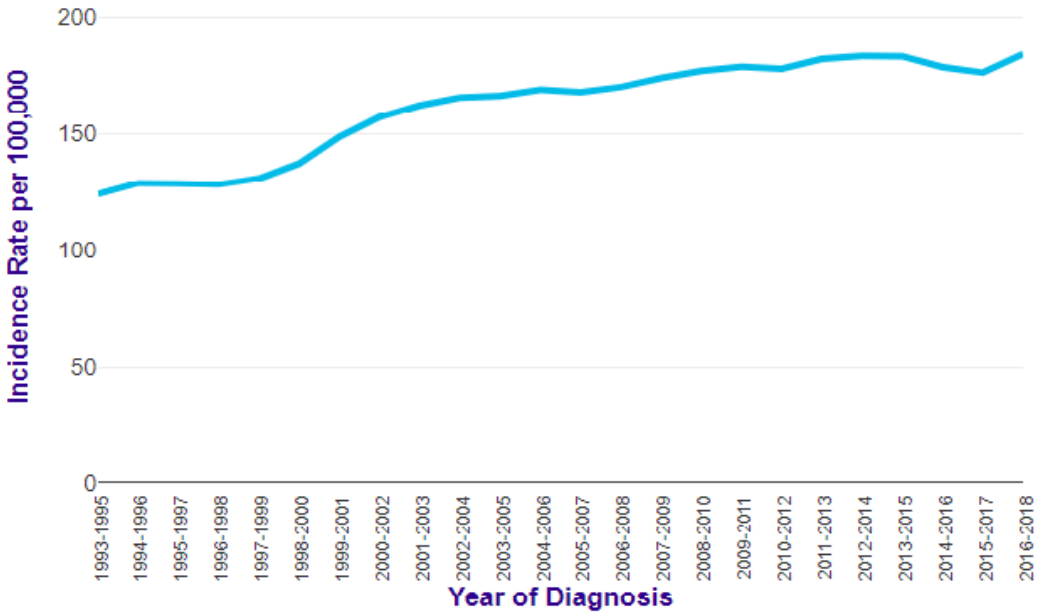


Figure 1 - Incidence Rate per 100, 00 by year of diagnosis. Illustrating the previous incidence rate of prostate cancer and the increase in diagnosis from 1993-2018. A clear indication of the increase of diagnosis of prostate cancer within the UK population.

However, survival rates of prostate cancer have also increased due to development and improvement in cancer treatments for prostate cancer. In 2019, the Office for National Statistics reported the one, five and 10-year survival statistics of prostate cancer patients as 96.3%, 86% and 77.6% respectively. The main treatments available to these patients are active surveillance, radical prostatectomy,

brachytherapy and external beam radiotherapy (EBRT), with treatment selection dependent on disease staging and progression (Pettersson et al., 2018).

External beam radiotherapy has long been a cornerstone of prostate cancer treatment for both radical treatment intent and for metastatic disease. Using evidence based practice, it is a fast evolving discipline and in recent years has employed treatment and technological advances to improve outcome, reduce toxicity and increase the quality of life of prostate cancer patients whilst reducing the burden of the disease and subsequent treatments. The primary aim of radiotherapy treatment is to deliver a high dose of radiotherapy to the target volume whilst minimising the dose to the surrounding healthy organs or structures. However, variances in pre-treatment procedures and treatment execution can adversely affect the accuracy of treatment delivery (Honda et al., 2021). One such fundamental concern with prostate radiotherapy is the localisation of the target volume, which in the case of prostate cancer is the whole gland. Due to the anatomical position and variability in prostate position largely caused by rectal variations, the target volume is mobile. Therefore, the ability to monitor intrafraction motion, the motion that occurs during treatment delivery, and to account for it during treatment, has the potential to reduce geographical uncertainties in prostate position during treatment delivery. Furthermore, this would ensure optimum target coverage and reduce toxicity to the surrounding tissues.

Historically, various methods have been employed to minimise prostate motion both prior to (interfraction motion) and during treatment delivery (intrafraction motion). Interfraction motion can be minimised by the implementation of dietary advice or bladder and rectal filling protocols. For instance, the administration of daily pre-treatment enemas can ensure the consistency of the rectal volume and bladder preparation protocols can ensure a uniform bladder volume at each treatment fraction (Nasser et al., 2021). Advances in image guidance technology ensures accurate positioning of the high dose target volume, in this case the prostate using various methods of on board imaging systems such as kilovoltage (kV) imaging and cone beam computed tomography (CBCT). On board imaging (OBI) systems are an integral component of linear accelerators which allows for a series of images to be electronically acquired prior to and during treatment delivery to assess and correct for positional variations using several imaging modalities. In addition, ultrasound (US) can be used to provide real time localisation of the target volume, which can also be combined with kV and CBCT data to ensure optimum dose delivery to the treatment

target. Moreover, image guided radiotherapy is essential when implementing a hypofractionated dose escalation treatment, which involves the delivery of larger doses per treatment fraction to achieve tumour control and optimum dose delivery in much fewer treatment fractions (Ghadjar et al., 2019). The Royal College of Surgeons of England (2020) published the National Prostate Cancer Audit Annual Report stating that 91% of men receiving radical radiotherapy for intermediate-risk disease received a hypofractionated regimen and that this standard should be maintained and increased within radiotherapy centres. Randomised control trials have produced guidelines regarding the use of stereotactic body radiotherapy (SBRT) dose escalated treatments and whether these offer therapeutic benefit in comparison to standard radiotherapy regimes. One such trial is the PACE B trial which is an international multicentre phase III trial where patients are randomised between standard hypofractionated radiotherapy (7800 centigray (cGy) in 39 fractions or 6000cGy in 20 fractions) and SBRT of 3525cGy in 5 treatment fractions (Morrison et al., 2018). The guidelines for dose prescription from the PACE study are currently used within the Edinburgh Cancer Centre for prostate patients undergoing prostate SBRT as part of the wider PRINToUT (Using Breath Analysis to Predict Normal Tissue and Tumour Response During Prostate Cancer SBRT) research trial and for the patient cohort for this thesis.

Historically, prostate radiotherapy was given in prolonged schedules ranging from four to 8 weeks, which can be difficult for patients; however, emerging evidence suggests that hypofractionated radiotherapy results in comparable outcome (Nicosia et al., 2019). Michalski et al. (2018) stated that patients receiving radical prostate radiotherapy, dose escalation using intensity-modulated or image-guided radiotherapy improves biochemical control with acceptable toxicity. An effective method of hypofractionated image guided radiotherapy is stereotactic body radiotherapy. SBRT is defined as high-dose external beam radiotherapy typically delivered in only a few fractions using advanced techniques that allow for relative sparing of nearby normal tissues (Bouman-Wammes et al., 2017). For example, in a reduction in treatment schedule from 39 fractions to five fractions due to dose escalation.

Prostate SBRT delivery requires more stringent localization, verification and the use of sophisticated image guidance and monitoring of the target volume due to the high daily doses used in the protocols (Ding et al., 2018). Real time motion management is an effective method of motion management and as such, there are many methods

employed clinically to achieve effective motion management. Real time imaging allows for localization of the target volume and following analysis by trained radiographers, positional changes can be made if required throughout treatment delivery to allow for optimum target coverage. Kilovoltage imaging prior to and during treatment delivery is universally used as one such method due to its ease of use, low cost implementation and reliable results. However, the use of pre, during and post treatment CBCT is becoming more common, either as a standalone method of image guidance or in combination with kV imaging. Triggered imaging is a form of real time imaging which involves acquiring a series of kV images at defined intervals, for instance whether at set equipment angles, an elapsed time or at dose intervals. However, one limitation of all of these methods is that they do not provide continuous real time motion management; they provide positional information at specific intervals, therefore not providing continuous imaging data. Although all of the previously mentioned systems allow for online corrections to positioning, this is on the evidence of single images taken at one point in time, whereas a system that allows for continuous imaging and online correction can lead to increased accuracy of treatment delivery. One such real-time positioning system is the RayPilot® system. This motion management system is comprised of a geographical positioning software (GPS) transmitter that is implanted in the prostate and remains in situ for the treatment duration. It collates continuous data in relation to the motion of the prostate allowing for real time online positional corrections.

RayPilot® is an emerging technology and as such, the first department in the United Kingdom (UK) to implement the system was the Edinburgh Cancer Centre in November 2017. The system uses continual target tracking with the use of electromagnetic transmitters and a surgically implanted antenna within the prostate in combination with pre and post treatment CBCT and pretreatment kV images acquired for verification purposes. The continual positioning data allows for real time online correction of patient positioning. As previously mentioned this is imperative in the delivery of dose-escalated radiotherapy, the current protocol for this patient cohort being 3625cGy in 5 treatment fractions.

As the only radiotherapy treatment Centre in the UK using the RayPilot® technology, follow-up data analysis could positively impact treatment delivery for this patient cohort and lead to improve dose escalation regimes. This is against a backdrop of increasing disease free survival and reducing long-term toxicity for prostate cancer patients.

The subsequent chapters will illustrate the methodology used, the clinical results and comprehensive discussion of the resultant data and audit findings. This will be in relevance to the previous literature regarding real time intrafraction motion management systems and the subsequent effects these have on prostate radiotherapy delivery. The following chapter provides a review of relevant literature and the justification of the literature review search strategy. The underpinning and key literature reviewed will be used to review and assess the efficiency of the RayPilot® real time motion management system in the clinical setting and the potential for further future development of treatment delivery, techniques and the clinical use of the system.

The overall aim of the thesis is to evaluate and analyse the data collated rom the RayPilot® real time motion management system assessing its efficiency and using this data to inform whether treatment target margins could be reduced in the future. This would allow a further dose escalation treatment schedule to be used clinically, for example higher doses per fraction and reduced total treatment time. Essentially the audit consists of two parts in tandem:

1. The analysis of the RayPilot® data providing evidence and guidance on the feasibility of the reduction in current clinical treatment margins.
2. Based on the results of 1, is it feasible to introduce a new fractionation and dose escalation regime of 2400cGy in three treatment fractions?

In addressing this important problem, the significant contributions to knowledge in the field have been:

1. Independent assessment of the efficiency, implementation and integration of the RayPilot® and the clinical contribution of a real-time motion management system.
2. Future research and development of a further reduced SBRT dose and fractionation for the patient cohort.
3. Promotion and enhancement of the radiographer role within clinical teams and the research arena.

2 LITERATURE REVIEW

2.1 SUMMARY OF INTENTIONS.

The aim of this literature review is to summarise the most relevant published studies in the field covering the following areas: prostate motion; intra-fraction motion planning margins; and margin formulae and the methods of prostate motion management. The review also covers literature in relation to hypo-fractionated prostate radiotherapy and the impact of motion management systems including RayPilot®. The review allowed a deeper critical analysis to be performed and knowledge gaps to be identified. From this, it was possible to set out a plan for a comprehensive audit and thereby address the clinical audit aims of the thesis.

2.2 SEARCH METHODOLOGY.

The research question was synthesised using the PIO (Population, Intervention, and Outcome) framework (Polgar and Thomas, 2000). The population under study being prostate patients undergoing radical external beam radiotherapy adhering to the inclusion criteria set out in the methodology chapter. The intervention is the use of ultra hypofractionated radiotherapy regime utilising the RayPilot® real time motion management system; more specifically an investigation of the effects of an ultra hypofractionated dose of 3625cGy in 5 fractions versus current clinical standard treatment regimes of 7800cGy in 39 fractions or 6000cGy in 20 fractions. The outcome measurements were reported toxicity. The resulting data on intrafraction motion, planning target margins and long-term toxicity of the participating population was assessed and reviewed in comparison to patients receiving the standard treatment regimes. The primary output of the audit was to assess the efficiency of the RayPilot® real time motion management system and establish whether it could be used clinically to reduce planning target margins and allow for a further dose-escalated regime.

The preliminary literature search was carried out using Medline, PubMed (National Centre for Biotechnology Information (NCBI), 2018), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database and The Cochrane Library to establish a comprehensive and critical overview of the available literature on motion management in prostate radiotherapy. This included Stereotactic Body Radiotherapy, RayPilot® and intrafraction motion searches. Open Grey was also used as a search database to include current research records in relation to the search strategy as a

multi-disciplinary repository which includes theses, conference literature and technical reports to reduce publication bias.

Primary search terms that were used for all database searches were prostate stereotactic radiotherapy, prostate SBRT, RayPilot® and intrafraction motion. Boolean operators of and, or, were used to focus the search along with wildcard characters such as * to include alternative spellings and variations (Table 1).

Table 1 - Search strategy. Illustration of multi-database search strategy including keywords, Boolean operators, wildcards and limitations on results.

SEARCH	KEYWORDS
1	Prostate SBRT (MeSH); prostate stereotactic body radiotherapy (MeSH); prostate SBRT (tw); stereotactic prostate radiotherapy (tw); OR prostate SBR* (tw); stereotactic prostate radiothera*y (tw)
2	Intrafraction motion (MeSH); prostate motion (MeSH); intrafraction motion (tw); prostate motion (tw); OR intrafractio* motio* (tw); prostat* motio*(tw)
3	RayPilot® (tw); OR Raypilo* (tw)
4	Real time motion management (MeSH); real time motion management (tw); OR real time motio* managemen* (tw)
5	**AND/OR** 1/2
6	**AND/OR** 1/3
7	**AND/OR** 1/4
8	**AND/OR** 2/3
9	**AND/OR** 2/4
10	**AND/OR** 3/4
11	**Limit** 1-10 – all publications
12	**Limit** 1-10 – last fifteen years
13	**Limit** 1-10 – English language only
14	**Limit** 1-10 Full text only

Only articles written in English were included in the review and PubMed searches were sorted using the “most relevant” prioritisation. Based on the scope of the project, preference was given to journals that included intrafraction motion, real time tracking, prostate motion management, radiotherapy and prostate SBRT. After initial reading, it was noted that there were incidental findings not considered in the original search that became of interest, for example research papers using similar methodologies on other motion management systems. There were also papers of interest that became

known through study of the references listed in a number of journal articles; however, the downside of this was that some articles were found to be older and fell outside of the search criteria. This is a process known as “snowballing” and although can be a useful means for providing further context on a subject or paper, it can also dilute the focus of the search (Naderifar et al., 2017). To mitigate this any keywords or systems found through snowballing were also fed into further systematic searches on the previously identified search databases.

All literature was assessed acknowledging the hierarchy of evidence. Hierarchy of evidence is an influential tool for appraisal of medical and scientific literature and is viewed as a central part of evidenced based medicine and clinical practice (Djulbegovic and Guyatt, 2017). The levels of evidence within the hierarchy allow for interpretation of the validity and reliability of the clinical evidence and resultant data obtained. This is beneficial in clinical research and studies to allow for assessment of current clinical knowledge and evidence, to identify gaps in the current clinical knowledge and to allow for the conception of clinical study aims and hypotheses. The levels of evidence ascend from case studies or reports, case controlled studies, cohort studies, randomised control studies to systematic and meta-analysis reviews being considered the strongest sources of evidence (Katz et al., 2019).

With thousands of relevant publications available, it was essential to focus the review on preferred topics and to look at what research has already been carried out, where the gaps in the knowledge base appear to be and how these gaps could be filled. This created the trajectory for seminal research in the chosen speciality. For example, there has been significant research into prostate motion and its management, however, RayPilot® is a relatively new technology and as such, searches using the term RayPilot® produce relatively few papers. The following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram illustrates the results of the literature search (Figure 2.)

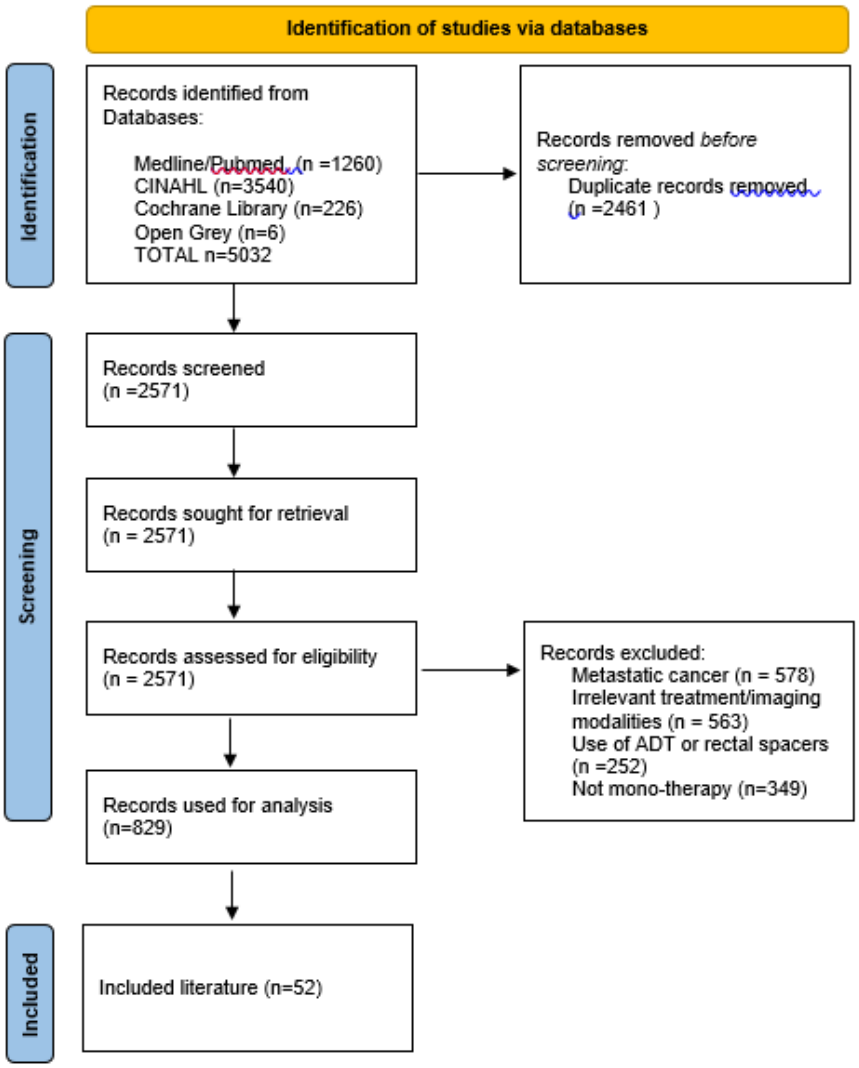


Figure 2 - PRISMA diagram for literature search results showing records found, records screened and records included in the literature review.

Whilst an extensive literature base was found in the search, it was both necessary and practical to omit much of this from this review, following the technique proposed by Pinchbeck et al. (2018) for systematic review. This framework can provide consistent assessment on each journal and ensure that their inclusion is critiqued against the aims of the review. This was carried out retrospectively using the same rationale used in the initial searches, however future reviews could begin with this method or follow the structure of the critical appraisal skills programme (CASP) checklist appropriate to the method of research being undertaken (Critical Appraisal

Skills Programme, 2018). Table 2 is an example of literature records found that were of interest in this thesis.

Table 2 - Example of literature relevant to and included in the literature review in alphabetical order. Table incudes exemplars in relation to intrafraction motion, prostate SBRT and motion management systems of the most cited relevant literature.

REFERENCE	METHODOLOGY	SAMPLE SIZE	COMMENTS/KEY FINDINGS
BRAIDE, K et al., (2018). Clinical feasibility and positional stability of an implanted wired transmitter in a novel electromagnetic positioning system for prostate cancer radiotherapy. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*, vol. 128, no. 2, pp. 336–342.	Feasibility study assessing transmitter implantation procedures; Qualitative study on patient experience; Qualitative study on transmitter displacement from fiducial markers. Data acquired by 3D orthogonal kV imaging.	10 patients	Implantation well tolerated with minimal side effects reported. One patient had transmitter 3D shifts >9 mm, but also inter-marker shifts >6 mm mean inter-marker shift in the remaining patients was <1 mm. In four patients, maximum transmitter 3D shifts were 5–7 mm (mean >2 mm). In three patients, mean transmitter 3D shifts were <2 mm. RayPilot was well tolerated and reliable however, due to migration of transmitter should be used in tandem with on board imaging and real time tracking using imaging.
BRAND, D.H., et al., (2019) Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *The Lancet Oncology,* vol. 20, no.11, pp. 1531-1543.	international, randomised, open-label, phase 3, non-inferiority trial 37 centres PACE B trial. 7800cgy in 39 fractions or 6200cGy in 20 fractions for hypofractionated 3635cGy in 5 fractions for SBRT	874patients 441 – hypofractionated radiotherapy 433 - SBRT	Outcomes measured using RTOG and Comparable toxicity outcomes in both groups.

BUDIHARTO,T et al., (2011). Intrafractional prostate motion during online image guided intensity-modulated radiotherapy for prostate cancer. *Radiotherapy and Oncology*, vol. 98, no. 2, pp. 181–186.	Retrospective clinical audit. kV – MV localization and verification imaging prior to 5 field IMRT technique. Patients had 4 fiducial markers, online kV auto marker match acquired and matched to MV image to calculate and record intrafraction motion. This was calculated retrospectively offline. Van Herk margin formula used to confirm current clinical margins.	27 patients	Motions of 2.3±1.5mm, 0.2±1.1mm, -0.1±1.1 in AP, SI, LR directions respectively. Motion is highest in posterior direction. IMRT utilized to reduce toxicity to surrounding tissues. Treatment time should be kept to a minimum as greater displacements recorded in longer overall treatment time.
DEARNALEY,D et al (2012). Conventional versus hypofractionated high dose intensity modulated radiotherapy for prostate cancer: Preliminary safety results from the CHHiP randomised controlled trial. *The Lancet*, vol. 13, no. 1, pp. 43-54.	Multi-phase,Multi-centre (n=11) randomized control trial. 3 arm design - 7400cGy in 37#, 6000cGy in 20# or 5700cGy in 19#. Toxicity scoring completed with RTOG. Routine PSA and MRI imaging for assessment of bRFS and long-term toxicity or radiation damage.	7400cGy – 138 6000cgY- 137 5700cGy - 143	Hypofractionated EBRT resulted in comparable toxicity scoring in all patient cohorts as that of conventional EBRT and therefore is equally tolerated. Aim to keep treatment time consistent to allow for continual localization of the high dose volume.
JACKSON, W.C et al (2019). Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies. *International Journal of Radiation Oncology*Biology*Physics*, vol. 104, no.4, pp. 778-789.	Systematic review and meta-analysis study. 22 clinical trials – 17 phase 2 or phase 3 trials comprising 2174 patients. Longitudinal study - median follow up 39months. Physician reported outcomes regarding toxicity. Patient reported outcomes of QOL.	6116 patients	5 year bRFS 95.3% 7 year bRFS 93.7% Toxicity grade 3 ≥ 2.0% at 5 years, 1.1% at 7 years. Favourable tumour control, bRFS and toxicity in the SBRT cohort as conventional regimes.

	Mean follow up 39 months.		
KOTTE, A et al (2007). Intrafraction Motion of the Prostate During External-Beam Radiation Therapy: Analysis of 427 Patients with Implanted Fiducial Markers. *International Journal of Radiation Oncology*Biology*Physics*, vol. 69, no. 2, pp. 419–425.	Retrospective clinical analysis Single institution study. 5 beam IMRT using 3 implanted fiducial markers. 7600cGy in 35# Bladder preparation regime – empty bladder. kV imaging (auto marker match) to localise and verify fiducial marker position – verified by two competent radiographers. No online corrections performed.	427 patients. 11,426 fractions.	Motion of ≥ 2mm occurred in 66% of treatments. Motion of ≥ 3mm occurred in 66% of treatments. Timescale of treatment 5-7 minutes – following this an increase in intrafraction motion vectors. Concludes a 2mm margin is more than acceptable to account for intrafraction motion in this cohort.
SIHONO, D et at (2018). Determination of Intrafraction Prostate Motion During External Beam Radiation Therapy With a Transperineal 4-Dimensional Ultrasound Real-Time Tracking System. *International Journal of Radiation Oncology*Biology*Physics*, vol. 101, no. 1, pp. 136–143.	Retrospective clinical analysis Single institution study. Retrospective analysis of 770 imaging sessions using US imaging. US reviewed and analysed prior to treatment by radiographers.	38 patients. 770 US images	% of # motion ≤2mm 97.01%, 92.24%, 95.77% in LR, AP and SI directions respectively. Smallest variations in motion in LR direction, largest in AP direction. Vector lengths of prostate motion >2mm at various timestamps: 60 seconds – 0.67% 120 seconds – 2.42% 180 seconds – 6.14% 240 seconds – 9.35% Reducing treatment time reduces intrafraction motion.
SPRATT, D et al (2013). Long-term Survival and Toxicity in Patients Treated With High-Dose Intensity	Single institution prospective phase I study. Patients	1002 patients.	7 years bRFS 98.8%, 85.6%, 67.9% (95%CI) in low, intermediate

Modulated Radiation Therapy for Localized Prostate Cancer. *International Journal of Radiation Oncology*Biology*Physics*, vol. 85, no. 3, pp. 686–692.	stratified by prognostic group. 8640cGy in 48# 5.5 years follow up. Toxicity outcomes measured using CTCAE criteria. GU toxicity measured using IPSS.		and high risk groups respectively. 7-year ≥ grade 2 toxicity 4.4% for gastrointestinal toxicity and 21.1% genitourinary toxicity. Comparable outcomes for high dose IMRT as for conventional regimes.
TREE, A.C. et al., 2022. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE B): 2 year toxicity results from an open label, randomised, phase three, non-inferiority trial. *Lancet Oncology*, vol. 23, no. 10, pp.1308-1320.	open-label, multicohort, randomised, controlled, phase 3 trial 35 centres 7800cgy in 39 fractions or 6200cGy in 20 fractions for hypofractionated 3635cGy in 5 fractions for SBRT	874patients 441 – hypofractionated radiotherapy 433 - SBRT	Outcomes measured using RTOG and Comparable toxicity outcomes in both groups.
TONG, X et al (2015). Intrafractional prostate motion during external beam radiotherapy monitored by a real-time target localization system. *Journal of Applied Clinical Medical Physics*, vol. 16, no. 2, pp. 51–61.	Single institution study. Calypso motion management system used - 4D localization. 5mm tolerance for localization.	236 patients. 8660#	Mean treatment duration was 8.0±3.9 (SD) mins. Number of # motion of 2, 3, 5,7mm for > 30 seconds – 56.8%, 27.2%, 4.6% and 0.7% respectively. Time motion tracked was > 3mm in the posterior direction is five times higher than any other direction. Treatment time is largest contributing factor to intrafraction motion.
VANHANEN, A., SYRÉN, H., and KAPANEN, M., (2018). Localization accuracy of two electromagnetic tracking	Dual institution study. Controlled trial.	22 RayPilot ® patients – total of 582#.	kV versus RayPilot® displacement values – 0.3±2.2mm, -

systems in prostate cancer radiotherapy: A comparison with fiducial marker based kilovoltage imaging. *Physica Medica*, vol. 56, pp. 10–18.		26 Calypso patients – total of 335#. Total analysed # 917	2.2±2.4mm, 0.0±1.0mm in AP, SI and LR directions respectively. Localisation of RayPilot® device is affected by transmitter position and should be used in tandem with set-up verification imaging modalities.
VASSIL, A et al (2010). Five Year Biochemical Recurrence Free Survival for Intermediate Risk Prostate Cancer After Radical Prostatectomy, External Beam Radiation Therapy or Permanent Seed Implantation. *Urology*, vol. 76, no. 5, pp. 1251–1257.	Single institution study. Controlled trial. Minimum 2 yr. follow up – median follow up 35 months. Nadir +2 definition of biochemical failure was used for RT – same as host centre. bRFS was calculated using Kaplan-Meier analysis.	6076 patients	Five years bRFS rate was 82.8% for all patients (89.5% PI, 85.7% RT, 79.9% RRP, and 60.2% LRP) Concluded that patients receiving brachytherapy, prostate or prostate and pelvic irradiation had delayed bRFS compared to laparoscopic prostatectomy patients.

2.3 PROSTATE CANCER AND TREATMENT.

Globally, 1,414,259 new cases of prostate cancer and 375,304 prostate cancer related deaths were recorded in 2020 (Sung et al., 2021). Cancer Research UK (CRUK, 2017) cited 46,700 new cases of prostate cancer in 2014, making it the second most common cancer in the UK. Prostate cancer accounts for 26% of all male cancers in the UK population (CRUK, 2017). Global incidence and mortality rates are strongly related to age with the highest incidence in men over 65 years of age (Rawla, 2019). This is due to prostate cancer being classified as an age-related disease, with the likelihood of men developing prostate cancer increasing with age. Prostate Scotland (2020) states that by the age of 80, 80% of men will have prostate cancer cells within the prostate, however not all of these men will become symptomatic. Over the last decade, prostate cancer incidence rates have increased by five percent,

attributed mainly to an increased incidence in prostate specific antigen (PSA) testing (Cuzick et al., 2014). The increase in prostate cancer incidence is expected to continue in the coming years with projections inferring that between 2014 and 2035 the incidence will be 233 cases per 100,000 males in 2035. This is an increase in incidence of approximately 12% in relation to the 5% increase in the previous decade (Figure 3, Cancer Research UK, 2019).

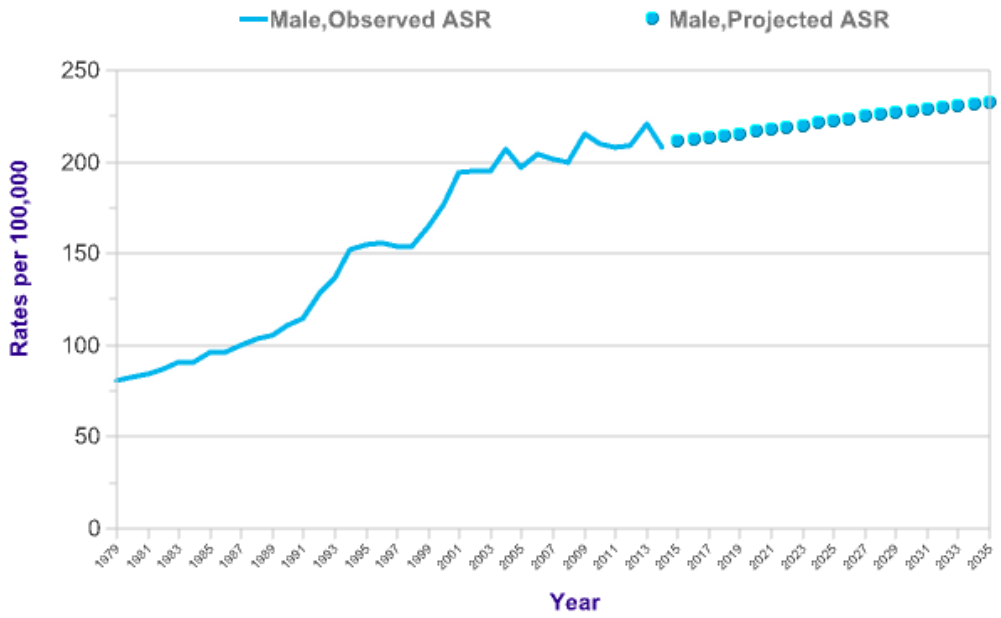


Figure 3 - Projections of incidence of prostate cancer (CRUK 2019). Observed and projected age standardised incident rates per 100,000 males from 1979-2035 based on future projections illustrating a continual rise in incidence.

The projected increase is attributed to the increase in lifespan of the general population; people are living longer than in previous decades and due to a greater awareness of prostate cancer signs and symptoms resulting in patients seeking medical intervention much earlier. Prostate Cancer UK (2017) states that approximately 400,000 men are living with prostate cancer in the UK, 26000 of which are living in Scotland, 325,000 in England, 21,000 in Wales and 9000 in Northern Ireland. Prostate cancer was the most common cancer in men in Scotland, with Information Division Scotland (2019) citing that prostate cancer accounted for 22.2% of all cancer registrations. The incidence rate suggests that one in eight men will be diagnosed with the disease in their lifetime. CRUK reports that almost 95% of men diagnosed with prostate cancer survive their disease for one year or more, 9 in 10

(90%) men survive their disease for five years or more and that 8 in 10 (80%) men diagnosed survive their disease for ten years or more. Although prostate cancer still accounts for 14% of all cancer deaths in males, the mortality rate of prostate cancer has decreased by a tenth over the last decade with projections inferring that this will continue fall by 16% in the UK between 2014 and 2035, to 48 deaths per 100,000 males by 2035 (Smittenaar et al., 2016). The decrease in mortality rates is associated with treatment advances and earlier diagnosis with the five-year survival in this group of patients 81.4% in England and Wales (Ettridge et al., 2018).

Improvements in organ confined prostate cancer survival rates have been well established in recent years (Vassil et al., 2010; Spratt et al., 2013; Tilki and Evans, 2020). Organ confined prostate cancer is defined as cancer of the prostate which has remained in the prostate gland only with no sign of extracapsular spread and is referred to as T1 or T2 stage prostate cancer (Matoso, 2019). Public Health England (2020) state that 55% of prostate patients have organ confined prostate cancer at diagnosis. A recent study concurred with the previous cited papers that stated a vast improvement and substantial increase in prostate cancer survival rates with reductions in morbidity and mortality from prostate cancer (Badal et al., 2020). Each paper discussed the role of external beam radiotherapy and concurred that EBRT had aided in the improved overall outcome and survival of prostate cancer. Historically, external beam radiotherapy has been a principal treatment for prostate cancer. EBRT involves the use of targeted high energy x-rays to treat cancer by damaging the deoxyribonucleic acid (DNA) of the tumour cells whilst causing minimal damage to surrounding organs and tissue (Parker et al., 2018). All papers used a multivariate analysis approach and included intensity-modulated radiotherapy (IMRT) and EBRT in survival and disease free survival. Spratt et al. (2013), and Vassil et al. (2010), used the largest cohorts of 979 and 1002 patients respectively. Medial follow up was comparable in both studies (65 months and 66 months) however Vassil et al. focused on disease free biochemical failure quoting 85.7% (P=0.0038) 5 year recurrence free survival using Kaplan-Meier analysis. Due to the age of the study, external beam radiotherapy patients were treated using standardised conventional doses of 8000cGy with 72% of patients being planned with IMRT and 27% using conformal radiotherapy (static three-field technique). These aging techniques are not as technically complex as dose escalation techniques such as volumetric arc therapy (VMAT) and can have a greater impact on toxicity. The use of earlier treatment techniques as opposed to more advanced techniques used in future studies including hypofractionation and SBRT would account for the variation in biochemical relapse

between this study and subsequent studies. Spratt et al. (2013) however, stated 7 year biochemical relapse at 98.8% for high dose IMRT treatments with statistical significance of P <0.001, and death rates from prostate following high dose rate (HDR) IMRT as 3.3% and 8.1% (P=0.008) in low risk and high risk patients respectively. Radical external beam radiotherapy is a treatment of choice for prostate cancer patients with T1-3 stage disease and increases disease free survival. This is attributed mainly to dose escalation; advancement in treatment techniques such as IMRT, VMAT, greater localisation and motion-tracking methods such as the implantation of fiducial markers into the prostate gland is making visualisation and localisation of the organ increasingly accurate on Electrical Portal Imaging Devices (EPIDS) (Gomez-Millan et al., 2015). A more recent development is the use of implanted motion tracking devices. These are tracking devices that are surgically implanted into the prostate gland, which, through various modalities and technologies, track the motion and displacement of the prostate in real time (Rossario et al., 2018).

Image guided radiotherapy (IGRT) using intensity modulated radiotherapy and volumetric arc therapy has become the gold standard of care for prostate cancer, with improvements in biochemical control while reducing urinary and rectal toxicity (Zelefsky et al., 2011). The common IGRT strategies available are implanted fiducial markers, cone beam computed tomography using on board imaging, bladder and rectal preparation programmes and real time tracking for motion management. Technological advances in the delivery of external beam radiotherapy have led to increased curative doses being delivered to disease situated in the prostate gland and surrounding nodal volumes (Koontz et al., 2015). However, attention must be given to the effect of the larger delivered doses on normal surrounding tissues and the related toxicity of this to patients. Increasing the radiotherapy doses can lead to an increase in PSA relapse free survival, and result in curing more patients. It can also lead to a potential increase in acute and cumulative late radiation effects, such as long term urinary issues including incontinence, impotence and rectal issues, which can impact on quality of life (QOL) (Fransson, 2021).

A non-randomised controlled trial investigated fractionation in prostate radiotherapy and concluded dose escalation programmes, also known as hypofractionated radiotherapy, have led to enhanced overall survival rates as well as improving bio chemical relapse free survival in organ confined prostate cancer cases (De Meerleer et al., 2007). A more recent study also concluded that hypofractionated prostate radiotherapy increased relapse free survival but further concluded that toxicity from

hypofractionated and ultra hypofractionated regimes were comparable. The authors stated that this is due to advances in treatment techniques and tracking of the prostate. However, increasing the overall treatment dose requires consideration of verification techniques, intrafraction motion management, treatment dosimetry and planning margins (Marvaso et al., 2019) .

The development of a hypofractionated treatment protocols allows larger doses to be delivered to the target (the whole prostate gland) in a shorter treatment regimen. One of the largest multicentre and most influential studies on the effectiveness of hypofractionated radiotherapy to the prostate was conducted from 2010 to 2012 with a cohort of 3216 participants (Dearnaley et al., 2012). Since the interim results of the CHHiP (Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer) study published in 2012, the host department has used a moderately hypo-fractionated dose of 6000CGy in 20 fractions against the standard 7400cGy in 37 fractions (Benjamin et al., 2017), using fiducial markers for image guided IMRT. Accumulated evidence suggests that due to alpha beta ratio of the prostate, these patients particularly benefit from the hypofractionation. The results of the CHHiP study was presented at European Cancer Congress (ECCO) 2015. After a 5-year follow up, 6000cGy in 20 fractions was non-inferior to 7400cGy in 37 fractions for progression free survival and yielded comparable acute and long-term side effects for the patients. Median follow up was 62.4 months (interquartile range, IQR 53.9-77.0) and 5 year biochemical events were 111 in 1065 patients, 88 in 1074 patients and 132 patients out of 1077 patients in the 7400cGy, 6000cGy and 5700cGy groups respectively. Five-year biochemical failure free survival (bFFS) rates were 88.3% (95% confidence interval, CI 86.0-90.20 in the 7400cGy cohort, 90.6% (95% CI 88.5-92.3) in the 6000cGy cohort and 85.9% (95% CI 83.4-88.0) in the 5700cGy cohort. Toxicity was evidenced by analysis of patient reported toxicity questionnaires. At five years post-radiotherapy the frequency of grade 2 or worse bowel, bladder, and sexual toxicity across clinician-reported toxicity scales was similar across fractionation schedules. The CHHiP research study methodology was appropriate for its application and used combined methods using both patient and clinician reported outcomes. The findings were also evenly distributed in the study due to the careful cohort planning for each study arm. Each participant group contained on average, the same number of patients (n=1043 in the 7400cGy group, n=1051 in the 6000cGy group, and n=1056 in the 5700cGy group). This is one of the most comprehensive and evenly distributed cohorts in recent prostate radiotherapy studies. They identified no significant differences in the incidence of late grade 1 or worse, grade 2 or worse,

or grade 3 or worse bowel, bladder, or sexual symptoms in either hypofractionated group compared with the control group at any time point using any of the clinician-reported toxicity scales. These findings also therefore, confirm the aforementioned alpha/beta ratio assumptions in relation to hypofractionation.

It is worthy of note that the alpha/beta ratio responds to the cell repair/cell death of tissue during radiotherapy. It is a difficult concept to document however, this quote from Hegemann et al. (2014) provides a comprehensive explanation:

"*The Linear Quadratic Model with its alpha/beta value describes the curvature of cell killing both for tumor control and normal tissue complications in relationship to radiotherapy dose. The alpha/beta ratio is the dose where the linear as well as the quadratic component cause the same amount of cell killing. , the higher the alpha/beta ratio is, the more linear the cell survival curve is. Whereas the lower the alpha/beta ratio is (high beta relative to alpha), the more curved the cell survival curve is. This is important, as tissues with a low alpha/beta are relatively resistant to low doses in contrast to tissues with a high alpha/beta. Thus early responding tissues or rapidly proliferating tumors have a high alpha/beta ratio and late responding tissues or slowly proliferating tumors have a low alpha beta ratio*." (Hegemann et al. 2014 p275).

This is an important concern in dose regimes and fractionations as the fundamental principle of radiotherapy, especially SBRT is to cause extensive cell death within the tumour but reduce the dose, and therefore toxicity to surrounding tissues. In the case of prostate cancer, the alpha/beta ratio is low and almost comparable to normal cells. Brenner and Hall (1999) conducted a pioneering study concluding that the alpha/beta ratio for prostate cancer was low and for many years this conclusion was unchallenged, and in fact, supported by later studies. Future studies stated that when taking cell repopulation into account (which was not a consideration in the works by Brenner and Hall), that the alpha/beta was slightly higher than the 150cGy reported previously but still in clinical terms low (alpha/beta ratio of 310cGy). Conversely, further research conducted by Mirabell et al. (2012) found that the overall alpha/beta ratio was 140cGy. Their work was a multi-centre cohort of 5969 patients from international institutions and provided a more comprehensive inclusion criterion including androgen deprivation therapy (ADT), cell repopulation and overall treatment time to assess sensitivity. This study thus appears more methodologically robust than the previous works. It concluded:

"*The overall α/β value was consistently low, unaffected by AD deprivation, and lower than the appropriate values for late normal-tissue morbidity. Hence the fractionation*

sensitivity differential (tumor/normal tissue) favors the use of hypofractionated radiotherapy."(Mirabell et al. 2012 pp.e17-e24)

Clinically the alpha/beta ratio of prostate cancer is assumed to be low ranging from 100 – 180cGy (Datta et al., 2018). Concurred in a later study stating that the rationale of fractionation in radiotherapy is also based upon the higher repair-capacity of normal tissue compared to tumour cells, allowing an immediate repair of normal tissues between the fractions and thus allowing a relative tumour-specific therapeutic effect (Leborgne et al., 2012). A further reason for hypofractionated prostate cancer treatment is that the surrounding late-responding organs at risk, i.e. rectum or bladder have a higher alpha/beta ratio than prostate cells, therefore it can be concluded that prostate cancer cells are more responsive to a larger fraction size due to a lower alpha/beta level of prostate cancer cells in comparison with the surrounding normal cells (Brand et al., 2021). This knowledge and previous studies have led to the introduction of further hypofractionated regimes, known as stereotactic body radiotherapy, where larger curative doses of radiotherapy are given in only 3-7 large fractions of 500-800cGy, compared to the current clinical departmental standard of 300cGy fractions over 20 days or 200cGy fractions over 40 days. Cihan and Cihan (2018) reiterated that hypofractional radiotherapy to the prostate is based on modern radiobiology knowledge (alpha/beta ratio) and advances in SBRT. Many trials of hypofractional radiotherapy in prostate cancer (Dearnaley et al., 2016; Guo, 2019; Schorghofer, (2019), have demonstrated that hypofractionation treatment provides the same or better tumour control than standard fraction radiotherapy, while late and early toxicity remains unchanged in normal healthy tissue. According to clinical data presented in the cited studies, large fraction doses are biologically superior in prostate cancer to small fraction doses.

Brand et al. (2019) published a comprehensive and most recent multi-centre trial assessing the toxicity outcome of the PACE trial of IMRT versus ultrahypofractionated SBRT. The results are of particular interest in relation to this research as the dose and fractionation comparison is identical to the regimes used in this research (the conventional fractionation of 7800cGy in 39 fractions, moderated hypofractionation of 6200cGy in 20 fractions and SBRT of 3625cGy in 5 fractions). The study concluded that substantially shorter treatment regimes did not increase genitourinary (GU) or gastrointestinal (GI) toxicity. This was evidenced in 874 men who were randomised to conventionally fractionated or moderately hypofractionated radiotherapy (n=441) or stereotactic body radiotherapy (n=433). Four hundred and thirty-two (98%) of 441

patients allocated to conventionally fractionated or moderately hypofractionated radiotherapy and 415 (96%) of 433 patients allocated to stereotactic body radiotherapy received at least one fraction of allocated treatment. Worst acute Radiation Therapy Oncology Group (RTOG) gastrointestinal toxic effect proportions were as follows: grade 2 or more severe toxic events in 53 (12%) of 432 patients in the conventionally fractionated or moderately hypofractionated radiotherapy group versus 43 (10%) of 415 patients in the stereotactic body radiotherapy group. Worst acute RTOG genitourinary toxicity proportions were as follows: grade 2 or worse toxicity in 118 (27%) of 432 patients in the conventionally fractionated or moderately hypofractionated radiotherapy group versus 96 (23%) of 415 patients in the stereotactic body radiotherapy group. No adverse events (grade four toxicity or worse) or treatment related deaths were recorded in the study.

The PACE trial is the largest multi-centre, randomised control trial that has been conducted into prostate cancer in some time. The trial is an open-label multicohort phase 3 trial conducted at 35 centres in the UK, Ireland and Canada. PACE A was comparing SBRT to surgery and comparing the long-term bowel and bladder toxicity following treatment and overall survival. More relevant to this research audit is the PACE B arm of the study. PACE B compared SBRT to conventional radiotherapy regimes (7800cGy in 39 fractions or 6200cGy in 20 fractions) to prostate SBRT using 3625cGy in five fractions. PACE B randomised men over 18 years of age with low or intermediate risk histologically confirmed prostate adenocarcinoma which mirrors the inclusion criteria of this clinical research audit.

PACE C has not reported at this point, but is concerned with intermediate or high-risk patients randomised to conventional or SBRT arms of the trial following 6 months of adjuvant hormone therapy (Tree al., 2022).

Jackson et al. (2019) conducted a similar systematic review and meta-analysis of previous studies and found that substantial evidence exists for the efficacy of ultra-hypofractionation, with over 6000 patients treated in prospective studies and excellent 5-year biochemical progression-free survival in their recent meta-analysis (95.3%).

In delivering this treatment, particular attention must be given to the planning margins used in the planning stages of the patients' treatment, but other factors during a SBRT schedule must be taken into account due to the high dose per fraction. These include, the irradiating volume being as small as clinically possible to ensure target volume coverage whilst limiting irradiation of normal tissue and interfraction and intrafraction motion of the prostate.

2.4 PROSTATE MOTION.

Prostate motion and its associated consequences have been well documented in radiotherapy literature (Kotte et al., 2007; Button and Staffurth 2010; Budiharto 2011; Das et al., 2014; Dang et al., 2018; de Muinck Keizer et al., 2021). As treatment techniques have advanced, the dosimetric impact of prostate motion requires greater consideration due to the increased doses used and the decreases planning target margins required for such techniques as IGRT, VMAT and SBRT (Bocklemann et al., (2020). Prostate motion can lead to a geometrical geographic miss of the intended high dose target leading to areas of under or over dose and this will ultimately impact overall treatment toxicity, outcome and disease free survival. It is worthy to note that earlier studies would not have required IGRT and therefore neither study or included the use of implanted fiducial markers. Fiducial markers are gold marker seeds that are 3mm long and 1mm in diameter which are made of medical grade gold and are implanted into the tissue of the prostate to aid in localisation of the gland. The introduction of prostate fiducial markers has improved accuracy in pre-treatment prostate position verification (Kotte et al., 2007). In this approach, three gold grain marker seeds are inserted in the prostate gland in advance of radiotherapy treatment planning. The seeds are located in the apex, base and medial aspect of the gland. The seeds are well tolerated by the body, are radio-opaque and therefore easily visualised using kilovoltage imaging. In both studies, fiducial markers and pre-treatment imaging significantly reduce and correct for interfraction motion. Within the initial research study (Wu et al., 2001) the patient cohort was extremely small and limited. This study only used 13 patients and assessed 272 pre-treatment images. In contrast, the later work (Kotte et al., 2007) utilised a much larger cohort of 427 patients and pre-treatment imaging for an average of 27 treatment fractions per patient. This equates to a total of 11,426 fractions worth of data, resulting in a more robust data set using a larger sample than the previous work. Both studies used comparable methodology and analysis methods. Both studies used comparable treatment techniques of 5 and 6 field IMRT with an average treatment time of 5-7miutes allowing for comparability of results. However, both studies omission of a rectal preparation protocols or dietary advice and the effect of this on the resultant motion data was not acknowledged. Rectal variation can cause a varying degree of prostate motion both during treatment and in between treatments and therefore this could skew the results (Peng et al., 2011). Although this early work illustrates the prevalence of interfraction

motion, it is worthy of note that no online corrections were applied in either study. Therefore, no assumptions can be made in relation to the trajectory of prostate interfraction motion and whether this occurs sporadically or over the course of the treatment duration. With the improvement in treatment techniques, on board imaging capabilities and enhanced planning systems this would not be acceptable in current practice.

Fiducial markers are identified by on board imaging software and applied prior to treatment (online corrections) to account for interfractional positional changes prior to treatment delivery. Typically, when using IGRT, radiographers match and align daily images with the original treatment planning images, sometimes with the help of computer-assisted registration software. The alignment should be based on imaged target volumes and other anatomical structures. The process is subjective due to the correct alignment of anatomical structure, image registration quality, target volume or anatomical changes that could potentially lead to incorrect patient set-up. Clinically, a mismatch of the fiducial marker positioning leads to the target volume not receiving the prescribed dose, whilst a greater volume of surrounding tissue may be irradiated which is of concern for the proximal organs and surrounding tissues at risk. Therefore, the use of fiducial markers and image registration and matching software can reduce the potential for human error due to its objective nature (Handsfield et al., 2012). However, radiographers will always be required to carry out a physical sense check of the match result to ensure the software has correctly identified the fiducial markers. Each fiducial marker is cylindrical and measures 3 millimetres (mm) x 1mm and is medical grade gold and therefore, well tolerated by body tissues. The material requires to be radio-opaque and be well visualised on computerised tomography (CT) and kV imaging whilst reducing radiological artefacts (Kohsa et al., 2010). However, due to proximal anatomical structures, for example, pelvis bony anatomy, the software does not always identify the fiducial marker and physical matching of the fiducial must be carried out by the radiographers. For example, prostate calcifications are small solid masses due to a build-up of calcium phosphate and calcium carbonate and are reported to be present in almost 90% of prostate tissue specimens (Smolski et al., 2015). It has been reported that up to 35% of patients undergoing prostate radiotherapy have calcifications visible on imaging (Zeng et al., 2008) which have shown to be similar in size and dimensions to fiducial markers that are then commonly identified by the software incorrectly. A retrospective imaging study used a produced phantom to assess the precision of the software in identifying implanted fiducial markers. Fiducial marker positions were found to be reproducible with 0.5 mm of

precision. In addition, fiducial markers were identified correctly within 3mm of actual position in 60% of instances, not identified in 33% and not found in 7% of instances (Korpics et al., 2019). However, the study concludes that implanted fiducial markers greatly reduce interfraction uncertainties in prostate radiotherapy and could be used to reduce and monitor intrafraction motion with the possibly of fiducial markers being used to aid in margin reduction.

Whilst interfraction motion refers to the change in position of the target in between daily treatments, intrafraction motion refers to the movement or change in the position of the target during the actual treatment delivery. Intrafraction motion is typically seen in all directions (Poli et al., 2016) with a higher value in the superior/inferior (SI) direction followed by the anterior/posterior (AP) direction. Retrospective CT analysis for 15 patients reported the mean systematic internal prostate variation was 0.1 +/- 4.1mm and 1.2 +/- 7.3mm in the anterior/posterior axis, -0.5 +/- 2.9mm and -0.7 +/- 4.5mm in the superior/inferior axis, and 0.2 +/- 0.9mm and -0.9 +/- 1.9mm in the lateral axis, respectively (Frank et al., 2008). The mean magnitude of the three-dimensional (3D) displacement vector was 4.6 +/- 3.5 mm for the prostate. A subsequent study (Pang et al., 2011) assessed the interfraction motion in 20 patients using 486 pre-treatment CBCTs and reported that the mean prostate motion of 5.8 ± 3.1mm for all treatment fractions, with a maximum variation of 20 mm. This resulted in a dosimetric impact due to the fact that approximately 5% of the treatment fractions, the prostate volume receiving 100% of the prescription dose decreased dramatically (15-20%) compared with its intended dose. Variance in delivered dose versus intended dose can greatly impact the overall treatment outcome and the success of the treatment. The variance in the anterior/posterior aspect is attributed to rectal volume variations (Wahl et al., 2017). The variance in the superior/inferior aspect is attributed to variance in bladder volume (Cramp et al., 2017). It is therefore essential that bladder volume and rectal volume standardisation protocols are utilised prior to treatment to account for interfraction motion.

Evidence indisputably concurs that interfraction motion occurs due to the anatomical position of the prostate gland. It is positioned inferiorly to the bladder and anteriorly to the rectum. Therefore, variations in rectal and bladder filling can influence the positioning of the gland. Early works (Ogino et al., 2008; Nijkamp et al., 2008; Hatton et al., 2011) agree that the rectal volume should remain consistent and reproducible throughout radiotherapy, whether this is empty or comparably full due to a rectal preparation programme (Ogino et al., 2008). Interestingly there was no significant

difference in which method of bowel preparation was used i.e. empty ‘v’ distended rectum, enema ‘v’ dietary preparation, as long as the method of rectal preparation was consistent through the patients treatment (Yaver et al, 2015). Therefore, departmental policies in rectal filling could be patient centred or standardised. Gas and matter within the rectum cause the most significant variations in prostate positioning in the anterior/posterior direction and superior/inferior direction. Bladder volume also has an impact on prostate positioning and therefore an effect on interfraction motion (Roch et al., 2019), however in many studies bladder volume has much less of an impact than rectal volume variations (Graf et al., 2012; Fuchs et al., 2019). Again, very little significance is placed on the bladder filling regimes with the main goal being volume consistency; as long as it is consistently reproduced throughout treatment, for example, whether the patients follow an empty bladder protocol or a standardised filling protocol (Jain et al., 2012). Clinically, patients must therefore be given clear instructions on the bladder or rectal preparation required. This varies clinically within departments but patient comfort and compliance must be given consideration prior to the implementation of such protocols.

There is very little clinical evidence throughout the literature in relation to bladder filling protocols that has assessed the actual variation in prostate position rather than bladder volume. A point of interest in future studies would be assessing pre and post treatment CBCT to not only assess intrafraction bladder filling but also to assess the movement of the prostate in accordance with this. Studies suggest that bladder filling and inconsistency of bladder volume throughout treatment can change the position of the small bowel lying superiorly to the bladder and prostate therefore accounting for the larger deviations in the S/I vector (Nasser et al., 2021).

Intrafraction motion is the motion that occurs in the target volume during treatment delivery. Primarily intrafraction motion is attributed to changes in rectal volume, intrafraction bladder filling and patient motion. Erratic motion of the prostate, including rotation, was also reported in several studies (Kupelian et al., 2007; Ng et al., 2012; Hunt et al., 2016; Chi et al., 2017). Intrafraction motion of the prostate can also lead to changes in dosimetric coverage, and although intrafraction motion is proven generally to be smaller in magnitude than interfraction motion, it must be addressed clinically. Previous studies have concluded that prostate motion occurs in a three dimensional vector rather than actual fluctuations or changes in the shape of the gland and can therefore be accounted for prior to treatment (Mutanga et al., 2012; Haekal et al., 2018). In an initial study into intrafraction motion (Kotte et al., 2007) conducted

a study of 400 patients and found that motion changes less than 2mm in any direction occurred in 66% of the total treatment fractions and 28% of which showed motion of less than 3mm in any direction . The clinical implication of reduced intrafraction motion means a more homogenous distribution of dose and a more targeted treatment to the high dose volume as intrafraction motion reductions produce a more stable target. This concurs with a larger study that yielded similar results in 68% of their patient cohort. These previous results are comparable to the results of this study with 40%, 59% and 72% showing motion in the longitudinal, lateral and vertical directions respectively of less than 3mm (Budiharto et al., 2011). Unfortunately, one of the limitations of these studies are that, due to the methodology, accurate numerical values were not reported, just rather a 'less than' value. A less than value is beneficial however, when using increased daily doses and shielding of critical structures or organs at risk to sub millimetre accuracy, the reported data in these studies should be as accurate as possible. As methodologies for assessing intrafraction motion have advanced, for example the use of IGRT or real time tracking, numerically accurate values are being recorded, to sub millimetre accuracy. A more recent study of 1929 fractions (Koike et al., 2018), resulted in the mean absolute shifts of 1.54 ± 1.37, 0.59 ± 0.56, and 1.59 ± 1.44mm in the superior/inferior, left/right (LR) or laterally, and anterior/posterior directions, respectively. Roch et al. (2019), found similar results citing that the prostate intrafractional motion was larger in the vertical ($\mu = 0.3$ mm; $\sigma = 2.3$ mm) and longitudinal axis ($\mu = -0.4$ mm; $\sigma = 2.6$ mm) than in the lateral axis ($\mu = 0.1$ mm; $\sigma = 1.1$ mm). Therefore, prostate motion was almost completely contained within the sagittal plane. Most of the displacements of the prostate were found in the posterior–inferior (30%) and in the anterior–superior quadrants (34%), while the displacements in posterior–superior (21%) and anterior–inferior (15%) quadrants were less frequent. The cited studies demonstrated greater prostate motion in the anterior/posterior vector, and this aligns with the ideology that variations in rectal volumes are the main contributors to changes in prostate position (due to the tubular nature of the rectum, if increased gas is present then the rectum will distend therefore pushing the prostate forwards, if the rectal gas or matter dissipates this leads to the rectum falling back).

One of the limitations of the studies previously mentioned is the omission of the issue of fiducial marker migration. It is a known phenomenon that fiducial markers can move and migrate from the initial implantation position (O'Neill et al., 2016). This can be attributed to implantation position, anatomical anomalies, inflammation and haematoma or haemorrhage in the prostate tissues at the time of implantation (Fawaz

et al., 2014). For example, Mutanga et al. (2012) do not discuss the stability of the gold seeds, used as a surrogate for the prostate position. If these migrated this could falsely indicate a shift of target position. This is a potential disadvantage of a retrospective study, as verifying this information will be dependent on the information gathered in the study. The addition of 3-D CBCT images would have assisted this as the position of the seeds could be referenced against the 3-D anatomy of the patient as well as their co-ordinates in the imaging space. There is no mention of the dosimetric impact of the motion observed, which would have helped put the risk of intra-fraction and inter-fraction motion in a clinical context with organs at risk (OAR) positions or doses also omitted and which would be of interest for SBRT.

From data in almost all previous studies, the resulting displacement in the anterior/posterior axis was expected to be higher than in all other vectors. Evidence for this suggests that patients relax within the treatment time and the prostate settles in the posterior direction. As previously stated this can also be due to rectal variations and internal rectal movements and gas for example.

In critically evaluating the literature on intrafraction motion, it is apparent that extensive studies have been carried out yielding similar results. Clearly, the multicentre data is more clinically robust and significant due to the large sample patient numbers. However, consideration must be given to the varying methods of determination of prostate motion. As previously stated in this chapter, prostate cancer treatment and techniques have advanced dramatically in recent years and as such so have the methods of data collection in regards to prostate motion. For example, the earlier works relied on pre and post kV imaging as a way of determining the displacement of the prostate from the beginning of treatment to the end. A retrospective randomised study (Scobie et al., 2015) reviewed pre and post treatment images and found that 98% showed positional changes of <2mm in all directions. These results were comparable to a study of a larger patient cohort that found prostate motion was <2.5mm in all vectors (Kron et al., 2010). Studies of this nature give an indication of prostate motion however, do not account for any motion of the prostate during treatment delivery; they only give the difference in the prostate position from two timestamps, the beginning and end of treatment. A further development in methodology of estimating prostate motion was the use of kilovoltage intrafraction monitoring (KIM). Using imaging technology available on current linear accelerators, the kilovoltage images are taken at specific points throughout the treatment beam delivery. This is more accurate at representing the motion of the prostate. It was the

initial crude real time tracking method employed for the initial studies which found that the mean difference between the retrospective triangulation and real-time KIM was, in mm, LR 0.22, SI 0.56, and AP −0.07. The standard deviation of the difference was, in mm, LR 0.57, SI 0.27, and AP 0.32 (Keall et al., 2015). KIM was used in subsequent studies to further study prostate motion; however, they collated results factoring time into the equation. They found that the prostate was within 1 mm of its initial position for 84.8%, 1–2 mm for 14%, 2–3 mm 1.2% and ≥3 mm only 0.4% of the treatment time. The authors did not reveal the motion values however, it is inferred that there were no displacements greater than 3mm in any vector (Legge et al., 2017). As this was a single patient case study, inference and generalisability of results to the larger population must be considered. However, the methods and data analysis were deemed appropriate.

Latterly, studies investigating prostate motion have relied on real time tracking of the prostate, which gives a more comprehensive indication of the motion of the gland as the treatment beam is being delivered. Real time tracking relies upon implanted devices within the prostate to allow for localisation and tracking. Real time motion management devices and systems are discussed further in this chapter. It is largely apparent in the literature that real time tracking provides increased accuracy in prostate motion estimations and this is evident in the reduction of the mean values in all directions. A real time tracking study stated that the intrafractional prostate movements were generally small (i.e. ≤2mm), but could be substantial (e.g. 5mm) for a small number of patients (Tong et al., 2015). They observed the main trends of intrafractional prostate movement such as occasional fast shifts (e.g., due to muscle contraction, within seconds), short-term shifts (e.g. due to gas passage, within several to tens of seconds), continuous displacement (e.g. due to rectal/bladder filling), and the combination overall treatment time affects real time intrafraction monitoring (Tong et al., 2015). The study looked at not only the displacement values but also the percentage of the fraction that the prostate position had altered. The study tracked intrafraction motion of the prostate during 8,660 treatment fractions for a total 236 patients. The results showed that the percentage of fractions in which the prostate shifted by > 2, 3, 5, and 7 mm off the baseline in any direction for > 30 s was 56.8%, 27.2%, 4.6%, and 0.7% The percentage of tracking time during which the prostate shifted > 2, 3, 5, and 7 mm was 27.8%, 10.7%, 1.6%, and 0.3%, respectively. The percentage of tracking time for a > 3 mm posterior motion was four to five times higher than that in any other direction. Based on the previously cited literature is assumed that this is attributed to rectal gas motion. The clinical implication of such variances

in prostate position and the time that the prostate is out of the correlating planned position results in a geographical miss of the target volume and areas of under dose in the target volume and areas of over dose to the organs at risk. Baker and Behrens (2016), conducted their study, using ultrasound guidance, and found that of the maximum intrafractional displacements were [mm]; SI: 0.2 ± 0.9; LR: −0.2 ± 0.8; and AP: −0.2 ± 1.1, respectively. The largest displacement was 2.8mm in the posterior direction. The percentage of fractions with displacements larger than 2.0mm was 4 %, 2 %, and 10 % in the IS, LR, and AP directions, respectively. A recent study by Sihono et al. (2018) again utilised ultrasound tracking to review 770 treatment sessions and found that the mean (μ), the systematic error (Σ), and the random error (σ) of intrafraction prostate displacement were μ = (0.01, −0.08, 0.15) mm, Σ = (0.30, 0.34, 0.23) mm, and σ = (0.59, 0.73, 0.64) mm in the LR, AP and SI directions, respectively. The percentage of treatments for which prostate displacement was ≤2 mm was 97.01%, 92.24%, and 95.77% in the LR, AP, and SI directions, respectively (Sihono et al., 2018). This concurs with the previous KIM study conducted by Legge et al. (2017). In further studies by Liu et al. (2016) reviewing 28 patients, totalling 225 images, and found that the mean intrafractional prostate displacements in the left/right, superior/inferior and anterior/posterior directions were 0.61±0.50, 0.68±0.69, and 0.70±0.67 mm, respectively. Levin-Epstein et al. (2020) yielded similar results in their research of 205 patients finding the mean (± 1 SD) (standard deviation) intra-fractional target displacement in the LR, SI, and AP directions was 0.07 ± 0.05 cm, 0.13 ± 0.07 cm, and 0.14 ± 0.09 cm, respectively. The study is of particular relevance to this research project as it also used the intrafraction motion as the basis of the Van Herk margin formula (VHMF) (Van Herk, 2004) which follows the methodology of this research project and will provide immediate comparison.

The literature suggests that regardless of the modalities of real time imaging, the intrafraction motion is evidently more accurate and smaller in value than other methods of estimating prostate intrafraction motion.

The quantification of intrafraction motion is essential in relation to dosimetry of VMAT prostate radiotherapy. By accurately and correctly monitoring the motion of the prostate sufficient clinical margins can be applied in the dosimetry process to ensure geometric accuracy in treatment delivery.

2.5 DOSIMETRIC PLANNING MARGINS.

The implementation of increased real time verification and localisation of the prostate throughout treatment delivery allows the issue of planning margins in relation to intrafraction motion to be analysed. By assessing the intrafraction motion of the prostate, we can provide evidence to prove or question the planning margins used for prostate radiotherapy. Planning margins used in radiotherapy centres are normally historical, based on previous formulae or medical opinion, not necessarily always using evidence based practice. However, as clinical practice and treatment techniques evolve, it is crucial to assess the current margins used. Generally, a planning margin is added to the gross target volume (GTV) to account for subclinical disease which creates a clinical target volume (CTV). A further margin is added to account for any geometric uncertainties; this creates the planning target volume (PTV). The PTV is a geometric concept that takes into account all the potential geometric variations, including systematic and random errors, to ensure the margin applied to the treatment area results in the CTV receiving the correct prescribed dose throughout treatment (International Commission on Radiation Units and Measurements (ICRU) 1999; Meijer et al., 2008) (Figure 4).

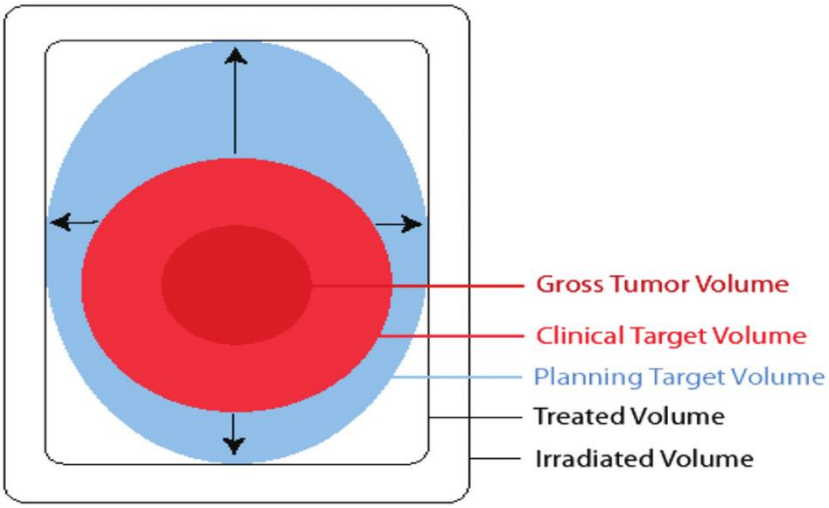


Figure 4 - Planning margin illustration (ICRU, 1999) illustrating the growth from the clinical target volume to the planning target volume to treated volume and overall irradiated volume.

Historically, margins were obtained by using margin formulae such as the Van Herk margin formula (van Herk, 2004; Witte et al., 2017). The VHMF takes into account random and systematic errors in patient positioning and movement, and set up errors

in equipment and calibration devices, to therefore suggest a numerical measurement of margins for error to ensure that the PTV fully encompasses the CTV during treatment, minimising the risk of geographically missing the target volume.

The PTV margin ensures the target volume receives the highest clinically achievable dose but ensures protection for the organs at risk. To ensure that these constraints are met, it is essential in radiotherapy planning that all geometric uncertainties are taken into account, to ensure that the PTV is representative in the real time dose delivered in the moving clinical target volume (The Royal College of Radiologists (RCR), 2015). Skarsgard (2010) first addressed the issue of real time planning margins in prostate radiotherapy stating that if too narrow margins were used in the planning process, this could actually mitigate the risk of a geographical miss or an increased dose to the organs at risk, due to daily uncertainties in location of the prostate. Again, proving that intrafraction motion requires to be taken into account when developing departmental planning protocols.

It is crucial that PTV margins are calculated in accordance with which verification and localisation modality is in use in the institution. For example, one study reported that using kV imaging with bony anatomy registration alone required margins of 0.31cm LR, 0.89cm SI and 1.07cm AP. However, when localised using fiducial markers and daily kV imaging these margins were then calculated at 0.4cm (LR), 0.39cm (SI) and 0.34cm (AP) respectively (Lerma et al., 2009). This confirmed similar results, by Litzenberg (2006) stating that positioning with implanted fiducial markers reduced required planning margins to 0.18cm LR, 0.58cm AP and 0.71cm SI. The results of this study were solely based on daily kV imaging with fiducial seed matching. Using pre-treatment and post-treatment kV imaging is an indirect method of assessing intrafraction motion in comparison to real time tracking systems, and therefore, may be less accurate in determining the prostate position throughout treatment. Nonetheless, the results of this study are comparable with previous studies stated using the same technique. More recent studies that included all vectors in the imaging verification process reported varying results. A later study found that using fiducial markers and daily imaging could reduce margins from 1cm in all directions to 0.7cm in all directions (Paluska et al., 2013). However, this assumed heterogeneity of the prostate gland. The most recent literature suggests that anisotropic planning margins are applied, with a reduction on the posterior aspect to reduce rectal toxicity. A retrospective study of nine patients used daily CBCT data to assess prostate planning margins. The initial planning margins applied to the treatment plans were 8mm in all

directions apart from posteriorly which was 5mm, referred to 8/5mm. The treatment plans were then recreated using the daily CBCT data with decreasing margins ensuring that all dose constraints were still adhered to. The study assessed planning margins of 6/4mm, 4/2mm and 2mm uniformly in all directions. It reported that a reduction in planning margins to 6/4mm was clinically achievable. A reduction to 4/2mm or 2mm resulted in inadequate dose to the prostate (Li et al., 2016). A limitation of the study was the small patient cohort and the study relied heavily on the use of IGRT and daily isocentre repositioning. The results of this study are similar to previous work using similar methodology and sample size. This study reduced planning from 10/6mm to 5/3mm and 3mm uniformly. The results suggested 5/3mm margins were clinically achievable as margins of 3mm resulted in a reduction of complication free tumour control of 13.6% (Wen et al., 2013).

It is evident that as time and treatment techniques advance, the accuracy of quantifying intrafraction motion increases and the values are more reliable to sub millimetre accuracy. It is therefore suggested that before adopting any published margin recipe, factors that can potentially impact upon margins should also be taken into consideration (Gupta et al., 2007). In terms of this research real time tracking of intrafraction motion is imperative.

Subsequent recent research (Langen et al., 2008; Bottero et al., 2020) has concluded that continuous real time tracking of intrafraction motion can reduce the maximum localization error in patients by 20% on average. With the motion corrected, the duration prostate beyond 1 mm from its initial treatment position can be reduced from 37% to 22% of the total treatment time (Han et al., 2018). This is comparable with Richter et al. (2020), who using a larger cohort found that intrafraction monitoring resulted in a mean prostate displacement of (-0.06 ± 0.49) mm, (-0.09 ± 0.61) mm and (-0.01 ± 0.78) mm in the SI, LR and AP directions, respectively. Even though large deviations up to 8 mm were detected, the frequency of occurrence was less than 0.1%. The prostate moved within ±2 mm in 99%, 98.1%, and 96.6% of the treatment time in the SI, LR and AP directions, respectively.

The implication of the reduction in displacement values of intrafraction motion is of great importance to the planning target margins used in SBRT techniques for prostate cancer. Due to the large dose per fraction, it is imperative that margins allow for optimal target coverage but allow for tissue sparing of normal tissue. Therefore, it follows that if intrafraction is in fact smaller than previously reported then planning

target margins should be reduced accordingly, which has led to the main question underpinning this thesis.

Does RayPilot® allow for significant reductions in planning margins to allow for ultra-dose escalation?

To answer this question, intrafraction motion will be assessed and then used in the Van Herk margin formula to quantify required treatment planning margins.

The purpose of the Van Herk margin formula is to ensure the CTV receives 95% of the prescribed dose in 90% of the population. However, the model contains assumptions on the proposed treatment plan, namely:

- The formula assumes that the dose distributions created in the plan conform exactly to the previously derived PTV;
- The recipe does not take into account the target size, variations in tissue density along the path of the treatment beams or the type of treatment being used, for example conformal, IGRT or VMAT techniques (Alonso-Arrizabalaga et al., 2007).

Van Herk (2004) and Meijer (2008), suggest that the appropriate size of PTV margins is inversely proportional to the number of radiotherapy treatment beams present in the treatment plan. This is relevant in the application of the margin recipe in relation to the techniques used in clinical departments with advances in technology and treatment techniques. However, the formula has not evolved to consider this. Given that the formula has not evolved to take into account advancing treatment techniques, this may be a limitation for using such methodology.

The Van Herk margin recipe states the contribution of systematic errors is approximately 1.5 times greater than that of the random error component ($2.5\Sigma + 0.7\delta$). Therefore, systematic errors contribute to a larger portion of the PTV than random errors, suggesting that reducing the overall Σ value results in a better shrinkage effect on the required PTV margin. Random error contributions are a smaller portion of the PTV and are unpredictable so therefore, harder to account for. Clinically this is of value and should receive diligent consideration. Practical reduction of systematic errors can be achieved by pre-treatment correction. For instance, as previously mentioned, rectal volume variations can be accounted for and minimalized, as well as using and pre-treatment isocentre positioning using image guidance. Further systematic errors can be accounted for in the margins that are applied at the

treatment planning stage; for instance, mechanical set up errors and organ delineation. Reducing systematic errors and therefore, total applied planning margin, significantly reduces irradiation to surrounding tissue minimising toxicity to the patient. A key systematic error mentioned in previous studies is in the outlining stages of treatment planning. Organ delineation is the process of outlining critical structures including the primary target of the prostate and associated organs at risk. There are numerous studies evaluating organ delineation in pelvic radiotherapy, however, they are highly variable with different numbers of observers, datasets, and methods of comparison (Gardner et al., 2015; Nassef et al., 2016; Tyagi and Hunt, 2018; Ailotta et al., 2019). Comparison between studies is therefore difficult due to the variance in methodology. Alasti et al. (2017) conducted an observational study requiring five clinical oncologists to delineate organs at risk and the high dose volume, the prostate, using CT planning scans. It concluded that the mean inter-observer variability is 2.0 ± 0.6mm. This work did not show significant differences in organ delineation variability to an earlier study conducted by White et al. (2009) in which the mean standard deviations for left–right, anterior–posterior and superior–inferior boundary displacements were, respectively, 1.8, 2.1 and 3.6 mm. Khoo et al. (2012) also evidenced inter and intra observational variability of prostate delineation with 15% and 9% variation respectively. As organ delineation has a major impact within the systematic error component of the VHMF, the reduction in variation can lead to the reduction in margins.

Ideally, utilising image guidance and online correction should eliminate interfractional uncertainties and therefore, result in a much smaller magnitude of intrafraction motion. Due to the advancements in treatment techniques and technology systematic errors have greatly been reduced and organ motion is accounted for and corrected prior to treatment. Therefore, the value of organ motion in the systematic component of the calculation becomes zero due to all systematic errors being corrected for using isocentre repositioning prior to treatment delivery. Gupta et al. 2018 suggested that by increasing the use of IGRT and daily imaging, the mean systematic error and the standard deviation of the systematic error is decreased. With increased image guidance frequency, the systematic error for organ motion can be decreased therefore allowing for the decrease of CTV-PTV margins without compromise on the coverage of the high dose volume. The study analysed 2700 pre-treatment set up images and the data was used to recreate planning margins using the resultant set-up error data. Pramanik et al. (2020), also concluded that IGRT reduced set-up errors to effectively zero, however the data collected was anatomically multi-site therefore,

reducing their pelvic sample. However, even with perfect IGRT conditions factors of organ delineation and intrafraction motion continue to have a significant impact on the margin calculation.

Smaller magnitudes of intrafraction motion are obviously advantageous and Adamson and Wu (2010) suggested that smaller intrafraction motions of less than 2mm will resolve spontaneously and the prostate will return and remain within the PTV in 25% of instances. This complies with previous studies already mentioned which reported higher percentages of organ motion reversal in patients. Two types of intrafraction motion were observed in these studies: slow posterior and inferior drifting which does not resolve spontaneously but remains within the allowed PTV and sudden transient motion that shows greater levels of spontaneous reversal. This follows the assumption in the Van Herk margin recipe that suggests the random error component is of less value in PTV definition due to smaller magnitudes and spontaneous correction.

Observations in the aforementioned studies, demonstrate that intrafraction motion varies considerably per patient. It is therefore essential that planning margins applied are relevant to the patient population which will inevitably vary by clinical site. In this case of prostate volumetric arc therapy within the host centre, the planning margins employed and dictated by the CHHiP protocol are larger than the values defined in recent literature. Currently, the margins used for prostate planning is 0.8cm and 0.5cm on the posterior aspect. This justifies the discussion of margin reduction in SBRT prostate patients due to the larger dose per fraction. By reducing the CTV to PTV margin, the treatment volume will be reduced resulting in less toxicity to the patient without affecting treatment outcomes. However, this study and studies like it also open the debate for patient specific margins or adaptive planning techniques. Patient specific margin calculations would require increased manpower and would also require a lengthier planning process which would, in turn, lead to a delay in the patient commencing treatment, which could prove detrimental to treatment outcome, as such the margins derived should be cohort specific not patient specific.

2.6 MOTION MANAGEMENT TECHNOLOGY.

Following an extensive review of the literature, it is apparent that the fundamental issue in hypofractionated prostate radiotherapy is monitoring and managing prostate intrafraction motion. The most effective way of doing so is by the implementation of

real time motion tracking. As such, the following section will review various methods of prostate motion management systems.

There are a variety of real time tracking systems available for SBRT in prostate cancer, for example Calypso® (Varian Medical Systems 2016), Cyberknife® (Accuray, 2019) and RayPilot® (Mircropos Medical Systems 2019). Each system records intrafraction motion and allows for correction prior to the radiotherapy beam being initiated for treatment. The differentiating factors between the systems are the equipment required and the modality of imaging required. For the purposes of the literature review, it was essential that the system implemented in the department was compatible with the current clinical equipment (Varian linear accelerators) and the imaging modalities available (kilovoltage, megavoltage (MV) and cone beam computed tomography).

Each system allows for real time tracking of intrafraction motion using implanted fiducials of some form. The software for each system also facilitates departmental tolerances to be entered into the software and initiates a 'beam hold' or 'beam off' feature that terminates treatment beam delivery if the intrafraction motion exceeds the stated tolerance. All motion management systems also record patient specific data in relation to intrafraction motion and positional corrections made. This feature enables the data to be analysed and used for margin estimation and future SBRT developments. In the case of this research this will be the data that will be entered into the margin formula to assess whether margins can be reduced and assess whether further dose escalation is possible. A brief overview of the available systems will follow.

Calypso®

The Calypso® motion management system (Varian Medical Systems, 2019) uses three electromagnetic transponders, implanted at the left and right base and apex of the prostate and uses the centroid position of each as a surrogate for the position of the prostate. The tracking of the transponder position is carried out using a monitoring station located in the treatment unit (Bell et al., 2017). Each Beacon transponder consists of a sealed glass capsule containing a miniature electrical circuit measuring 1.85mm in diameter and 8.0-8.7mm in length. Transponders emit signals when excited by the non-ionizing electromagnetic field generated by the system's array. Each transponder emits a response signal at a unique frequency specific to that transponder which can be detected by sensors within the array. The system then interprets the shape of the transponder signal measured across the array to determine

the position of each transponder. The Calypso® System console is a movable unit and contains the system components that generate and detect the electromagnetic signals used for patient alignment and continuous monitoring of target position.

Muralidhar et al. (2013) published preliminary results of quality assurance study of the accuracy of Calypso® and found that it provided accurate, objective, and continuous localization of a treatment target for patient alignment and target position monitoring during radiation therapy to an accuracy of 0.01cm (Muralidhar et al., 2013). Unfortunately, they did not follow up their study with patients' data so the quality assurance testing regarding the accuracy of the Calypso® system did not take into account intrafraction motion, variations in rectal volume or any clinical issues due to the work only being carried out on a static phantom.

Bell et al. (2017) discussed their initial experiences with the system, successfully utilising Calypso® for 116 out of 120 fractions. Some changes to their workflow were required as part of implementation. Due to the significant artefact observed on the magnetic resonance imaging (MRI) scans with the Calypso® beacons present, MRI scans were taken before implantation.

The rotations of the prostate were outside of their designated 10 degrees' tolerance in 28 of the fractions. When this was observed, their protocol advised for a CBCT image to be taken to verify that the prostate was within the target volume. There was no discussion of the number of cases requiring adjustment. Rotations can be accounted for on some linear accelerators, however at present the host department does not correct rotational variations and therefore, the impact of rotation will not be used in this research. Nevertheless, it is still important to consider these when assessing motion management systems.

Calypso's® accuracy was assessed by Hamilton et al. against CBCT and 2 dimensional (2D) kV imaging using an anthropomorphic phantom (Hamilton et al., 2017). The phantom was imaged in different positions with the imaging systems localising. Their literature review noted a number of studies on positional differences between Calypso® and orthogonal planar images, but few included rotational positioning. They used seed matching software, whereas in clinical practice they used manual matching. Therefore, these results could differ if they were implemented clinically. There are advantages of using matching software however, because it removes any user bias so the results can be translated to other centres despite differences in local manual matching conventions.

Vanhanen et al. compared Calypso® transponders against two-dimensional (2-D) kV imaging. Bland Altman analysis was used to compare the differences in positional correction between the electromagnetic and the kV tracking system. They also looked at the stability of the implants for each modality. The mean coordinate difference between the kV system and Calypso® was -0.19mm (AP), 0.14mm (SI) & -0.05mm (LR) which was consistent with other published literature (Vanhanen et al., 2018).

Lovelock et al. (2015) studied the benefits of positional monitoring of the prostate compared with X-ray pre-treatment imaging for prostate SBRT patients. They noted that the beam was halted due to the target moving outside of their tolerance in more than a third of the fractions, which would not have been highlighted using pre-treatment imaging alone. The median time between set-up imaging and the end of treatment was 6 minutes 40 seconds, and despite some interventions, the mean impact on treatment time was only 30-40 seconds. They found 15 delivered fields where a displacement of 4mm or more was identified using Calypso®. The dosimetric impact of this was calculated, and for nine patients (10% of the study) the minimum PTV dose was lower than 90% of the prescribed dose, with the lowest being 77%. There was no discussion of the impact of this on OARs such as the bladder or rectum (Lovelock et al., 2015).

The literature concludes that Calypso® is an accurate and efficient method of tracking prostate motion in real time.

Cyberknife®

The Cyberknife® system consists of a robotic radiosurgery system that uses dynamic image guidance during treatments (Accuray, 2019). It consists of a linear accelerator mounted on a robotic arm and a kV imaging system, with radio-opaque markers implanted into the target in order to track its position. The system will then automatically correct for motion of the target in real-time, with the robotic arm adjusting the position of the treatment delivery as the motion occurs (Accuray, 2019).

Accuray recommends implanting a minimum of four (one more than required) and a maximum of six platinum fiducials for Cyberknife® tracking. The four key principles in placement are a minimum of 2.0cm between fiducials; a maximum distance of 5-6cm from the lesion; non-colinear placement (within the orthogonal imaging plane) and at least 15-degree angulation between any grouping of 3 fiducials. This can lead to difficulty in the implantation procedure, as, even under ultrasound guidance, these stringent parameters can be problematic to achieve. This can be due to prostate

volume, location of tumour volume, and implanter experience. In the host department, this would require major amendments to the implantation process already in place.

The system has been established in radiotherapy for a number of years and has been used as a localisation and verification system in prostate radiotherapy including SBRT (King et al., 2012). Holmes et al. looked at marker implantation protocols for prostate SBRT patients (Holmes et al., 2018). The “relative pose problem” (Murphy, 2002) is where the translations of the x, y and z axes in the planning and treatment spaces can be mapped. In order for this to be mathematically possible 3 fiducials are required, and the Cyberknife® manufacturers recommend 4. Issues can arise if the markers are too close together as the software cannot distinguish between them. The established protocol for implanting the markers caused errors in the rotational tracking of the prostate for 26% of their patients so they established their own protocol and compared its positional accuracy and any subsequent errors against the original protocol. In the host department only three fiducial markers are currently implanted into the prostate prior to treatment.

The results of the study showed no instances of rotation errors observed with the new protocol. The dosimetric impact of the findings was assessed by rotating the dose distributions on the planning system and calculating the target coverage and rectum dose. They concluded that a rotation of 3 degrees could lead to a decrease of 9% of the target dose and an increase of 4% to the rectum dose with larger rotations worsening these effects.

Choi et al. (2018) carried out a retrospective study on clinical outcomes for prostate SBRT patients treated with Cyberknife® by utilising the collated patient data from the software to determine prostate motion. They observed only 21.1% of patients exceeding 1mm of motion in the AP direction and less than 4% with more than 1mm motion in the other directions. There was no evidence of prostate motion being greater than 2mm in any direction.

They showed that there was a statistically significant difference in the rectal and bladder toxicity between patients with more than 0.73mm motion in the AP direction. They also showed a statistically significant difference in rectum toxicity due to radial motion above 0.92mm. They concluded that there was no significant statistical evidence that motion had an impact on treatment outcomes for this group, analysed separately for the low, intermediate and high-grade patients (Choi et al., 2018).

RayPilot®

The RayPilot® real time motion management tracking system comprises an implantable transmitter, a treatment couch top array and the accompanying software package for determining and recording patient specific intrafraction motion. The device is implanted into the patient using a transperineal approach and is in situ until completion of the treatment. It comprises of a small patient specific transmitter (17mm by 1mm) and a cable (approx.30cm in length) that protrudes from the patient and is then attached to a tabletop array, which is fitted to the treatment couch. Within the tabletop array are the antennas that detect the co-ordinates of the implanted device and then calculates the motion of the device in all vectors throughout treatment. This will then be graphically represented and recorded in the treatment software. If the motion is recorded over a predefined tolerance, then the radiation beam can be interrupted and the treatment stopped. It will then be resumed when the device returns to the treatment position or motion corrections have been repeated to ensure the prostate is returned to the treatment position (Micropos Medical, 2019).

The RayPilot® system has been developed by Micropos Medical as a stand-alone real-time tracking system, without the need for additional X-ray imaging (Vanhanen et al., 2016). It consists of a tabletop array of antennae, and the transmitter that is inserted transperineally into the prostate. When the antennae detect the transmitter signal, the position of the transmitter is given. The transmitter is attached to a thin wire that will protrude from the patient and remains in position until after the treatment has concluded after which time it can be removed. Braide et al. (2018) reviewed their initial experiences using RayPilot® for prostate radiotherapy, where seeds were also implanted into the patient and used for imaging. Patient tolerability of the device was assessed as good although a number of patients recorded some minor discomfort. The implantation of the device was discussed, where a clearer and more standardised approach could be useful. They also found that manufacturer recommendations on the transmitter angle (within 30 degrees of the horizontal plane) were not achieved in three patients, which could impact the recording of real-time positional data, although this was not applicable in this study. A large transmitter shift was observed for one patient (6.2mm) which may be due to organ expansion as seen on radiographic imaging. The position of the transmitter relative to the seeds (which were assumed to be stable based on established literature was assessed using Matlab) was reviewed. If it was recorded as being displaced by more than 2mm these were deemed to be unstable and of no clinical use both by the manufacturers and the radiographers. The results of the study showed that only four of the patients had their transmitter defined as stable, with the maximum displacement recorded as 5mm. They concluded that

the device was feasible and safe to use, but more evidence was required for it to be used as a primary imaging device for prostate treatments and further evidence on the stability of the device would be required.

As RayPilot® is a relatively new treatment technology, studies conducted until this point, have used fiducial markers as a method of prostate localisation and to confirm the efficiency of the RayPilot® device. It is a clinically ethical methodology to ensure the device provides accurate data (Integrated Research Application System (IRAS), 2018). As such, Braide et al. (2018), suggest that there is no strong evidence in the paper for the stability of the transmitters, and therefore the requirement of additional imaging throughout treatment is advised for future seminal research studies.

Although the RayPilot® data was gathered retrospectively, the researchers were looking quantitatively at positional coordinates and therefore their method appeared appropriate. The impact on the positional accuracy of RayPilot® due to device migration was shown, with migration corrected values giving better results. As the RayPilot® patients were treated over 20 or 39 fractions; their transmitters were inserted for longer than an SBRT treatment. This could lead to larger discrepancies in device instability due to the extended period of time from implantation to completion of treatment.

For the RayPilot® study, due to their being only one transponder, the relative pose problem would not apply. The relative prose problem relates to the position of the fiducials (a surrogate for the target position) being calculated through back-projection and the geometry of the X-ray imaging system. The fiducial coordinates in the planning CT and the fiducial coordinates during treatment are used to solve for the position (translation) and orientation (rotation) of the target during treatment (Holmes et al., 2018). In fact, the device may not be suitable for determining rotational errors due to the fact that there is only one transmitted and not multiple fiducials which can be triangulated to assess rotational variations. This should be explored in future studies. It may also be worth looking at the impact of placement protocol of the transponder, as this will be carried out following the manufacturer's instructions.

Delcoudert et al. (2017) used CBCT imaging as a reference for the positional verification of their implant. The advantage of this comparison is that the benchmarking imaging system gives 3-D information about the position of the device, although there would be additional time between imaging. The mean difference in position between the transmitter readout and its CBCT position was 1.34mm, which was noted as being of the same order of magnitude as prostate motion during the

CBCT acquisition and therefore may have been caused by this rather than differences between the imaging systems (Delcoudert et al., 2017). The correlation was therefore seen as a suitable match. For this study, this will be important as the position of the device will be verified by both CBCT and kV/kV planar imaging. There should be some consideration for the impact on intra-fraction motion and the acquisition time of the CBCT scans on any results.

Vanhanen et al. (2016) found that the mean inter-marker shifts in the ten patients included in the study was <1 mm. In four patients, maximum transmitter 3D shifts were 5–7 mm (mean >2 mm). In three patients, mean transmitter 3D shifts were <2 mm.

2.7 CHAPTER SUMMARY.

In summary, it is apparent from the literature search that prostate motion, motion management systems and prostate SBRT have been thoroughly researched within the medical research community. This review was successfully carried out and used to identify the research aim for this study and inform some of the detail of what these should involve, the methodology used and the data that should be collated. Although there is a large body of work available to call upon for this topic, due to the niche aspects of RayPilot® there are opportunities for novel approaches to previous studies along with possible applications where there is little evidence such as for dose escalated SBRT. What was clear from the wide range of literature is that for prostate motion management there is no system clearly evidenced as superior, indeed it was noted that there is little comparison of existing devices that include clinical follow up. This would be useful information for radiotherapy centres about to purchase and implement a system for prostate motion management. It is essential in this climate that any motion management system should be cost effective and compatible with current equipment installed in the department.

For clinical studies to have impact on the specialist area, it is imperative to assess gaps in current knowledge or research and attempt to fill this gap using appropriate research methods. The implementation of new technology, treatment techniques or systems provide are all areas where there are opportunities to conduct research and clinical audit, often driven by the need to find answers to important clinical questions. Following the literature review, it is evident that there is scope to conduct novel research on RayPilot® because it is a relative newcomer to the field and because of

this, there are many questions associated with its use. As such, RayPilot® was chosen as the motion management system to implement.

This clinical audit explores the impact of RayPilot® on treatment margins and dose escalation in prostate volumetric arc therapy. However, following the literature review there are excellent opportunities for further future research into the RayPilot® system following on from this initial study. **Thus, the clinical audit aim is to assess the efficiency of the RayPilot® real time motion management system and the analysis of the RayPilot® data providing evidence and guidance on the feasibility of the reduction in current clinical treatment margins and to evaluate if it is feasible to introduce a new fractionation and dose escalation regime.**

3 RAYPILOT® SYSTEM COMPONENTS

3.1 THE RAYPILOT® SYSTEM.

The RayPilot® system comprises of an implantable transmitter device, the couch top array that houses the global positioning system antenna and software and an external visual display unit (Figure 5).

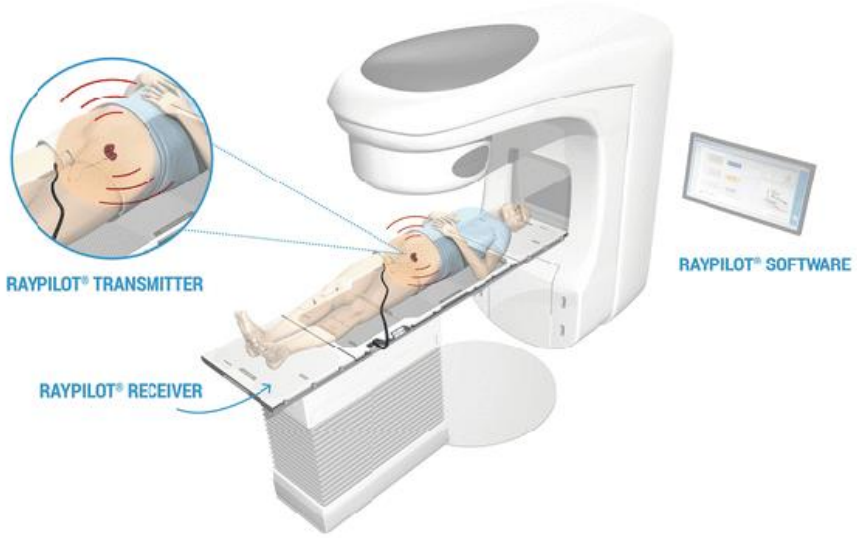


Figure 5 - The RayPilot® system. The system comprises of the couch top array that is the RayPilot® receiver, the implanted RayPilot® transmitter (shown in situ in the prostate) and the external visual display unit.

3.2 TRANSMITTER DEVICE.

The RayPilot® transmitter device comprises of the transmitter tip, which houses the unique patient identifier chip, which is 17mm by 3mm in diameter and is surrounded inferiorly by plastic barbs which are designed to inhibit migration by anchoring into the prostatic tissue (Figure 6). The transmitter is attached to a cable which is the only thing that protrudes from the patient. The cable is 1.6mm in diameter and 383mm in length. The entirety of the RayPilot® device is a wire based implant covered with a biocompatible polymer material. At the opposite end of the device from the implanted portion, is the metal adaptor port for connection to the RayPilot® receiver system.

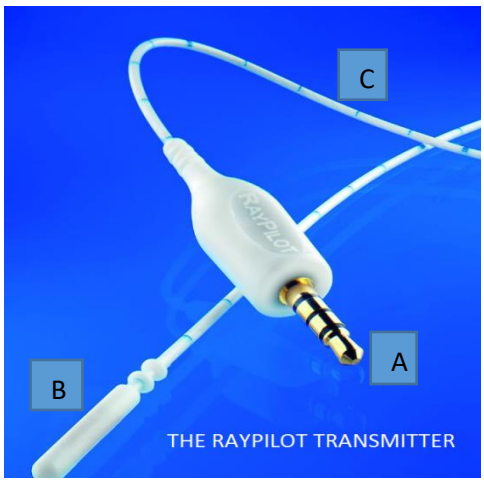


Figure 6 - The RayPilot® transmitter device. The figure shows the connection port (A) which attaches to the couchtop array, (B) is the transmitter which is surgically implanted into the prostate gland and (C) which is the polymer-coated cable which protrudes from the perineum.

The transmitter tip contains a patient specific data chip, which when first connected to the RayPilot® will require to be paired to the data for that specific patient. The transmitters are one patient use and should therefore only be registered to the RayPilot® software once. It will store the treatment plan and positioning data for each patient and relate this to the software upon each connection prior to each treatment fraction. The chip also houses the electromagnetic antenna structure that is designed to determine the position of the electrode within the body and track it.

The chip located at the tip of the transmitter is arranged to emit an electromagnetic signal when energised by an external excitation source (the connector cable to the control unit). The electromagnetic (EM) signal is of low frequency, and is initially generated from the control unit and is thereafter transmitted by the transmitter. The electromagnetic signal is adapted to propagate with a wavelength within the body and a phase difference of the electromagnetic signal is detected by the RayPilot® receiver. The RayPilot® technical specifications describe it in depth as:

" *the transmitter is arranged in relation to the treatment area, each transmitter emitting an electromagnetic signal, wherein said electromagnetic signal is adapted to propagate with a wavelength in said body so that a phase difference of said electromagnetic signal in at least three positions is detectable by a receiver for tracking variations of a position of each transmitter relative to said receiver, wherein said wavelength is selected so that a distance from the transmitter to each of said at least three positions is within the same integer number of wavelengths of the*

electromagnetic signal, characterised in the system further comprising; an externally arranged control unit, wherein each transmitter is connected to said control unit, in which said electromagnetic signal of each transmitter is generated before transmission." (Micropos 2019).

As the transmitter is surgically implanted and designed to minimise migration following implantation, therefore, the initial co-ordinates of the transmitter can be obtained from the imaging planning system. These co-ordinates provide the implanted device position relative to the target area to be treated. Therefore, the implanted device serves as a reference for the target area position.

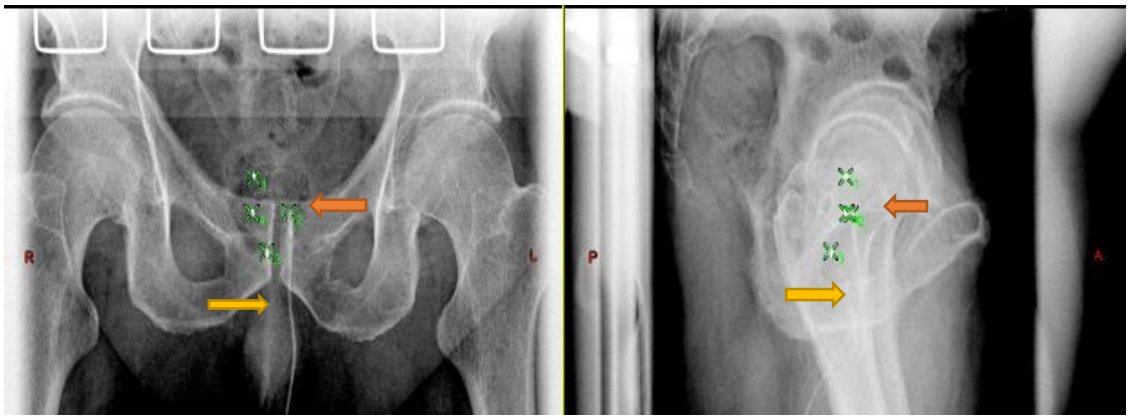


Figure 7 - RayPilot® kV imaging - the RayPilot® transmitter tip can be clearly visualised on kV imaging (orange arrow). The yellow arrow shows the transmitter cable and the green crosses indicate the fiducial markers in relation to the placement of the RayPilot® transmitter.

Figure 8 - RayPilot® CBCT imaging - sagittal CBCT showing placement of the transmitter cable (A), the transmitter tip (B), the outlined rectal volume (C- outlined in red) and the outlined bladder volume (D - outlined in yellow). The corresponding colour wash outlines depict the high dose target volume and expected dose delivered to the surrounding tissues.

Figures 7 and 8 illustrate the visualisation of the RayPilot® implanted transmitter on both kV imaging and CBCT imaging. The transmitter is easily visualised and using the external beam planning system, the co-ordinates of the tip of the transmitter can be calculated. The resulting co-ordinates are then used as a fixed reference point for the RayPilot® software system to use for localisation (described in the next section).

In the case of prostate radiotherapy, the whole of the prostate gland is included in the target volume therefore; the advantage of the RayPilot® implantable device is that the transmitter can be surgically implanted directly into the target volume i.e. into the prostate gland. In turn, this leads to accurate and localised positioning data in relation to prostate motion and dose delivery.

3.3 RAYPILOT® RECEIVER UNIT.

The RayPilot® system also comprises a receiver unit, also known as a couch top array (Figure 9).

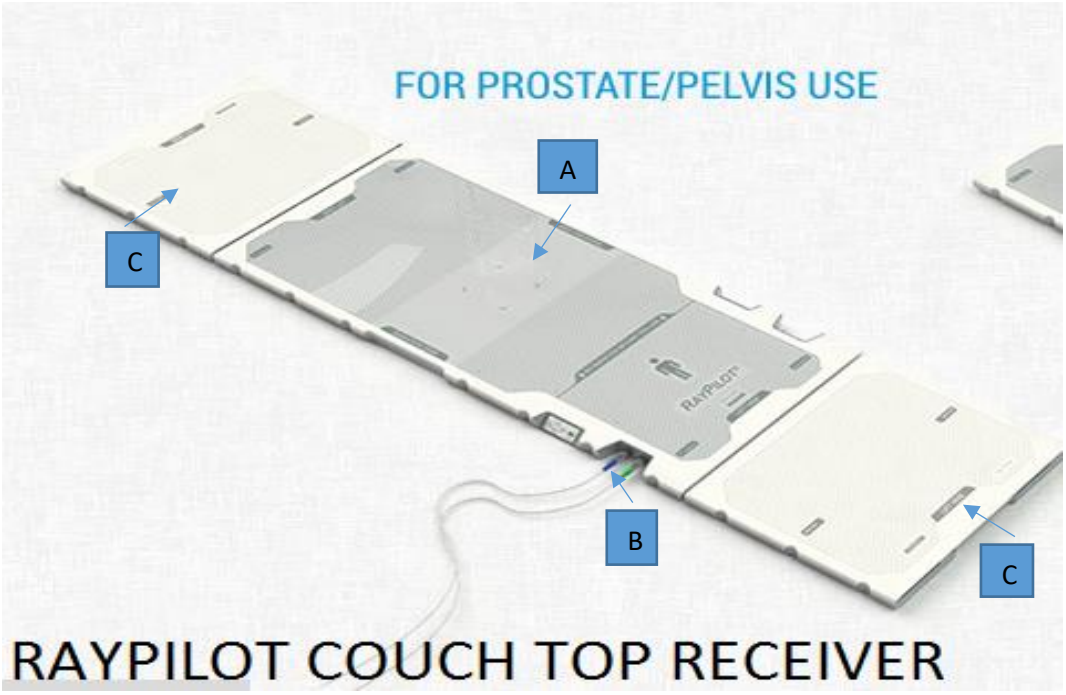


Figure 9 - RayPilot® couch top array. The couchtop array is placed on the couch top of the linear accelerator. The patient is then positioned with the pelvis located in the radiation zone (A) and the transmitter cable protruding from the perineum is attached to the couch top array using electronic ports on both sides of the couch top array (B). The couch top array includes extender portions to allow for uniformity of the couch top (C).

The receiver unit houses electromagnetic sensors. The electromagnetic signals generated by the implanted transmitter are detected by the array provided with sensors located exterior to the patients' body (within the radiation zone of the couch top receiver). The sensors are designed to measure the phase difference of the incoming electromagnetic signals coming from the implanted transmitter. The sensors are located following predefined geometry that enables the array to serve as a fixed reference co-ordinates system from which the implanted transmitter position is calculated. The sensors are connected to the within the receiver array which is then designed to supply a data processing unit (DPU) to process that information. The data processing unit determines the real time implant position within the body relative to the array by means of incorporated algorithms. The measured phase differences using the sensors are converted by geometric 3D position calculation methods such as trigonometry or neural networks.

As previously mentioned, the transmitter co-ordinates can be used as a positioning isocentre, the prostate, separate to the treatment isocentre. Since the target area is located at a predetermined position regarding the already located transmitter implant the target area is calculated by the data processing unit using the implant position information. Further, the target area position is compared with the radiotherapy treatment plan isocentre. The displacement of these positions provides the real time tracking data.

The positions of both isocentres are given relative to the array which serves as the fixed co-ordinate reference system for the calculations of displacement. If the target area isocentre and treatment isocentre are misaligned, such that they are not 3 dimensionally coincident with each other the data processing unit provides displacement information and instruction for target readjustment. Thus, the patient or treatment couch is moved in such a way that the two isocentres become substantially three dimensionally coincident and treatment can commence. The transmitter and array assess the electromagnetic signals 30 times per second therefore equating to real time tracking.

The receiver array contains a marked radiation zone. The patient must be placed in this area with the transmitter in the marked zone before treatment can commence (Figure 10). This area houses the electromagnetic sensors. This is the defined limited area for the distance that the implanted transmitter can be located relative to the target volume to ensure that they can be properly correlated. If the implanted transmitter is located or positioned beyond the limited marked area, the fluctuations of the target area may not be accurately recorded by the system and therefore produce inaccurate displacement or real time intrafraction motion values.

Figure 10 - RayPilot® system in the clinical setting– patient positioned on the couch top array in treatment position. The RayPilot® transmitter cable can be seen attached to the couch top

array and the patient is ready for treatment. The system requires minimal extra equipment in the clinical setting.

3.4 DATA PROCESSING UNIT/RAYPILOT® SOFTWARE.

The data processing unit is the processing system that receives the information from the sensors in the receiver couch top for further processing. The DPU determines the real time implant position within the target volume relative to the array by means of incorporated algorithms. The measured phase differences using the sensors are converted by a geometric 3D position calculation method of triangulation. Since the target volume is located at a predetermined position by the implanted transmitter, the target area position is calculated by the DPU using the implant position co-ordinate information. The target area position is then compared to the treatment isocentre position co-ordinates and thus, provides real time motion information.

The DPU includes a monitoring assembly that is arranged to provide the data from the DPU to a user interface, the visual display unit (VDU). The RayPilot® software then provides a graphical representation of real time intrafraction motion during treatment delivery that allows the clinical users to assess the motion and make amendments as appropriate within the treatment protocol (Figure 11). For instance, if the motion exceeds pre-determined limits then the treatment delivery can be halted mid beam and the patient repositioned if required.

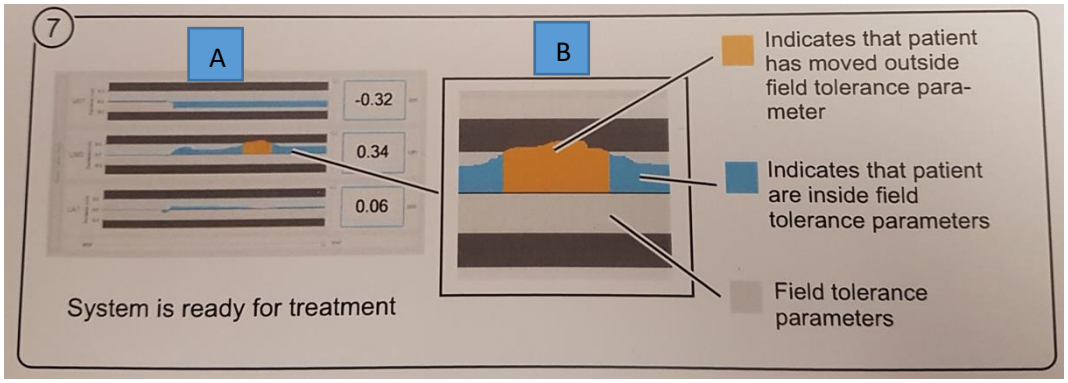


Figure 11 - RayPilot® software representation - illustration of the optics of the VDU. The graph representation of continuous real time motion tracking (A) is shown from treatment initiation until completion providing a visual display of motion in all vectors and (B) shows the motion indicator meanings. Yellow warning indicates patient motion out with the predetermined tolerance and blue tracking indicates that the patient motion is within the predetermined treatment tolerance.

The RayPilot® software then collates the data and provides tabulated results per patient showing the real time intrafraction motion measurements and then collates and records the collective data of all patients for analysis. All displacements are calculated to six decimal places, showing the length of time the prostate was displaced, the magnitude and direction of displacement and any treatment delivery interruptions. The resulting values were used for data analysis.

4 METHODOLOGY

4.1 CHAPTER SYNOPSIS.

The methodology chapter will provide a description of how the clinical audit was fulfilled. It discusses the clinical audit design and implementation strategies. Furthermore, it provides justification for the sample size and inclusion and exclusion criteria used in the study. Data collection and analysis will also be discussed in this chapter including the proposed quantitative analysis methods required.

As discussed previously, the RayPilot® technology is only approved for clinical use within the guidelines and protocols of the PRINToUT clinical trial. Consequently, the clinical audit and aim of this thesis relied upon patient recruitment and the patient pathway of the PRINToUT trial. For the aims of the clinical audit to be fulfilled, the patients involved had to comply with the inclusion criteria for the PRINToUT trial and had to undergo the described implantation process, planning process and treatment schedule prior to the collection of the required data for the clinical audit to begin.

As such, the following chapter is divided in to two main component sections, with further subsections as follows:

The first section of the chapter provides general background on the in relation to the larger PRINToUT (Using breath analysis to PRedIct Normal TissUe and Tumour Response During Prostate Cancer SBRT) research trial from which the cohort used in this study was derived. The inclusion of the PRINToUT section is for information purposes only and to provide and understanding and fundamental knowledge of the processes required for the patient within the clinical setting prior to commencing treatment. The full protocol is included as Appendix 1. The inclusion of this section provides inclusion and exclusion criteria, implantation processes and protocols and planning guidelines that all patients using the RayPilot® real time motion management system must comply with prior to treatment delivery. It also includes the follow up schedule and methods of toxicity monitoring used in both the larger research trial and the clinical audit that followed.

It is imperative to note that the PRINToUT trial and the clinical audit are two separate entities, however as the clinical audit relied upon the recruitment of patients to the PRINToUT trial to provide the patient cohort for the clinical audit, it is essential to contextualise the clinical audit to the PRINToUT research project. The clinical audit

used collated data for the patient cohort and was conducted upon completion of treatment within the wider PRINToUT research study.

The second component section will focus on the clinical audit for the thesis. It is structured as follows; methodological theory, clinical audit design and implementation, methods, data analysis and limitations and the process of assessing the study aim, The clinical audit aim was to assess and evaluate the the efficiency of the RayPilot® real time motion management system, the effect on dosimetric margins and treatment delivery in hypofractionated prostate radiotherapy and to assess whether this could lead to a further hypofractionated regime and reduction in fractionation.

For clarification of involvement, the lead GU radiographer (LGR) is the author of this clinical audit and will be referred to as LGR within the chapter.

4.2 THE PRINToUT TRIAL (USING BREATH ANALYSIS TO PREDICT NORMAL TISSUE AND TUMOUR RESPONSE DURING PROSTATE CANCER SBRT) PROTOCOL OVERVIEW.

The PRINToUT trial is concerned with how normal tissue reacts to treatment and how this is an important indicator for treatment related toxicity and quality of life. However, to improve local control and eradication of tumours we need to consider and understand the complex individual tumour biology. Tumour heterogeneity is likely to be greater than normal tissue due to the mutational drive that tumours possess. The effects of treatment will have dynamic effects on the tumour biology and we need to be able to measure these effects in real-time. A method of doing so is the use of Gas Chromatography, Ion Mobility Spectroscopy (GC-IMS) breath analysis (Riccio et al., 2022). Detection of volatile organic compounds (VOCs) released into the breath relating to radiotherapy normal tissue and tumour damage using GC-IMS breath analysis. Data suggests that the pattern of breath analysis VOCs changes over time, between patients with the same tumour type and between patients with different tumours. Individual prostate cancer patient heterogeneity in normal tissue and tumour response to radiotherapy can be detected via volatile alkane release during high dose per fraction stereotactic body radiotherapy (Waltman et al., 2020). The data can then be used to adapt the dose or fractionation schedule during a course of prostate SBRT to optimise outcome. In turn, this can be used to adapt the radiotherapy delivery to the patient's own response to treatment. Personalisation of the radiotherapy dose

and schedule would maximise the chance of cure and minimise the long-term post treatment toxicity, affecting quality of life (Eggener et al., 2020).

4.2.1 Methods

It is imperative to note that the methods of patient identification, inclusion and exclusion criteria and the patient pathway is the same for both the PRINToUT trial and the clinical audit undertaken for this study.

Eligible patients were identified using the TRAK electronic patient management system. TRAK contains all patient indexing episodes and all medical records, imaging requests and results, diagnostic and pathology results and all correspondence in relation to each individual patient and each clinical episode they have had within the NHS (National Health Service) trust. This is accessible by the uro-oncology consultants and the LGR in their role as genitourinary advanced specialist radiographer. Patients thought to be potentially suitable for the study were identified by the consultant clinical oncologist through the weekly multidisciplinary team meeting (MDM) or within the weekly GU Oncology clinics when seen as a new patient. The consultant clinical oncologist named in their care explained all the treatment options available to the patient and discussed potential side effects. If they concluded that the patient was eligible for the study, they explained the trial to them following all regulations in accordance with informed consent and clarity of information. The participant was made aware that any participation in the research study was voluntary and should be based on a clear understanding of what is involved in the study. The participants must be given adequate oral and written information. The oral information explained to the participant must cover all the elements specified in the Participant Information Sheet (PIS) (Appendix 2). The participant was given the approved and implemented research trial PIS, and in accordance with good clinical practice was advised to take the information home with them to refer to when making the decision whether to enter the trial or to refuse. They were instructed to take at least 24-48 hours to do so. After this time, they were contacted by the research or LGR to answer any questions or concerns they have relating to the information they have been given and the processes involved in their decision. If the patient wished to enter the trial, they were advised to return to have a further consultation with the consultant clinical oncologist and a radiographer from the trial team. At this point, they were required to complete the trial consent form and the radiotherapy consent form in the presence of the consultant clinical oncologist. The participant was also informed at this point that if they so wish they may withdraw from the study at any time by removing consent or

be withdrawn by the investigator if they are deemed medically unfit to continue. Any data already obtained would be held within the study unless explicitly expressed by the participant not to do so. An inclusion eligibility check was also conducted at this point. Inclusion and exclusion criteria are shown below (Table 3):

Table 3 – Inclusion and exclusion criteria for both the PRINToUT trial and the clinical audit for this thesis.

INCLUSION CRITERIA	EXCLUSION CRITERIA
Low risk prostate cancer T1-2, PSA < 10ng/ml (nanogram/millilitre), Gleason score (GS) of 3+3=6	T3/T4 disease
Intermediate risk prostate cancer with 1 or more of T1-T2, PSA10-20ng/ml, Gleason score ≤7 (3 +4 only)	PSA >20ng/ml
World Health Organisation (WHO) performance status 0-2	Gleason grade 8-10
Prostate volume ≤90cc (cubic centilitre)	Prostate volume >90cc
International Prostate Symptom Score (IPSS) Score ≤20	IPSS score >20
Q-max>10cc/sec	Q-max <10cc per second
Urinary residual <250mls total	Urinary residual >250mls
No prior transurethral resection of prostate (TURP)	Previous TURP
Medically fit for radical radiotherapy	Medically unfit for treatment
No contradiction to receiving radiotherapy such as inflammatory bowel disease	Unsuitable for radical radiotherapy due to inflammatory bowel disease
No previous pelvic radiotherapy	Previous pelvic radiotherapy
Able to give informed consent	Unable to give informed consent
Aged between 18-80 years of age	

4.2.2 Justification for inclusion/exclusion criteria

Due to the planning techniques and escalated dose per fraction, only tumours confined to the prostate gland were eligible for this trial. Therefore, only low and intermediate risk prostate cancer patients were considered for this study.

Low risk prostate cancers are classified as:

- a T stage of T1 to T2a
- a Gleason score no higher than 6

- a PSA level less than 10 ng/ml

Intermediate risk prostate cancers are classified as:

- a T stage of T2b
- a Gleason score of 7
- a PSA level between 10 and 20 ng/ml

As stated in the inclusion criteria, low and intermediate risk cancers are the more favorable curative cancer classifications and progression of the disease is slower. Therefore, at the time of staging the cancer is described as being organ confined. Clinically this means that there is less probability of extra capsular spread and micro metastases at time of diagnosis. In terms of the research study criteria, this is important due to the reduced planning target margins used in prostate SBRT techniques. It was clearly defined in the planning process of this research study that SBRT is to the prostate gland only without inclusion of seminal vesicles or surrounding lymphatic tissue. Therefore, only including low and intermediate risk prostate cancer patients should ensure that the cancer remains in situ within the prostate gland, allowing for localised treatment to the gland only.

High-risk cancers are classed as aggressive or advanced cancers and are classified as:

- a T stage of T2c or above
- a Gleason score between 8 and 10
- a PSA level higher than 20 ng/ml.

Normally, this classification has a higher probability and possibility of extra capsular and micro metastatic spread to adjacent structures and tissues. Therefore, these groups of prostate patients were excluded from the study. Due to the reduced target margins used in prostate SBRT, there would be great uncertainty regarding whether all of the disease is covered in the target volume, including any microscopic spread. Also, due to the RayPilot® tracking device being situated in the prostate, there is no way of monitoring intrafraction motion of any other structures that may need to be included in the target volume; for example, the seminal vesicles or lymphatics.

Prostate volume is variable depending on age and individual patients. The average ‘healthy’ prostate is between 25 – 40cc. In patients with prostate cancer, the prostate

volume can become enlarged due to disease extent. Patients with previous benign conditions, for example benign prostatic hyperplasia, can also exhibit larger prostates. Prostatic enlargement can affect a large percentage of the male population over the age of 50. In terms of prostate SABR, the volume of the prostate can prove problematic in planning adequate coverage of the target volume whilst reducing the concomitant dose to the surrounding healthy tissues and organs at risk. Subsequently it was agreed to include a maximum prostate volume within the inclusion criteria. This was capped at 90cc. The rationale for 90cc being that the participants did not have adjuvant hormone therapy to shrink the prostate so therefore if the prostate volume exceeded 90cc, the irradiated volume would increase resulting in a larger area of irradiation and greater risk of long term toxicity for the participants. There is no minimum prostate volume in the inclusion or exclusion criteria in the study. It is noted that due to the timescales for surgical interventions required in this trial, that patients are not given neo-adjuvant hormone therapy as they would be in standard radiotherapy to reduce the prostate volume prior to treatment commencing. This process would take a minimum of three months; it was deemed that this would not be feasible in the planning of the study and the timing of the patient's surgical interventions.

Patients who have a score of less than 20 using the International Prostate Symptom Score (IPSS) (Appendix 3), a maximum urinary flow rate (Q Max) of greater than 10cc per second and a urinary residual volume of less that 250ml were all eligible for this study. The justification for this is relating to the probability and possibility of urinary side effects following SBRT treatment. Acute and chronic urinary side effects are well documented, and previously discussed in this thesis, following prostate radiotherapy, in both SBRT and standard regimes. By ensuring that eligible patients have unremarkable genito-urinary symptoms or issues before they embark on treatment, the possibility of long-term urinary complications can be avoided or at least, reduced. Although an IPSS questionnaire is subjective as it is completed by the patient, if it is routinely completed at regular intervals pre and post treatment it can be a useful and reliable tool in grading patient's urinary symptoms. A flow test was carried out at the initial consultation by a clinical nurse specialist or the LGR. The patient performed the flow test and the recorded print out of the results was filed in the patients' medical notes. The flow test indicates the urinary flow rate and is used as the gold standard for eligibility. Following the flow test, the patient receives a bladder scan. Again, this was carried out by the clinical nurse specialist or the LGR. The ultrasound bladder scan was taken immediately following the patient voiding their bladder for the flow

test. This provided a record of the residual bladder volume, which for this study must be less than 250ml.

Patients with prior urinary symptoms were excluded from this study. Patients that record a Q Max of less than 10cc per second, score greater than 20 on the IPSS questionnaire or have a residual of greater than 250ml are therefore excluded. Patients already exhibiting signs of urinary obstruction or poor flow can have an exacerbation of symptoms, either acute or chronic following prostate radiotherapy. Similarly, patients with difficulty in fully voiding their bladder or showing early signs of retentive symptoms are also at risk of exacerbation of issues following prostate radiotherapy and were excluded from the study. All in accordance with the ethical stance that patients enrolling in a study should not be at greater risk of side effects than the standard conventional treatment that can be offered.

Patients that have had previous surgical interventions e.g. a trans urethral resection (TURP) of the prostate are also excluded from the trial. Previous surgical intervention is an indicator of prior urinary issues and therefore, as previously discussed above, dose escalated radiotherapy may not be in their best interest due to the side effects they may experience. In addition, previous prostate surgery can become problematic for placement of the RayPilot® device due to reduction in prostate tissue and scar tissue or damage from the previous surgery and surgical methods.

Previous pelvic radiotherapy was also included as an exclusion for eligibility as this would indicate that the patient has had a previous pelvic malignancy that could lead to long-term side effects. This could be problematic in SBRT planning, depending on the location of the previous treatment fields or technique, which could require extra dose constraints for surrounding structures. If there was the probability of overlap in the treatment fields, this can lead to severe long-term issues. Radiotherapy can also cumulate in long-term damage to tissues within the previous treatment field which would lead to scarring, tissue necrosis etc. This could make the long-term side effects problematic if we were to re-irradiate the pelvis. As such, patients were only eligible for the trial if they have never had previous pelvic radiotherapy.

In the same respect, patients that have increased co-morbidities for pelvic radiotherapy were also excluded from the trial, for example, ulcerative colitis. Due to the anatomical position of the prostate, the target volume includes as minimal a portion of the rectum as physically possible however; there will be a proportion of the

rectum included in the high dose treatment volume. As such, anyone with evidence of rectal colorectal issues will be at risk of long-term effects following prostate radiotherapy. Many of which can be severe and as per standard protocol, prostate radiotherapy may not be a treatment option for these patients. Dose escalated radiotherapy would definitely not be a treatment of choice due to the large daily doses. Subsequently patients with chronic bowel issues were excluded from this study.

Participants had to be medically fit, both physically and mentally for inclusion into the trial. For example, due to the requirements of the aftercare following implantation, patients had to be able to possess a level of mobility to be able to maintain hygiene in the perianal region. Mental fitness requires patients to have an understanding of the compliance required for study enrolment and, again, the aftercare required for the transmitter device, so patients with cognitive deficit may find this study confusing and frustrating. In this study participant compliance and understanding has to be assured due to the implantation of a medical device. The participant was expected to undertake the aftercare required until treatment is completed. It is also of note that all participants recruited into the trial must be able to comply with all regulations regarding informed consent and show capacity for all that entails.

The participant was then registered and given a unique patient trial identifier – this is numeric and follows the pattern of 001,002 etc. The lead investigators have access to participant details; therefore, participant details were not anonymised until the data was collected. This is due to patients having to be booked in for multi-disciplinary input prior to and including the radiotherapy treatment, to ensure that patients can be identified by all necessary medical professionals in accordance with local rules using their unique patient community health index (CHI) number.

4.2.3 The patient pathway.

The participant attended for a ‘one stop’ planning day for multidisciplinary input. This was done to reduce the number of hospital visits for the participant and to reduce impact on the clinical service. The patient had a magnetic resonance imaging scan at approximately 8am, then had three fiducial markers implanted, the RayPilot® device implanted and the radiotherapy planning computerised tomography scan at the end of the day. The advanced specialist radiographer (LGR) is involved in all processes.

The participant was instructed to use a micro enema prior to the MRI scan, which recreates the SBRT conditions for treatment. They also followed a standard bladder

filling protocol implemented in the department for pelvic radiotherapy (consume 300ml of water 30mins prior to scanning or SBRT treatments). As such, it was required be followed prior to the MRI scan also to ensure that the MRI recreates the conditions for planning and treatment. A standard multi-parametric prostate MRI was acquired. The participant was positioned supine, recreating the radiotherapy treatment position on a flat couch top, and the scope of the MRI was the prostate and pelvis. The MRI was then be used to aid in SBRT planning by being fused with the planning CT scan, providing enhanced localization and visualization of the prostate for the consultant clinical oncologist to outline the structures.

The participant was then admitted to the day bed suite for the implantation procedures. The participant administered a further phosphate enema at least 30 minutes prior to the implantation procedures. At this point, the LGR further explained the processes to the participant and gained informed consent for both procedures, the implantation of the fiducial markers and the implantation of the RayPilot® device. The participant then signed surgical consent in the presence of either the LGR or the radiologist. The participant was also given the approved aftercare information leaflet and information regarding their future treatment (Appendix 4).

Implantations were undertaken in sterile theatre conditions. Three fiducial markers were implanted using an ultrasound guided trans rectal approach by the LGR. The participant was positioned on their side and local anesthetic of lidocaine 1% was required to be injected to the prostate. The ultrasound probe was in situ in the rectum and the prostate localised. The fiducial markers were inserted using three 18 gauge pre-loaded 20cm needles. The fiducial markers are contained in wax at the tip of the needles, each individual needle housing one fiducial marker each. The fiducial markers are 3mm by 0.9mm in diameter and are specially knurled to inhibit migration. Using ultrasound guidance, the needles were progressed through the prostate to the desired positions and the trochanter within the needles was advanced to then ‘push out’ the fiducial marker at that position. They were placed in the apex, the base and the lateral aspect of the gland. Normally the triangulation pattern of the fiducial markers would span both sides of the prostate, i.e. two in one lobe and one in the other. However, to allow for placement of the RayPilot® device, study patients had all three fiducial markers placed in the same lobe i.e. all three on one side but still in the triangulated pattern of base, apex and lateral position. The procedure is relatively time effective, as most cases take a maximum of twenty minutes from start to completion. The procedure is well tolerated and the risks are comparable to that of a

trans rectal biopsy (Touzani et al., 2022). The participant may experience blood traces in urine and stools for 24 hours, the incidence of sepsis or infection is stated at less than 1%. However, patients are covered by prophylactic antibiotics of cyprofloxin; three doses post procedure.

The participant was then required to be repositioned as the RayPilot® device was implanted using a transperineal approach. The trial radiologist or the LGR carried out this procedure. The participant was supine in the extended lithotomy position. The ultrasound probe was advanced into the rectum using the ultrasound stepper. Further local anesthetic of lidocaine 1% was administered to the skin in the peritoneum and the deeper tissues. A guide needle was then placed under ultrasound guidance to visualize the desired position for the RayPilot® device within the prostate. Ideally, the transmitter is placed in the middle of the opposite lobe to the fiducial markers at a 30° angle; obviously, this is dependent on prostate volume and location of disease, which can alter the positioning. A hollow trochanter then follows this track. Once the desired position was reached, the inner part of the trochanter was removed and the RayPilot® device was advanced through the trochanter into position. Once the position was verified and confirmed, the outer coating of the trochanter was removed leaving the RayPilot® device in situ. The RayPilot® device consists of the transmitter tip, which houses the unique patient identifier chip, which is 17mm by 3mm in diameter and is surrounded inferiorly by plastic barbs that are designed to inhibit migration. The transmitter is attached to a cable which is the only thing that protrudes from the patient. The cable is 1.6mm in diameter and 383mm in length. Correct positioning and secure positioning of the device is imperative. Once this was verified, the patient was be kept for observation to ensure that they can urinate without complication then they could undertake the radiotherapy planning process.

4.2.4 Radiotherapy planning.

The participant was then transferred to the radiotherapy department for the radiotherapy planning CT scan. The participant carried out the previously described bladder filling protocol 30 minutes prior to scanning. They were positioned supine, using indexed foot stocks, an indexed knee rest and a head scoop. The scan was acquired using the field of view from L3/4 intervertebral space to 2cm below the ischial

tuberosities using 2.5mm slices. The CT radiographers then downloaded an isocentre following departmental protocols. At this point, the participant received treatment-positioning tattoos at the isocentre (two lateral and one anterior set up tattoo). The participant was not then required to attend the department again until commencement of treatment.

The MRI was fused with the radiotherapy CT planning scan using the Eclipse treatment planning system (Varian Medical Systems Inc.) with rigid and non-rigid mapping of the two scans. The consultant clinical oncologist then created the patient's treatment plan by outlining the proposed target volume. As described in the previous introduction chapter, planning target volumes are outlined by the consultant clinical oncologist. As the whole prostate gland is the target volume regardless of focal or multi-focal disease and location, there is no requirement for a GTV to be delineated. The clinical target volume was created by outlining the prostate gland; in the low risk patient cohort, this was the prostate only, in the intermediate risk patient cohort this was the prostate gland and 1cm of proximal seminal vesicles. The CTV was then expanded to create the planning target volume. The CTV to PTV margin is defined as the CTV plus 5mm except posteriorly where the prostate abuts the rectum, where a 3mm margin will be applied. Clinically this equates to PTV=CTV + 5mm anteriorly/superiorly/laterally and inferiorly and 3mm posteriorly on the gland. The consultant clinical oncologist also outlined the organs at risk for dose tolerance calculation purposes.

The treatment plan was then created in accordance with a prescription of 3625cGy in 5 fractions over 7 days. The prescription to the dose to the PTV is V36.25 ≥ 95%. This means that 95% of the planning target volume must receive 3625cGy. The prescriptive dose to the CTV is V40≥95%. Consideration must also be given to the dose constraints of the organs at risk and these are described in Table 4.

Table 4 - Prostate SBRT dose constraints. Table illustrates each organ at risk and the dose constraints that are applied within the inverse planning system to predict and minimise toxicity to the organs at risk and the surrounding structures.

OAR	Dose Constraint
Rectum	V18.1Gy <50% (i.e. less than 50% of rectum <18.1Gy)

	V29Gy <20% (i.e. less than 20% of rectum receiving 29Gy) V36Gy <1cc
Bladder	V18.1Gy <40% V37Gy < 10cc (optimal V37Gy <5cc)
Prostatic urethra	V42Gy <50% (optimal not mandatory)
Femoral head	V14.5Gy < 5%
Penile bulb	V29.5Gy < 50%
Testes	Blocking structure
Bowel	V18.1Gy <5cc V30Gy <1cc

Once the treatment plan was created and approved by the radiotherapy physics department and the consultant clinical oncologist, it is then assessed and approved at the GU peer review session. Once approved the patient attended for treatment within the trial specifications.

This section has provided a fundamental overview of the PRINToUT research trial from which the patient cohort of the clinical audit was obtained. As discussed previously the patients included in the clinical audit of the efficiency of the RayPilot® real time motion management system had to conform to the eligibility criteria and undergo the processes outlined above prior to having ultrahypofractionated prostate radiotherapy that is required for this clinical audit. This section is included for information purposes only and the following sections will describe the clinical audit to address the aim of this clinical audit - to assess and evaluate the the efficiency of the RayPilot® real time motion management system and the effect on dosimetric margins and treatment delivery in hypofractionated prostate radiotherapy and to assess whether this could lead to a further dose escalated regime and reduction in treatment fractionation.

4.3 CLINCAL AUDIT AND THESIS AIMS

4.3.1 Methodology theory.

The clinical audit allows for comparison of current practice or standards against that of proposed changes to treatment delivery to ensure that patient outcomes are not negatively affected. The National Institute for Health and Clinical Excellence (2016) describes clinical audit as **"a quality improvement process that seeks to improve patient care and outcomes through a systematic review against explicit criteria and the implementation of change. Aspects of the structure, processes and outcomes of care are selected and systematically evaluated against explicit criteria. Where indicated, changes are implemented at an individual, team or service level and further monitoring is used to confirm improvement to healthcare delivery."**

Clinical audit principles allows for clinical audits to be undertaken as a clinical improvement process to improve the quality of care patients receive using a systematic approach and evidenced based practice. This ensures that all patients receive the highest quality care and service during their treatment journey including the implementation of new service delivery techniques. The key stages and principles in conducting a clinical audit are preparing for the audit, selecting criteria, measuring performance, making improvements and sustaining the improvement with the overall aim of a clinical audit being to ensure that existing knowledge is being put into practice clinically, as opposed to research, which seeks to gain new knowledge (Malicki et al., 2023). Clinical audit can be referred to as a cycle, the topic is defined, the criteria and standards are defined, data is collected, data is analysed, findings are shared and changes implemented, re-audit and the audit loop is closed (Limb et al., 2017). Foundation audit principles allow for a systematic approach to the undertaking of a clinical audit. These include primarily, a clear definition of the aim of the clinical audit with a valid criteria which leads to an improvement in care that is evidence based, related to patient care with measurable outcomes. The clinical audit methodology should align with the aims of the clinical audit and include sampling methods, data collection methods, data analysis methods and a structured literature review to compare the development or improvement with the current best evidence based practice. Based on the outcomes of the clinical audit, information should be disseminated to all major stakeholders and multi-disciplinary teams who would have direct involvement in the implemented change in the first instance. This would also include management if there were service delivery and resource implications for the implementation of change.

Clinical audit is a fundamental component of continual service delivery and improvement and as such, the clinical audit must provide a clear aim, measurement standard and robust conclusions. Clinical audits, by design measure a clinical outcome or process against current standards of care and evidence based practice to assess the efficiency and efficacy of proposed improvements or changes in the current clinical standard of care. In relation to this thesis, the clinical audit consisted of two clinical components: the efficiency of the RayPilot® real time motion management system for use in prostate SBRT treatment delivery and the potential to use this technology to further increase dose and reduce treatment fractionation. This was then audited against the current clinical standard of 6000cGy in 20 treatment fractions.

Clinical audits are essential for maintaining and improving the quality of health care services, ensuring patient safety and complying with regulatory standards and guidelines. This requires a robust systematic methodology that complies with local clinical governance guidance and regulations. The seven pillars of clinical governance provides a robust and comprehensive evaluation tool for clinical effectiveness evaluation and service improvement. The seven pillars are risk management, education and training, patient and public involvement, staff management, clinical effectiveness and information (MacFarlane, 2019). Alignment with these seven pillars ensures robust clinical effectiveness principles that allow for the monitoring and improvement of outcomes for patients and service users.

The initial construction of a clear clinical audit aim allows for further development of the audit process in alignment with the seven pillars of clinical governance. For successful clinical audit, a clear audit aim must be established form the outset. The aim of the clinical audit in this thesis was to assess and evaluate the the efficiency of the RayPilot® real time motion management system and the effect on dosimetric margins and treatment delivery in hypofractionated prostate radiotherapy and to evaluate whether this could lead to a further dose escalated regime and a reduction in treatment fractionation resulting in non-inferior patient outcomes, including disease control and toxicity. To address this aim, the study requires a direct comparison of this emerging technology and treatment option to that of the standard clinical treatment option of standardized prostate radiotherapy. Therefore, a clinical audit was best placed to address the aim. This in turn will therefore evaluate over all clinical effectiveness in relation to clinical audit principles. The clinical audit was a retrospective evaluation of the efficiency of the RayPilot® motion management system

in a cohort of seven patients undergoing prostate SBRT as part of the wider PRINToUT study.

As mentioned, the patient data collected for this clinical audit relied upon enrolment into the PRINToUT research trial. Although the patient cohort for this clinical audit was acquired from the wider research study, the clinical audit was a stand-alone project. The PRINToUT trial is a research trial generating new knowledge, the clinical audit conducted was concerned with the evaluation of using this emerging technology in relation to clinical effectiveness, service improvement and delivery.

This resulted in the patient cohort of the clinical audit being a non-random convenience sample, including all patients participating in the larger research trial. It was based upon the availability and accessibility of patients rather than a random selection. The use of more rigorous sampling methodology such as stratified or random selection would not be possible in this circumstance due to the small patient numbers (in this instance n=7). Further justification of the use of convenience sampling is that all participants were recruited from the same treatment group and convenience sampling is often used in preliminary studies to gain insight or identify trends, this is pertinent in this clinical audit as RayPilot® is an emerging technology and a recently implemented treatment modality. The sample size and its limitations, such as representation of the population and generalisbility, are acknowledged in the discussion chapter.

The sample size in this clinical audit was extremely small in comparison to the overall population of prostate cancer patients treated in the host department and therefore the data analysis method must be given consideration. The two methods of statistical analysis are descriptive and inferential. Inferential statistics draw conclusions based on the sample to observe differences or relationships in the sample, which is likely to represent true differences, or relationships within the population under study. They are typically used when the in larger sample sizes representing a larger proportion of the population to allow for meaningful generalisation to the wider population under investigation (Williams and Bornmann, 2016). However, inferential statistics are not commonly used in clinical audits as the data collected in a clinical audit is concerned with measuring practice against a standard. Descriptive statistics are used to summarise the main features of a data set to understand tendencies, variables and the distribution of the data. Descriptive statistics are also more commonly used in smaller sample sizes where generalisation cannot be statistically proven. They are also commonly used in exploratory research and studies to explore data to gain

insight and identify trends. Therefore, the use of descriptive statistics was justified in this clinical audit.

The patient data was collect from the RayPilot® motion management system software. This was done retrospectively and analysed by the author independently. This is further described in the subsequent section.

As this clinical audit was using data collected from the RayPilot® real time motion management database, risk management considerations were deemed as low. The clinical audit did not alter the clinical process or protocol in the delivery of prostate SBRT for the patient cohort. As the data was collected retrospectively, no patient parameters were altered during active treatment delivery reducing the likelihood of human error or incident. The data collected and analysed was done so by the author only and was done so in compliance with local data protection rules, NHS Scotland clinical governance guidance, adhered to Cauldicott guidelines and was only available to the author using a password protected electronic device. Therefore, the risk of data protection incidents was also deemed low. Patients were not exposed to unjustified imaging procedures or unnecessary exposure to ionising radiation during the clinical audit as all data was acquired from the RayPilot® recorded data system therefore there were no implications in terms of adherence to IR(ME)R guidelines. There were no additional requirements in terms of staff training, resources required for data collection, or analysis as this was carried out by the author only. As such, the overall risk assessment determined that the risk of incident or harm was low and was mitigated as far as reasonably practicable.

Education and training was provided throughout the audit process. Initially to the team who were delivering the RayPilot® prostate SBRT treatments. This included the purpose, aim and methodology of the audit. Presentations were also given to the quality improvement management team, senior management, the radiotherapy management group, and the wider staff groups within the department including radiographers, nursing, physics and technology staff. This allowed for all members of the radiotherapy pathway to raise concerns or suggestions in relation to the implementation and evaluation of clinical efficiency of the RayPilot® system. By including all major stakeholders this increases rigour and robustness of the clinical audit and ensures that all aspects of the system are adequately considered when evaluating overall clinical effectiveness.

Patient and public involvement was limited within this clinical audit. The patient cohort has already consented to participation in the wider research trial and as this audit did

not involve any amendments to the treatment plan or delivery, further consent was not required; therefore, patients were not informed of the clinical audit. This aligns with departmental policy given that the data collected and analysed as part of the audit was available to the author and lead radiographer within the remit of their clinical role.

Staff management requirements were mitigated, as this was a clinical audit as all aspects of the clinical trial were only carried out and implemented by the author. The clinical audit did not require an audit team therefore; it was solely dependent on the author and individual management. The most challenging of which was that of time management as the author was not provided with protected audit time and this had to carried out in the individuals own time with consideration to their clinical role and responsibilities.

Clinical effectiveness within clinical governance is a vast term. In assessing clinical effectiveness of an implemented change, implications to the whole service need to be considered. Although the aim of the clinical audit was to assess the clinical effectiveness of the RayPilot® technology and the feasibility of its potential use to reduce fractionation and increase dose for prostate SBRT patients, this does not solely depend on the system doing what is expected of it. To ensure it is clinically effective in the clinical environment consideration must be given to a number of multi-faceted factors. For example, the cost to the service, both in terms of required equipment but also in staff resources. The treatment time required to deliver SBRT in this way, if this is increased then that will have a detrimental effect on patient output and the capacity on the linear accelerators. When implementing change in techniques or treatment delivery, staff training requirements also have to be assessed. All these elements are discussed in subsequent sections and chapters to align with the clinical audit aim and the conclusions drawn.

4.4 STUDY DESIGN

A clinical audit is appropriate as a methodology for the study aim because the clinical audit is a systematic process carried out in a healthcare environment to assess and improve the quality of patient care and outcomes. It involves reviewing current or emerging practices, comparing them to established standards or guidelines, enabling the development of standards, identifying areas for improvement, implementing

changes and monitoring the outcomes. Generally conducting a clinical audit requires the following methodology (Limb et al.,2017):

Defining the objective,

Establishing the audit criteria,

Planning the audit,

Collecting the data,

Analysis of the data,

Identification of gaps and opportunities for improvement or limitations,

Development of recommendations,

Implementation of the changes,

Monitoring and evaluation of the change,

Reporting and communicating findings and,

Follow up and future sustained implementation.

The following sections of this methodology chapter will discuss these points in further detail.

However, the defined objective of the clinical audit aim is to conduct a clinical audit to assess and evaluate the the efficiency of the RayPilot® real time motion management system and the effect on dosimetric margins and treatment delivery in hypofractionated prostate radiotherapy, and assess if this allows for a further hypofractionated regime and reduction of treatment fractionation. The patient cohort used to do this were patients undergoing radiotherapy for prostate cancer using a hypofractionated approach of 3625cGy in five fractions using the RayPilot® real time motion management system. It was achieved by analyzing intrafraction motion management data acquired from the RayPilot® real time motion management system for each patient. The collated qualitative data was then used in a planning target management formula to assess whether the current clinical planning target margins could be reduced allowing for a further escalation of dose and reduction in treatment fractionation. Using an inverse planning system, the original treatment plans were then recreated using the resultant planning target margins, dose and fractionation to assess whether this is clinically achievable and a clinically viable treatment technique for future consideration to the wider prostate cancer patient population.

Prostate cancer is the second largest patient cohort treated yearly in a local radiotherapy centre. As a large patient the required sample size for statistical analysis would result in a large research population, however, participants used in this study had to be eligible and entered into the PRINToUT study, therefore the sample used will be compliant with the PRINToUT research study protocols and eligibility. Therefore, due to the constraints of the clinical audit, data was collected using a convenience sample. All eligible patients meeting the inclusion criteria over the timescale of 24 months from the start date of the study were included. For confirmation, the sample size was reviewed by the statistics division and as this was an observational clinical audit there was no formal sample size calculation required. As per the PRINToUT clinical research trial, it was predicted that the participant numbers would be 1-2 per month. This was representative of the multidisciplinary approach required for successful implantation for example, fiducial marker insertion and RayPilot® device insertion in theatre conditions, complex radiotherapy planning requirements etc. Due to this, the resultant data was represented using descriptive statistics, as inferential statistics would be inappropriate for this size of patient cohort. The small cohort makes it difficult to interpret the small sample size mean results to that of the population mean. The small sample size also illustrates that this was a single centre clinical audit as it was the first clinical audit of the RayPilot® system use in hypofractionated stereotactic body radiotherapy within the UK.

Currently this dose and fractionation and the use of the RayPilot® real time motion management system is only authorized for clinical use in patients participating in the larger research PRINToUT project within the department. This links to the small sample size due to the single Centre approach, therefore the expectation is that of lower numbers of participants. As such, it is appropriate to include the following section of this chapter to provide an overview of the PRINToUT protocol for context. The full protocol is included as an appendix 1, however as the clinical audit required the patient cohort from this patient group it is essential that fundamental information regarding inclusion criteria and the planning process is understood to aid in the understanding of the implementation of this clinical audit and the importance and validity of its findings.

4.5 PLANNING THE AUDIT

The clinical audit aim of the thesis was to assess and evaluate the the efficiency of the RayPilot® real time motion management system and the effect on dosimetric margins and treatment delivery in hypofractionated prostate radiotherapy and to assess whether this could lead to a further hypofractionated regime and reduction in fractionation.

The subsequent sections of the chapter focus on the methodology of the clinical audit carried out to address the aim of the thesis.

As stated, the use of RayPilot® for research purposes had already been granted approval from the Radiotherapy Management Group (RTMG) within the host department and from The Academic and Clinical Central Office for Research and Development (ACCORD) in accordance with the previously mentioned PRINToUT study. Clinical audits are generally carried out in an individual practice for the purpose of Quality Improvement will not normally raise ethical issues or require formal ethics approval. As the data required for the clinical audit was retrospective and in relation to a treatment delivery modality in use in the clinical setting, additional approval for this sub-study within the scope of the original ethically approved PRINTOUT study was also sought from RTMG. An application for clinical audit approval was submitted to the Quality Improvement Team (QIT) (Appendix 5). Following this application, the clinical audit methodology and protocol was approved by the QIT within the cancer services department to ensure compliance with current clinical governance guidelines (Appendix 6).

4.6 COMMISSIONING OF THE RAYPILOT® REAL TIME MOTION MANAGEMENT SYSTEM AND ASSOCIATED DEPARTMENTAL DOCUMENTATION.

Prior to treatment approval, it was vital to ensure commissioning of the equipment and validation of the measurements of the system. To align with departmental guidelines all departmental protocols including departmental work instructions and imaging guidelines that confirm to the Ionising Radiation Medical Exposures Regulations (IRMER) (2017) had to be written by the lead radiographer and approved by departmental head of departments.

Commissioning of the RayPilot® system was conducted by Micropos and overseen by the LGR and head physicist. The Micropos specialist performed a number of software checks and ensured that the system was performing to the specified standards before approving it for clinical use. These included pre-programming the couch top receiver system co-ordinates and adjusting these if required, performing a robust quality assurance test and the use of pre-programmed treatment plans to ensure the system was working correctly within the specified clinical limits.

In accordance with trust and departmental policy, the LGR and lead physicist also conducted objective testing. However, to do so a test model was manufactured 'in-house'. Figure 12 shows the testing model that was created. This in house designed phantom allowed for the efficacy of the RayPilot® motion management system to be assessed in comparison to known physical movement. A phantom was designed to hold the RayPilot® transmitter and allow known movements in each of the x, y & z planes. It is recommended by the manufacturers Micropos that metal objects should not be placed within the treatment region whilst using RayPilot® as this can interfere with the electromagnetic signal. This was noted through commissioning and testing of the system. The phantom therefore had to fulfil this remit and was designed using Perspex with adjustable Perspex screws. This included a hollow cylinder that would allow the RayPilot® transmitter to be inserted inside and moved in each plane when required.

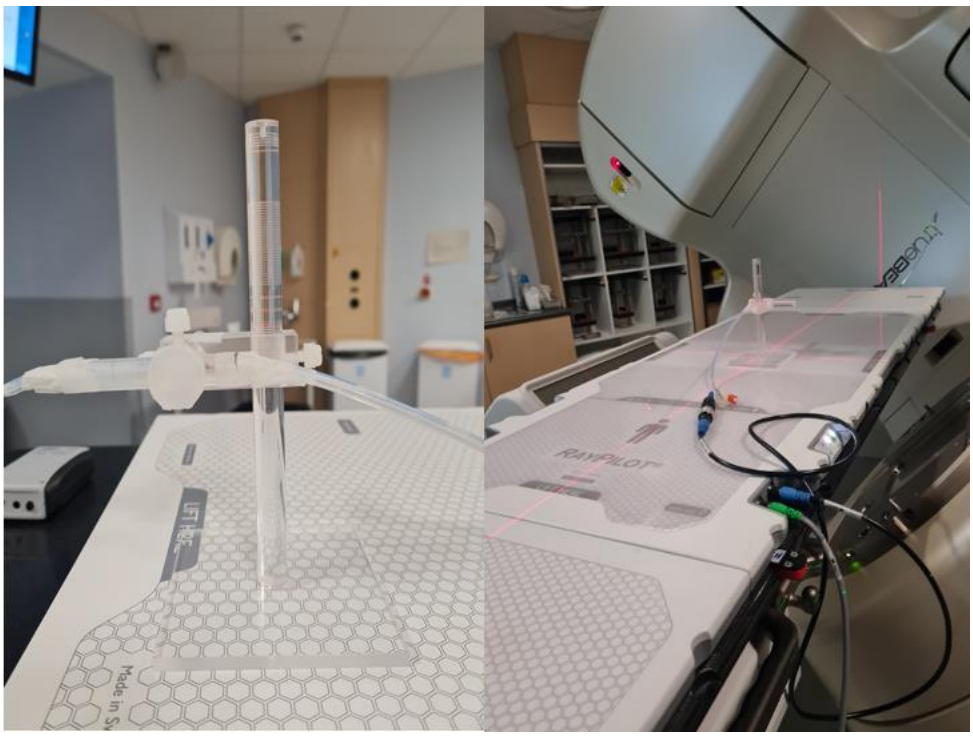


Figure 12 - Internal validity phantom used for commissioning the RayPilot® system. The phantom was moved at set intervals and the recorded RayPilot® data was assessed in relation to the physical recorded motion to ensure efficacy and validity of the results.

A CT image of the phantom (with catheter and transmitter inserted) was acquired using a Philips wide bore scanner. The catheter was taped to the cylinder to retain its position relative to the cylinder (as shown in Figure 12). The scan protocol used was consistent with the PRINToUT trial with 1mm slices. A test plan was created with appropriate set-up fields. The baseline position of the electromagnetic transmitter was recorded using the RayPilot® system readout, and a kV orthogonal pair and CBCT images were acquired.

The assessment of the efficiency of the RayPilot® real time motion management system was tested in two ways. The initial assessment was carried out using couchtop measurements and the RayPilot® system VDU only and then using the on board imaging modalities of the linear accelerator. The phantom was used for both methods.

Initially the phantom was positioned and imaged to allow alignment of the starting co-ordinates. The linear accelerator treatment couch top was then manually moved by known increasing amounts (1mm, 2mm, 3mm, 5mm and 1cm) in the lateral, longitudinal and vertical direction. The movement of the treatment couch top was

carried out using a physical measurement with a ruler, and then using the electronic readout on the linear accelerator. The graphical representation of motion on the RayPilot® system VDU was then analysed to ensure that the recorded displacement matched the physical properties of the manual change in position of the treatment couch top.

The position of the transmitter was altered by adjusting the phantom in x, y & z positions with the new positions verified using both ruler measurements and electronic values on the linear accelerator. After each movement, the displacement from the RayPilot® system was recorded. A kV orthogonal pair and CBCT image was also taken after each movement. These images were then analysed off-line by an entitled radiographer who registered the images and recorded the resultant displacement.

It was concluded that the RayPilot® software accurately verified and recorded that motion to the value of the physical displacement. It is worthy to note that the RayPilot® software records displacement values to six decimal places and, given that the graticule motion was carried out by eye, allowances were made for this. Both the LGR and lead physicists were satisfied that the RayPilot® system sufficiently and accurately recorded displacement values and that this was a true representation of recorded motion.

Departmental documentation had to be provided prior to implementation of the RayPilot® treatment technique. Clinical work instructions and protocols were devised by the LGR including the treatment process and radiographer training and competency entitlements (Appendices 7 & 8). Although the departmental documentation required was in alignment with the clinical implementation of a new treatment technique, (prostate SBRT in the PRINToUT research trial) it is also important in the context of the clinical audit to ensure that all data collected was done in accordance with the protocol and that all radiographers were following the same procedures to acquire the data.

These were done with consideration of local rules and external guidelines. This included the imaging protocol that was to be used for this patient group. Due to the increased imaging required for the clinical audit and initial information gathering within the PRINToUT study, it was imperative that this was done in accordance with current IRMER regulations. To comply with these guidelines, imaging protocols must ensure that operators comply with minimising unintended, excessive or incorrect medical exposures, justifying each exposure to ensure the benefits outweigh the risks and optimising diagnostic doses to keep them “as low as reasonably practicable” for their

intended use. Imaging protocols state the amount of images that would be classed as low as reasonably practicable for the intended use and are normally treatment site dependent. In this case, patients receive a pre and post treatment CBCT. The pre-treatment CBCT was used to assess the target volume position, OAR volumes and positions, and to verify the position of the RayPilot® transmitter device. The post treatment CBCT was used to assess intrafraction motion and intrafraction variations in bladder filling and rectal variation. An orthogonal kV imaging pair prior to each treatment arc (patients were treated with three treatment arcs) was required to record and verify the isocentre position using both the fiducial markers and the RayPilot® transmitter device. This equated to two CBCTs and six kV images. However, this is on the premise that the patient did not require re-positioning during the duration of the treatment. If the patient does require to be repositioned due to intrafraction motion, this then requires further imaging. As such, the imaging protocol has to acknowledge this to ensure compliance with current regulations. It was decided that the imaging protocol would allow for a total of 18 kV images, which would account for patient being repositioned up to three times per treatment arc and a further three CBCT acquisitions, again to allow for patient compliance e.g. if a patient has to be removed from the treatment room to increase bladder filling or to void bowel gas or matter.

Departmental work instructions are part of the service quality system and clinical governance framework. They outline the processes, structures and responsibilities that aim to standardise, enhance and monitor the standard of treatment provided to patients. The work instructions are a step-by-step systematic reference document that ensures that radiographers are able to carry out the treatment technique described and are aware of their role, responsibilities and scope of practice within the treatment process (Appendix 7). To ensure the accuracy and efficiency of the work instruction an ‘end to end’ test was carried out by a number of radiographers under the supervision of the LGR. The end-to-end test used a fictional test patient and the radiographers were asked to execute the treatment using the work instructions without any previous experience of the technique. Testing the work instructions in this manner ensures that the information and required steps are clear and concise and allows for amendment if required prior to clinical implementation.

In terms of planning a clinical audit, the documentation required for treatment delivery plays an important role in data collection. The adherence to departmental work instructions establishes uniformity in treatment delivery and therefore uniformity in the acquisition of data.

Further planning in terms of documentation required to execute the clinical audit was that of outcome measures. As described, the clinical audit included treatment outcomes and as such, the method of recording these had to be devised. Patient reported outcomes can be recorded in a number of ways, clinic appointments, interviews, questionnaires and universally used PROMS (patient reported outcome measures). It was decided that the EPIC-CP (Expanded Prostate Cancer Index Composite for Clinical Practice) used in the PRINToUT research trial would be used alongside a devised patient reported outcome questionnaire (Appendix 9). The questionnaire was designed to include urinary, gastrointestinal, erectile and QOL symptoms experienced by the patient cohort. Both questionnaires were then reviewed at all follow up appointments and assessed in accordance with the Radiation Therapy Oncology Group toxicity scoring guidelines.

4.7 TREATMENT.

Entitled radiographers carried out A RayPilot® quality control check prior to each treatment fraction. The couch top receiver was positioned on the Varian treatment couch and connected to the RayPilot® software for treatment recording and verification. Prior to the first fraction, the participant parameters must be set. The position of the transmitter and the position of the treatment isocentre must be entered into the RayPilot® software (Figure13). A treatment radiographer did this manually at the pre-treatment checks stage. Another radiographer then independently checks the entered values prior to day zero to reduce the likelihood of human error in transposing the values whilst entering the data into the system.

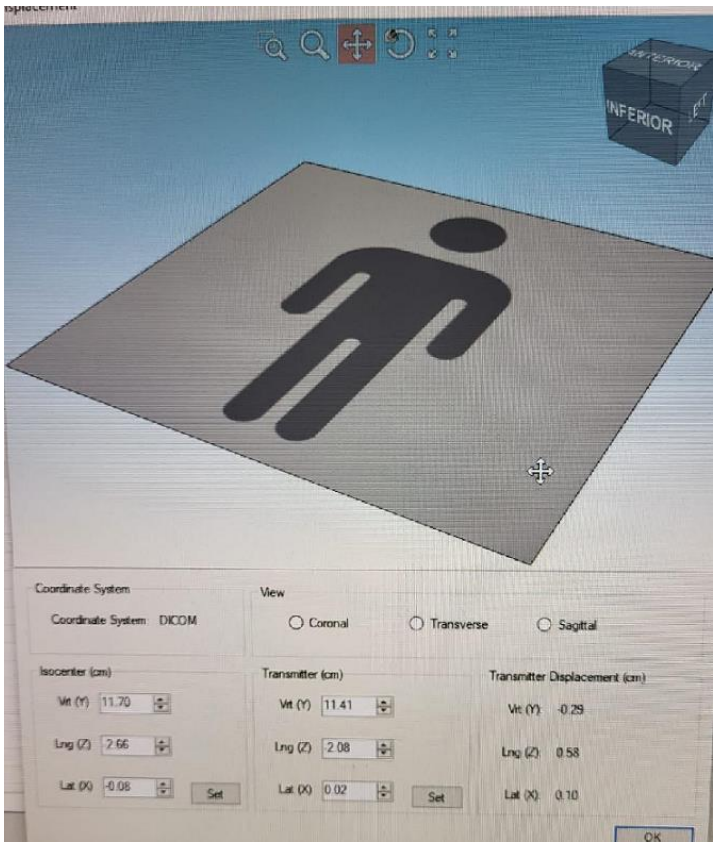


Figure 13 - The RayPilot® co-ordinates entry data showing the co-ordinates of the treatment isocentre (left hand column), the co-ordinates of the RayPilot® transmitter (middle column) and the displacement between the co-ordinates (right hand column). These values remain static throughout the treatment and are used for real time motion management verification.

Both sets of position co-ordinates were taken from the initial CT planning scan using the External Beam application. The co-ordinates are three dimensional (x, y, z to represent vertical, lateral and longitudinal position) and the RayPilot® software uses the displacement between the two co-ordinates to record the distance from the transmitter to the treatment isocentre. This is what the software uses to track motion. The displacement between the transmitter tip and the treatment isocentre should remain constant and can therefore be used to calculate and record intrafraction motion. At this point, the selected tolerance was entered into the RayPilot® software. In the case of this study, the tolerance will always be 2mm (Figure 14). The RayPilot® software calculates and tracks motion 30 times per second. If the motion exceeded the selected tolerance in any direction, the entitled radiographers were alerted when the graphical illustration of motion changing colour from blue to yellow.

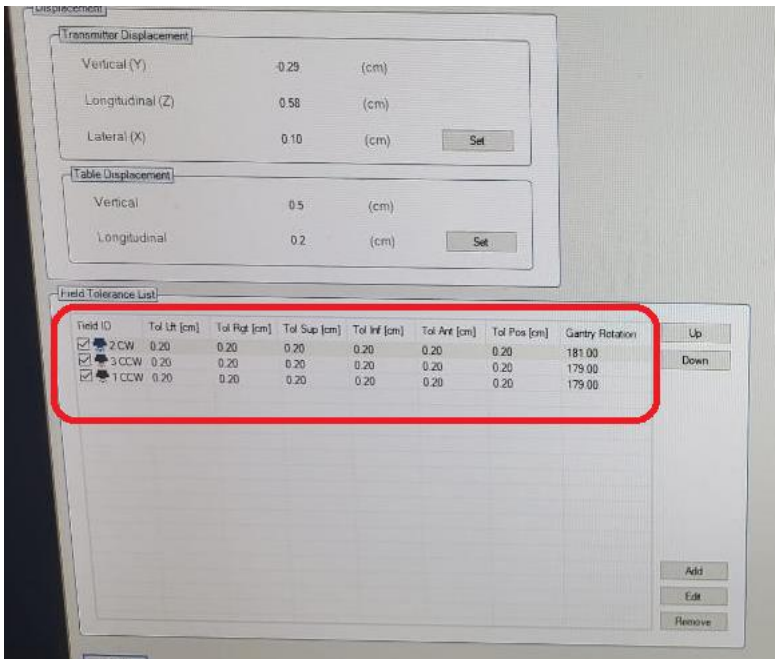


Figure 14 - the RayPilot® VDU data. The figure illustrates the tolerances that are set for all treatment fields (highlighted in red) which remains static throughout treatment at 0.2cm for all treatment arcs. This tolerance data remains static for all treatments unless manually altered.

The isocentre position was checked using the template attachment without the patient on the treatment couch. The resultant longitudinal and vertical parameters were recorded. The process was repeated with the patient on the couch top and the resultant longitudinal and vertical parameters were also recorded. This provided a record of couch sag, which must be taken into account for positioning. Couch sag occurs when there is a change in weight and positioning of the couch top. The patient once again had to adhere to the bladder filling protocol and rectal preparation using micro enemas approximately 30 minutes prior to treatment. The patient was positioned supine with indexed knee rest and foot stocks, replicating the position of the initial CT planning scan. The RayPilot® transmitter was attached to the RayPilot® receiver couch top using the connector cable.

The RayPilot® software was then ready to proceed. A minimum of three entitled treatment radiographers are required for treatment, one of whom takes overall responsibility for observing the results on the RayPilot® software. All treatments were carried out in accordance with departmental work instructions (Appendix 7). A pre-treatment orthogonal kV imaging pair was acquired and using the marker match tool on the Varian TrueBeam linac, the fiducial markers were matched to the current

position. A fourth marker was also overlaid with the tip of the transmitter as this is easily visualised on the kV imaging pair. This provides the resulting displacements and the shifts required to position the isocentre in all vectors. Once this had been carried out, a pre-treatment CBCT was acquired to assess bladder filling, rectal volume and PTV placement (Figure 15).

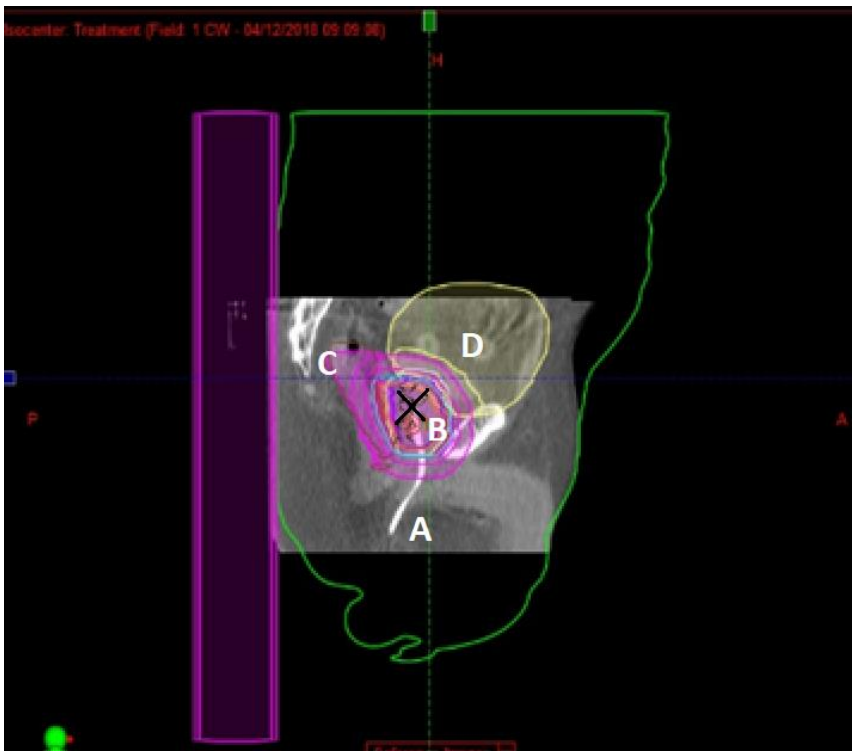


Figure 15 - Sagittal SBRT CBCT. A – The transmitter cable, B – the high dose volume isodose distribution, C – the rectum, D – the bladder. The black X depicts the tip of the transmitter co-ordinates used for localisation, verification and real time motion management. The bladder, rectal volume, fiducial marker position and transmitter placement is assessed and compared to the original treatment planning CT scan.

All imaging sequences were carried out in accordance with the departmental exposure packages. If the image verification was acceptable then the first treatment arc was delivered. The position of the RayPilot® transmitter and the couch top receiver provides a record of intrafraction motion and this was represented by a graphical illustration on the RayPilot® software (Figure 16).

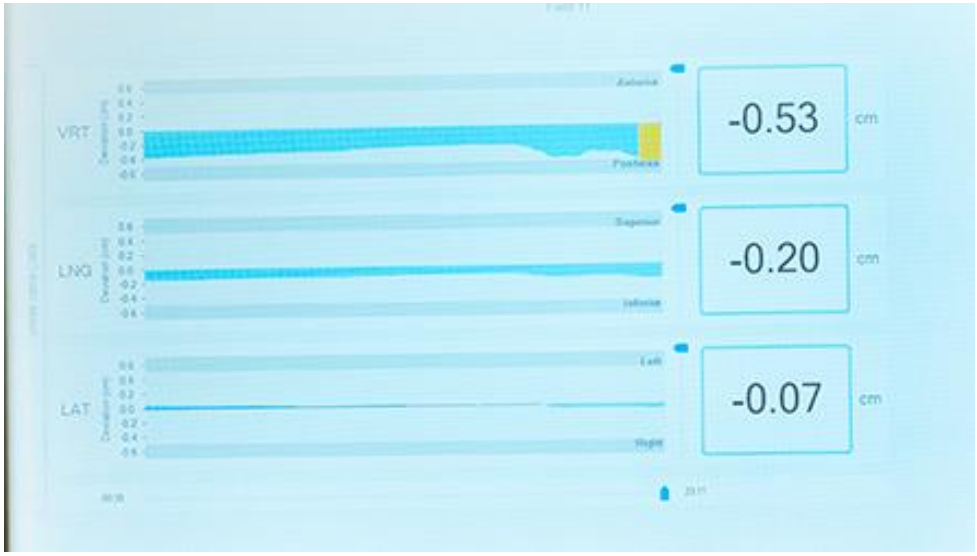


Figure 16 - RayPilot® VDU motion monitoring data. The VDU graphical representation of real time motion management in the vertical, longitudinal and lateral directions. Motion values within the clinically used tolerance (0.2cm) are indicated in blue and motion out with the stipulated tolerance is indicated in yellow allowing for patient repositioning if required.

If intrafraction motion was above a stipulated tolerance, in this case 2mm, then the radiation beam was manually halted until intrafraction motion settles. This step had to be done in a timely manner by the radiographers as, unfortunately at this juncture in time, the RayPilot® system is not interfaced with the Varian TrueBeam linac. The patient was observed for a minimum period of 90 seconds. If they returned to the initial treatment position, then the treatment beam was resumed. If not, they were repositioned following reimaging using an orthogonal kV imaging pair. If the patient did not return to the determined treatment position, repeat kV imaging was acquired to reposition the isocentre. This then became the new treatment position and treatment can commence. Most plans required three treatment arcs, so prior to each arc commencing a further set of kV images are acquired to check the positioning of the isocentre.

On the final treatment fraction, the device was removed in sterile conditions by the LGR. It was a non-invasive procedure. The device was removed by positioning the participant on their side and applying approximately 5 kilograms of force on the RayPilot® transmitter in a downwards motion. Pressure was then applied to the extraction site, and if the participant showed no signs of complication, they could leave. Complications would include profuse bleeding from the site, pain, or evidence of infection on the transmitter device following removal. If complications were to occur

then patients would be sent to the cancer assessment unit for further investigation or intravenous antibiotic infusion if required. Fortunately, there were no instances of complication within the patient cohort.

Participants were followed up routinely after completion of SBRT treatment in accordance with departmental protocol. The patient was reviewed at the follow up clinic in weeks 6 and 12, then at months 6, 12, 18 and 24 post treatment. At each review, they had a recent PSA blood test to assess response. They were required to complete an acute RTOG toxicity assessment (Appendix 10). RTOG assessment scoring is a universal globally used toxicity scoring system. The RTOG toxicity grading system is a systematic toxicity grading system that is site specific and ensures a standardised approach to toxicity reporting by providing comprehensive grading criteria for commonly experienced side effects following treatment. The use of consistent language, terminology and toxicity descriptions aids in the standardisation of outcome reporting in all treatment modalities throughout the patient treatment pathway. As such, it is routinely used in patient follow up consultations by clinicians and site specialists alike.

Patient reported outcome measures were recorded at each follow up appointment and used to assess acute and long-term side effects following SBRT. The PROM questionnaires were developed by the LGR and clinical oncologist and is included as Appendix 9. In addition to this method of PROM data collection, patients were also required to complete the universally used EPIC-CP questionnaire (Appendix 11) which assesses symptoms experienced (Einstein et al., 2019), however this PROM method was for use in the PRINToUT study. The data was used to compare SBRT side effects in relation to standard treatment regimes.

All processes within the study were carried out with consideration and accordance to the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP). It was also the LGR responsibility that all staff involved in the processes were adequately trained, competent and entitled to do so in accordance with the departmental and IRMER guidelines. Consideration had to be given to the fact that the use of RayPilot® technology is included in an approved wider trial. Therefore, overall responsibility for adherence to the regulations and guidelines is that of the primary investigator of the PRINToUT trial. However, the LGR was responsible for the adherence of departmental guidelines for the clinical audit. Working in tandem reduced the likelihood of breaches of regulation. The patients' medical notes were

the named source document. All relevant information remained stored in the patients medical notes. This included the consent forms, radiotherapy treatment sheet and treatment plan. Patient reported outcome measure questionnaires were kept in the patient notes. RayPilot® data was electronically stored and analysed.

4.8 DATA COLLECTION

All data required for the clinical audit was collected retrospectively.

Patient demographic data was obtained from the TRAK medical record system. Data collected included patient age, disease staging information, prostate volume and PSA laboratory results to provide a baseline measurement prior to treatment. TRAK was also used throughout the follow up process to access subsequent PSA results to assess treatment outcome. It was used to obtain patient and clinician reported outcomes and toxicities throughout the follow up period of 24 months upon completion of treatment. This data was available to the LGR in the role of uro-oncology advanced practitioner and all data was handled in accordance with Caldicott principles.

To establish the relationship between the RayPilot® device and patient compliance and tolerability, the time from implantation to completion of treatment delivery was also acquired. For some patients the time from implantation to treatment was a matter of ten days, however for some patients this increased to a matter of weeks (this is further discussed in the results and discussion chapters that follow). For completeness of the clinical audit, the LGR wanted to establish whether increased time from implantation to treatment completion had any bearing on overall patient compliance or physical effects e.g. oedema of the prostate or migration of the device. The data collected was recorded in days from the surgical implantation date until the day zero appointment. All records were then imported to an excel spreadsheet and the minimum, maximum and mean of the timeframe was calculated.

The most crucial data collected was that of the RayPilot® real time motion management system and was the data under investigation in the clinical audit. The RayPilot® system recorded transmitter co-ordinates 30 times per second and these were stored on the central RayPilot® database. They were patient specific and therefore, recorded in separate patient files. Each individual coordinate was recorded and can be viewed as a graphical representation of motion throughout the treatment

duration or as individual measurements. For the purpose of the clinical audit data analysis, all the recorded coordinate measurements were amalgamated into a single Excel spreadsheet to allow the data to be analysed.

The data required to address the aim of the clinical audit and the thesis aim was collected and analysed by the LGR only. This aided in the reduction of inter-observer bias as all data was handled and processed by one person only. The data was stored and used in accordance with the QIT rand Caldicott regulations. The primary researcher must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of information and will uphold the core principals of the Act. The data was not anonymised at this point due to records being identified by the patient specific CHI number. The primary researcher pseudo-anonymised the data for the purposes of the project once the data collection was complete. Any published results do not contain any personal data that could allow identification of individual participants.

Patient identifiable information was anonymised and each patient given a numerical identifier (001,002 etc) to ensure confidentiality of data. Only information and data relevant to the clinical audit was collected and was stored in a password-protected computer. Any physical data, e.g. patient questionnaires, were either compiled with the patients medical records or stored in a locked storage cabinet only accessible by the LGR. These documents were destroyed in accordance with local confidential waste rules following completion of the clinical audit, as they were no longer clinically relevant.

4.9 DATA ANALYSIS

The RayPilot® recorded data resulted in 54175 intrafraction motion measurements being recorded in total for the patient cohort in the clinical audit (n=7).

The RayPilot® software recorded the standard deviation and the mean intrafraction motion of each treatment arc. The software also provided motion data for all treatment

arcs and collated this to provide an overall insight into intrafraction motion of the prostate. This includes minimum and maximum motion in all vectors, how long the patient remained out of tolerance, the timeframe for treatment and the percentage of the treatment that is over the desired tolerance. The lead radiographer used this data to assess the efficacy of the RayPilot® device.

The data produced using the RayPilot® software was continuous quantitative data. It was measuring a limitless variable within the cohort group. Due to the small numbers recruited in this observational study, the data was underpowered to provide inferential statistics. In this instance, descriptive statistics were used. This was appropriate given that each motion value is a primary dataset and will not be compared to any other data.

The mean motion from each treatment arc and the calculated standard deviation is the most important data collated from the RayPilot® system. The mean calculations account for all the data set values and was algebraically defined making it more manageable. It is worth noting that the disadvantage of using the mean values is that it can be distorted by outliers, which can be detrimental to a small sample size. However, this study required the mean and standard deviation to be used for further analytical equations using the Van Herk Margin Formula (Van Herk, 2004). The standard deviation is also important as it can be described as an average of the deviations of the observations from the mean; again, this can prove meaningful in the case of outliers. If there was a reason for an outlier, e.g. rectal gas dispersion or bladder emptying, this was recorded in the patient treatment sheet to justify and account for that level of motion. The LGR was responsible for reviewing and assessing the outlier values and confirming the reasons for the variation in the recorded measurement. If this was evident as rectal gas motion or bladder filling (confirmed by imaging modalities) then this was recorded and monitored for subsequent treatment fractions. However, if there was no obvious or visual reason for the measurement variation, this was further investigated by the LGR and a physicist to ensure accuracy of the treatment plan for future treatments. If the outlying measurement recorded was due to external influence, e.g. patient motion, this was also recorded and monitored in future treatments.

The aim of this clinical audit was to evaluate if using the RayPilot® device for monitoring intrafraction motion, allows for reduced planning target margins leading to dose escalation and further hypofractionation of prostate SBRT. To address the aim

of the clinical audit, the data collated from the RayPilot® software was then used in a planning margin equation. The VHMF accounts for random and systematic uncertainties and provides a margin for error. It was developed to calculate the minimum margin on the target to provide full coverage by 95% of the prescribed dose to 90% of the population (Franco et al., 2022). Therefore, the VHMF margins are added to the tumour volume to ensure that the correct radiation dose is delivered to the tumour in the presence of geometrical uncertainties, both systematic and random. All data was used in accordance with the VHMF formula of: PTV margin = $2.5\Sigma + 0.7\sigma$ (where Σ = quadratic sum of systematic deviation of systematic errors and σ = quadratic sum of systematic displacement of random errors). The margin formula provided a numerical value for the margins that could be applied clinically. The purpose of the clinical audit was to then assess if the margins currently used can be reduced and what effect this has on the possibility of dose escalation and shorter treatment fractionation.

Once the margin calculation has been confirmed, it was reviewed against the current planning margins used in clinical practice. If the margins could be reduced, the treatment plan was then be recreated by the LGR using the Eclipse planning system (Varian Medical Systems Inc.). This was for study purposes only and was not approved for treatment. It was not be created until after the participant has completed their SBRT treatment to ensure there was no risk of the participant being treated on the wrong plan or prescription. It was also clearly be named as ‘study plan’, followed by the primary researcher’s initials to ensure it is easily differentiated in the system. The new calculated margins were added to the clinical target volume, which has already been defined by the consultant clinical oncologist and no amendments were be made to this. All dose constraints and organs at risk remained identical to the original treatment plan. The new margins, if applicable, were applied and the plan assessed for compliance with the required dose constraints. If the dose constraints were met, then the process of dose escalation could be reviewed. The underlying theory being, that if the margins are reduced, then the dose can be escalated with minimum effect on the organs at risk, therefore raising the possibility of increased daily dose in fewer treatment fractions. The clinical audit plan will follow normal planning protocols and required to be given clinical approval by the consultant clinical oncologist and the head of medical physics.

One of the fundamental considerations of a clinical audit is that it does not cause unnecessary harm or result in an increase in side effects experienced by patients. The study design includes the use of patient reported outcome toxicity scoring which will be reviewed during the follow up process. A baseline LENT SOMA questionnaire was completed by the participant on the first fraction of SBRT. It was then completed on the final fraction and at every subsequent follow up appointment (6 and 12 weeks, then at 6 monthly intervals until month 24). This provided quantitative data, which will be analysed to ensure that the acute and long-term side effects of SBRT treatment were not detrimental in relation to standard radiotherapy regimes. Participant toxicity was also graded against the RTOG toxicity scoring proforma and recorded at each follow up visit. The data provided percentage results and these were reviewed in relation to the expected side effects following standard radiotherapy, to ensure that the audit participants did not experience increased harmful acute or long-term toxicity following prostate SBRT with RayPilot®.

5 RESULTS

5.1 CHAPTER SYNOPSIS.

The following chapter reports the results of the clinical audit. The clinical audit aim was to assess and evaluate the the efficiency of the RayPilot® real time motion management system and the effect on dosimetric margins and treatment delivery in hypofractionated prostate radiotherapy and to assess whether this could lead to a further hypofractionated regime and reduction in fractionation. This following chapter evidences the results of the audit in relation to recorded patient intrafraction motion, which was used to calculate planning target margins using the VHMF, the effect this has on the feasibility of implementing an increase in hypofractionation and reduction in fractionation and patient recorded toxicity following treatment and clinical treatment outcome (measured by PSA reduction). These results illustrate the comparison between general treatment outcome and toxicity between standard hypofractionated regimes and prostate SBRT using RayPilot® as a real time motion management system. The chapter further uses the data to populate the VHMF to assess whether tighter planning target margins could be used clinically and therefore, allow for further escalation of total dose and a reduction in fractionation.

5.2 PARTICIPANT DEMOGRAPHICS.

The study recruited 11 patients, all participants included in the clinical audit fulfilled the criteria at time of recruitment based on medical history and biochemical, radiological and pathology investigation results. Recruitment requirement criteria as stated in the protocol (Appendix 1) and recruitment was carried out in accordance with protocol requirements and IHC-GCP guidance as discussed in the previous methodology chapter. However, due to clinical reasons discussed below, four patients were removed from the study resulting in a patient cohort of seven. Although the patient cohort was small, the cross section appears to be representative of the population in terms of age, socioeconomic status and disease epidemiology and aetiology. However, this is an assumption due to the small patient number and cannot be statistically inferred (Table 5).

Eleven patients were recruited into the study over a period of 14 months; however, four patients were withdrawn from the study prior to commencement of SBRT. The first patient to be removed from the study was due to device migration identified on the day zero appointment. It was clear in the pre-treatment CBCT that the device had migrated from the attendance at the initial CT scan. The transmitter device had migrated in two directions (sup/inf and ant/post) with a magnitude of 1.1cm in the sup/inf direction. The change in transmitter position therefore proved detrimental to the initial planned values, which could have resulted in discrepancies in relation to planning margins with the possibility of change in the high dose target volume and therefore areas of underdose or overdose to the treatment volume, and as such, the migration was clinically significant. As the device was implanted under surgical conditions, the position could not be amended. Due to the nature of the migration (the transmitter had moved inferiorly into the tract within the prostate tissue left by the implantation trochanter), the transmitter was then deemed unreliable in terms of locational reproducibility and therefore, the patient was removed from the trial. The device was removed and the patient went on to have conventional dose and fractionation. A further patient was removed due to disease progression at time of planning. Prior to starting SBRT the patients attend for MRI on the morning of the implantation procedure, the patient had not had a diagnostic MRI for approximately 5 months prior to the implantation MRI. Following radiology reporting it was confirmed that the patient had progressed in that time and was now ineligible for the trial due to evidence of metastatic disease. The device was removed and the patient then had standard clinical management appropriate for advanced disease. Due to an equipment failure of the RayPilot® couchtop array the hardware was returned for repair to the manufacturers and at this point, no patients could be treated using the RayPilot® technology. The transponders housed within the couch top receiver were not transmitting the signal required for detection of the transmitter device; this was due to a faulty transponder that required to be replaced. In the protocol documentation instances like this need to be given consideration and as a protocol amendment this patient was treated using the SBRT treatment plan but only the fiducial markers were used for motion management not the implanted device and as such was removed from the trial data. The last patient to be removed from the study was due to excessive post-implantation bleeding. Unfortunately, following the implantation procedure that patient developed a large haematoma in the implantation site causing complications including pain, bleeding and inflammation. After treatment as an inpatient, it was decided to remove the implanted transmitter. As the implantation occurs during

ultrasound guidance, there are no 'saved' or recorded images from the procedure and therefore this made it difficult to assess whether this was down to poor implantation technique, human error or the patients individual response to the implantation. The patient was removed from the study and went on to have conventional hypofractionated prostate radiotherapy. For these reasons, the removal of these four patients from the original recruitment of 11 patients, the resultant and final patient cohort for the study was seven patients (n=7).

*Table 5 - Patient demographics. All participant demographics (age, PSA at diagnosis and prostate volume at diagnosis) including the median values and inter quartile ranges for patient cohort (n=7). * Indicates deceased patient during follow up period.*

PATIENT	AGE (median = 69, IQR 69-72)	PSA@ DIAGNOSIS (ng/ml) (median= 9.1, IQR 8.2-11.8)	PROSTATE VOLUME @ DIAGNOSIS (cc) (median = 45, IQR 37.5-52.5)	PARTICIPANT STATUS
001	67	9.1	60	Completed study
002	69	12.9	45	Completed study
003	79	6.4	90	Completed study *
004	69	10.7	40	Completed study
005	69	9.1	45	Completed study
006	72	7.3	35	Completed study
007	72	18	35	Completed study

The epidemiology of prostate cancer suggests that its incidence is attributed to advancing age. Age-specific incidence rates rise steeply from around age 45-49, peak in the 75-79 age group. The patients included in the clinical trial were representative of this age range.

The maximum age of participants was 79 years, the minimum age was 67 years (median =69 years, IQR 69-72, IQR=3). At participation, 71% (n=5) were diagnosed as Gleason Score 6 with the remaining cohort all Gleason Score 25 (n=2). Prostate volume ranged from 35cc to the maximum of 90cc (median = 45cc, IQR 37.5-52.5cc, IQR=15). Only one patient was staged at T1, the remaining cohort was all staged at

T2 (n=6). Patients PSA levels at the time of participation ranged from 6.4ng/ml to a maximum of 18ng/ml (median = 9.1ng/ml, IQR 8.2-11.8 ng/ml, IQR=3.6).

5.3 IMPLANTATION TO DEVICE REMOVAL DATA

The maximum time from device implantation to removal was 35 days and the minimum time from device implantation to removal was 15 days. The median time from device implantation to removal was 26 days as illustrated in Figure 17 (IQR 20.5-27 days. IQR=6.5). The determining factor in the duration of the device remaining in situ was in the pre-treatment processes. For all patients the initial time constraint is that of radiotherapy treatment planning. Once the CT planning scan had been acquired, the treatment planners then required time to produce the treatment plan and then obtain treatment plan approval from the clinical oncologist and a physicist before it was authorised for treatment. In the context of this study, the planning department requested ten days from planning scan to day zero. In the majority of patients this was adhered to however, in the patient that had the device in for the minimum duration (15 days) this was reduced to 7 days (this was to comply with the patients request that the treatment was completed by a specified date to allow for a further surgical appointment for unrelated issues, not for a clinical reason).

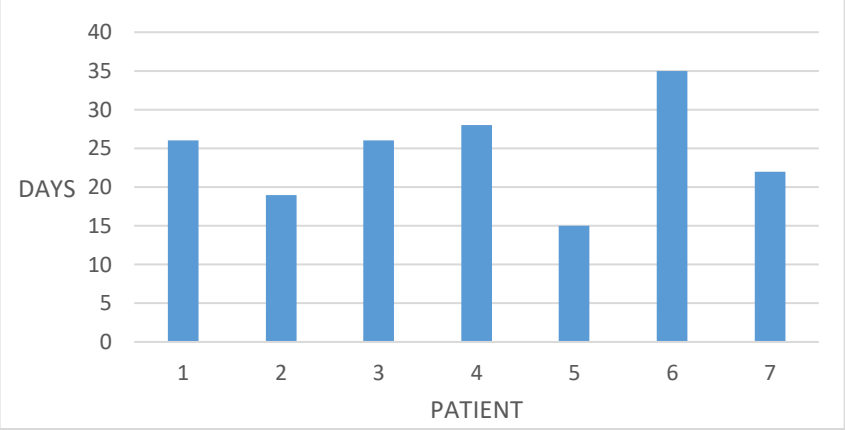


Figure 17 - Device implantation to removal duration for participants (n=7). Patient specific data regarding time from implantation until fraction one of SBRT (min – 15 days, max – 35 days, mean – 24 days).

The maximum time from implantation to removal was 35 days. The delay from implantation to treatment completion was due to the patient pathway logistics. Due

to availability of the clinical radiologist, the device implantation had to be brought forward by a period of over two weeks.

There appears to be no relationship between patient compliance with the device during treatment or complications at device removal and the overall time from implantation of the device until device removal upon completion of treatment. All patients in the study had the device safely removed by the LGR without complication. The process of removal was not affected by the length of time the device was in situ.

Due to the surgical nature of the implantation of the RayPilot® transmitter device can lead to trauma of the prostate tissue and, as any surgical procedure can cause risk of potential infection. A concern of the study was that as the patients' radiotherapy planning scan was acquired on the same day of implantation, there might be residual swelling of the prostate tissue. As the CT scan is a volumetric imaging study, any variation in organ volume between this and the first day of treatment, would effect and possibly negate the treatment plan. However, comparison of the patients initial CT planning scan and the CBCT taken on day zero did not provide any evidence of variation in prostate volume. Therefore, the concern regarding detrimental effects on treatment from the length of time the device was in situ was determined not to be significant.

5.4 TREAMENT DURATION

Figure 18 illustrates the treatment duration per fraction per patient for all completed treatment fractions (n=35). The system recorded measurements 30 times per second and therefore, the measurement varies per patient, per fraction due to treatment duration.

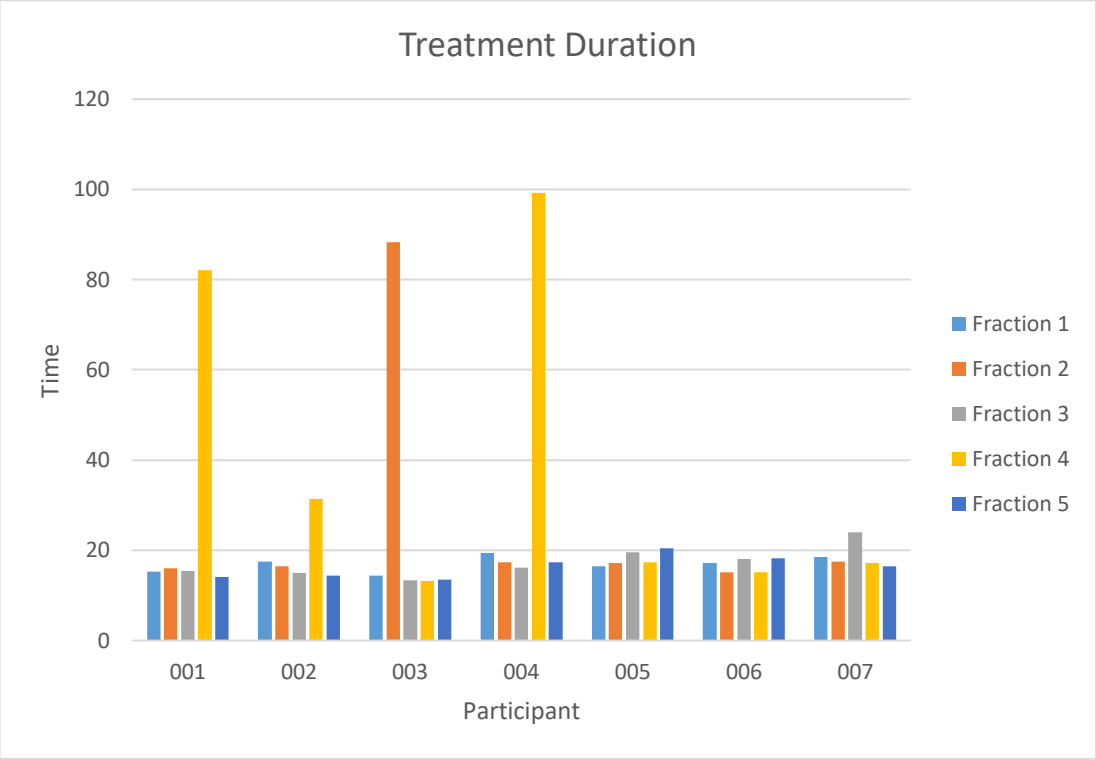


Figure 18 - Overall treatment duration. Patient specific treatment duration data evidencing overall treatment time (minutes) per fraction (n=35) per patient (n=7). Minimum treatment duration was 13 minutes; maximum treatment duration was 99 minutes, and median treatment duration of 17 minutes.

Median treatment duration of all treatment fractions was 17.2 minutes (IQR 15.1 – 18.5 minutes, IQR=3.4) with the minimum treatment duration being 13.3 minutes and the maximum treatment duration of 99.2 minutes as shown in Figure 10. Treatment duration was recorded from the moment the device was attached to the RayPilot® recording and monitoring software and completed when the patient device was removed from the software record and verify system. The resultant duration therefore, included imaging sequence time, patient set up time and all beam interruptions, including if the patient was removed and required to start the treatment process from the beginning. For example, the maximum time of 99.2 minutes was cumulative for one participant but included the time that the participant was removed from the

treatment room undertaking the bladder filling procedure that took approximately 20 minutes. The results show a correlation between increased treatment time and increased intrafraction motion. The longer the patient is on the treatment couch the greater the intrafraction motion, which then perpetuates a longer treatment duration.

5.5 MOTION MANAGEMENT DATA

It is noted that the RayPilot® software records readings to six decimal places, however, in the study this has been taken to one decimal place. The accuracy of the system is not translated to the clinical application, for example, planning margins within the host centre are in mm and the assumption that anything less than this is clinically achievable is not feasible. For the purpose of accuracy in determining the required planning margins in the VHMF, the values were taken to six decimal places to ensure the most accurate result; however, to then aid in clinical application these were calculated to two decimal places. This is a recurring theme in the data. Motion management and displacement data is described in terms of mean and SD due to the VHMF requiring calculation of the mean.

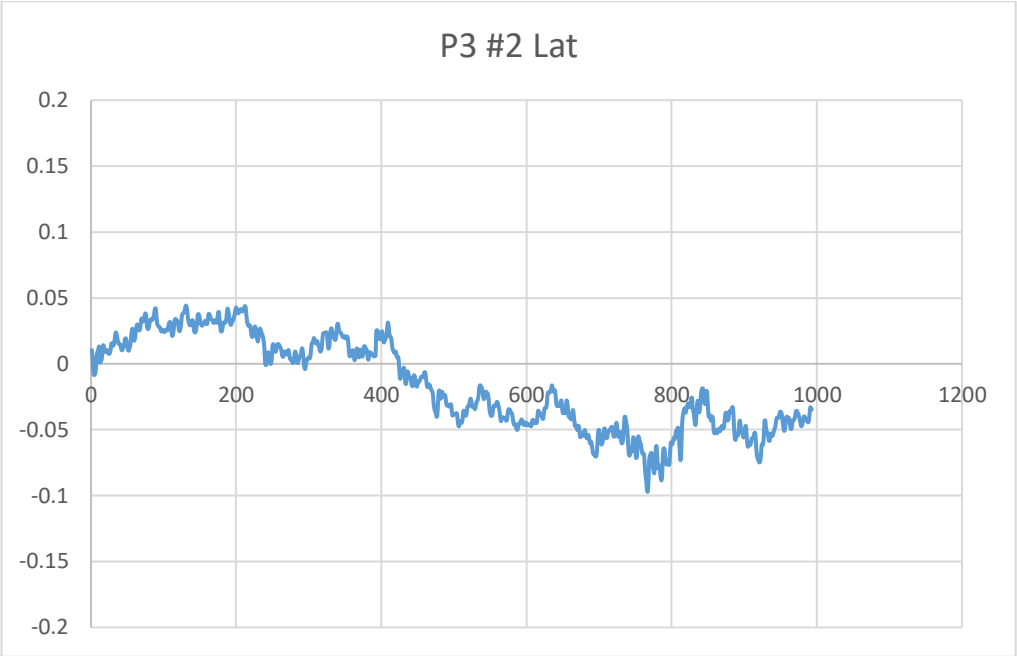
The RayPilot® recorded data resulted in 54175 intrafraction motion measurements being recorded in total for all seven patients in the study. The measurements recorded were cumulative over all treatment fractions (n=35). Table 6 is an example of the recorded motion management data for patients used for the clinical audit.

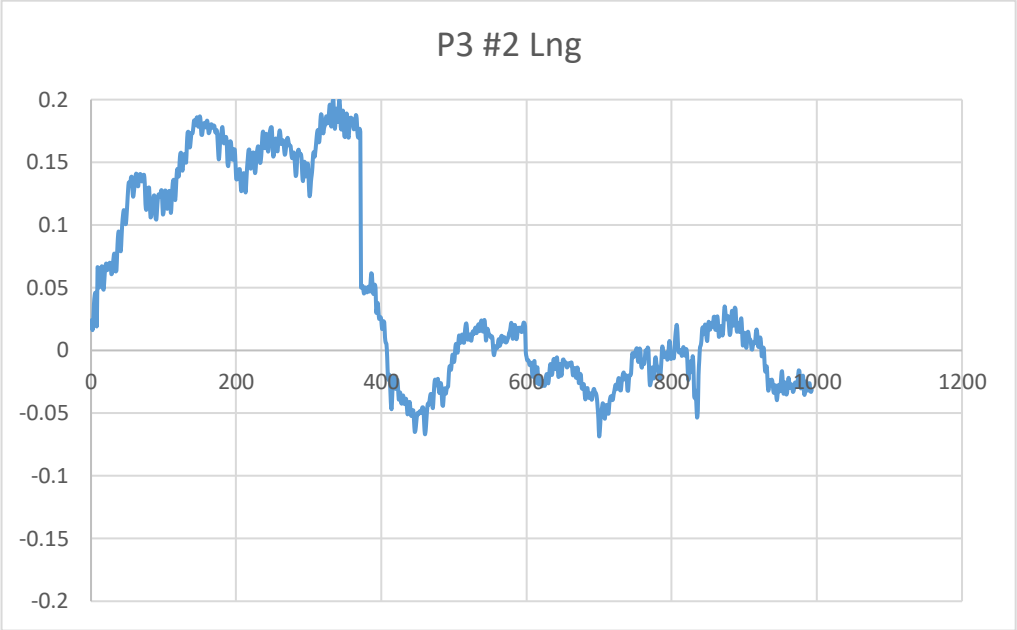
Table 6 - Example of the RayPilot® data record. This table is an example of the first 20 data records of one patient. The data collected reports motion in all directions and vectors

approximately 30 times per second. This is recorded to six decimal places. All measurements are in centimetres.

Readout	Lat	Long	Vert
1	0.010398	0.024226	-0.02922
2	0.005859	0.016182	-0.0297
3	-0.00398	0.023686	-0.03139
4	-0.00854	0.036628	-0.03279
5	-0.00814	0.043635	-0.03202
6	-0.00699	0.045817	-0.03167
7	-0.00131	0.036709	-0.0302
8	0.006732	0.020012	-0.02873
9	0.009079	0.06647	-0.01999
10	0.010673	0.063051	-0.02097
11	0.012916	0.050427	-0.02266
12	0.001024	0.052168	-0.02507
13	0.001122	0.060959	-0.02833
14	0.002375	0.065733	-0.02629
15	0.004787	0.066954	-0.02285
16	0.012485	0.058481	-0.01702
17	0.014168	0.04856	-0.0123
18	0.01212	0.052947	-0.01297
19	0.009576	0.062147	-0.01447
20	0.008923	0.067731	-0.01425

The table illustrates the first 20 recorded measurements in the RayPilot® system. For this particular fraction a total of 718 measurements were recorded during the treatment duration therefore this is included as an example of the data readout. Motion management data is in centimetres. All data was recorded in an Excel spreadsheet to allow for further analysis. This allowed data to be plotted to form a graphical representation of real time motion, which is easier to contextualise than individual measurements of this quantity (Figure 19).


P3 #2 Lat
0.2
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
-0.2
0
200
400
600
800
1000
1200


P3 #2 Lng
0.2
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
-0.2
0
200
400
600
800
1000
1200

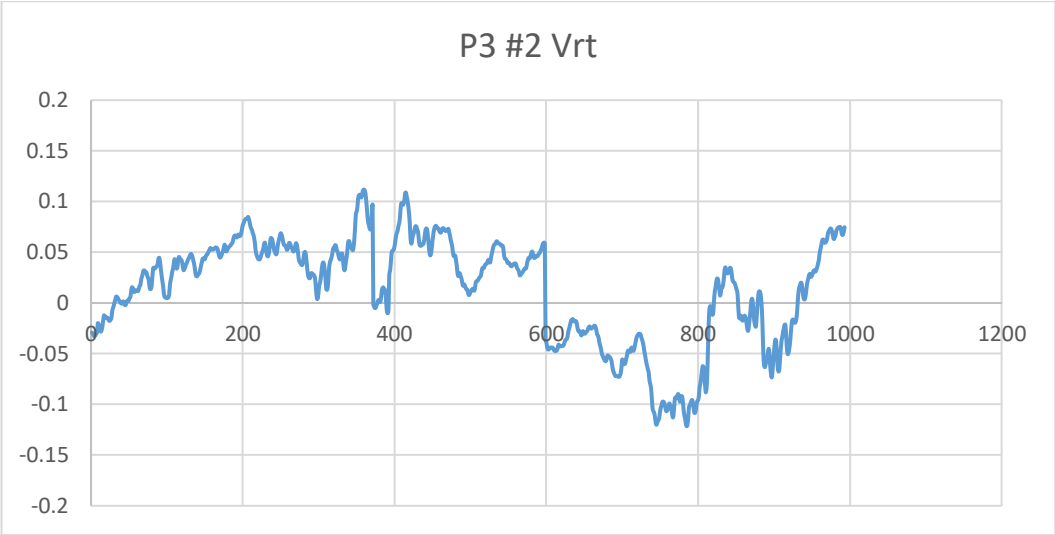


Figure 19 - RayPilot® recorded intrafraction motion. Graphical representation of intrafraction motion of one patient in the lateral, longitudinal and vertical directions over the treatment fraction duration. Motion is measured in centimetres and time is measured in seconds.

The total intrafraction motion data per patient for lateral, longitudinal and vertical directions and the cumulative motion of all 35 treatment fractions is recorded as follows in Tables 7-10:

Table 7 - Lateral displacement data in all patients (n=7). The minimum, maximum, mean values and standard deviation was recorded for patients over the total treatment duration of all five fractions. All measurements are in centimetres.

Patient	Min (cm)	Max (cm)	Mean (cm)	SD (cm)
001	-3.3	0.5	-0.5	1.0
002	-2.1	0.4	-0.0	0.3
003	-1.6	0.3	0.0	0.2
004	-0.6	0.2	-0.0	0.1
005	-2.5	0.2	0.0	0.3
006	-2.6	3.4	-0.1	0.4
007	-1.1	0.6	-0.0	0.2

Table 8 - Longitudinal displacement data in all patients (n=7). The minimum, maximum, mean values and standard deviation was recorded for patients over the total treatment duration of all five fractions. All measurements are in centimetres.

Patient	Min (cm)	Max (cm)	Mean (cm)	SD (cm)
001	-7.7	0.6	-1.8	2.4
002	-2.8	4.0	-0.0	0.4
003	-6.7	1.8	-0.1	0.9
004	-1.0	4.8	0.0	0.5
005	-4.6	0.4	-0.0	0.4
006	-5.4	6.0	-0.2	1.1
007	-5.7	4.0	-0.1	0.8

Table 9 – Vertical displacement data in all patients (n=7). The minimum, maximum, mean values and standard deviation was recorded for patients over the total treatment duration of all five fractions. All measurements are in centimetres.

Patient	Min (cm)	Max (cm)	Mean (cm)	SD (cm)
001	-6.7	0.4	-1.4	2.6
002	-6.6	0.4	-0.1	0.9
003	-7.2	1.2	-0.2	1.1
004	-5.6	0.2	-0.1	0.8
005	-5.8	0.2	-0.0	0.6
006	-7.6	1.6	-0.5	1.6
007	-7.8	0.3	-0.4	1.7

Table 10 - Cumulative displacement values for all patients (n=7) over all treatment fractions (n=35) showing the maximum, minimum, mean values and standard deviations of intrafraction motion in all directions. All measurements are in centimetres.

All	Min (cm)	Max (cm)	Mean (cm)	SD (cm)
LATERAL	-3.3	3.4	-0.1	0.5
LONGITUDINAL	-7.7	6.0	-0.3	1.3
VERTICAL	-7.8	1.6	-0.5	1.6

The minimum lateral displacement was -3.3cm, with a maximum displacement of 3.4cm. Mean displacement in the lateral direction was 0.10cm (SD± 0.5cm).

The minimum longitudinal displacement was -7.7cm, with a maximum displacement of 6.0cm. Mean displacement in the longitudinal direction was 0.3cm (SD± 1.3cm).

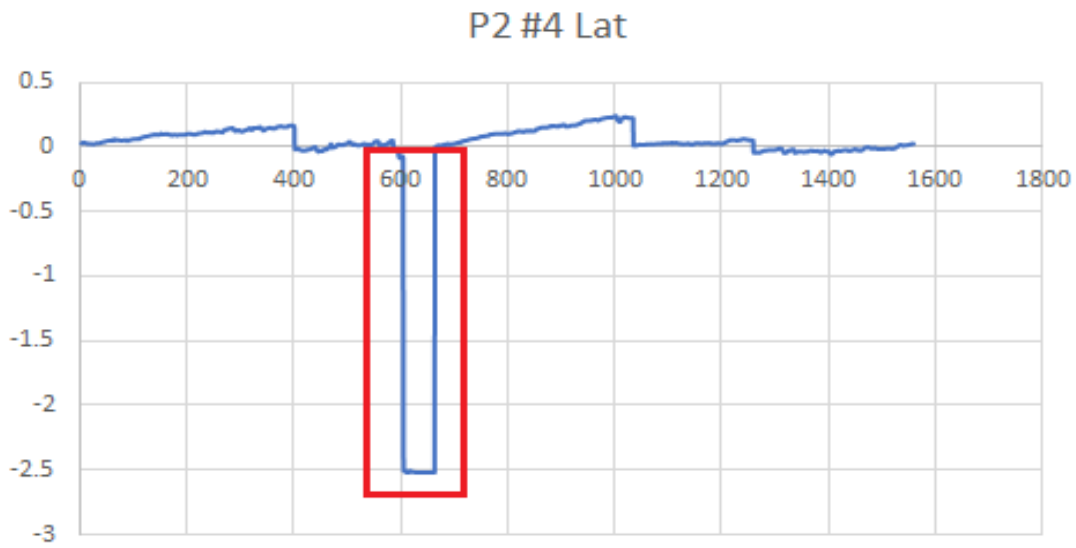
The minimum vertical displacement was -7.8cm, with a maximum displacement of 1.6cm. Mean displacement in the vertical direction was 0.5cm (SD± 1.6cm).

The RayPilot® software records all displacements that allows for collation of the overall percentage of treatment time that the target position is exceeds 1mm, 3mm and 5mm respectively. The results are shown in Table 11.

Table 11 – Intrafraction displacement data displayed as a percentage of time that the displacement occurs throughout the overall treatment duration shown for all patients (n=7) and total recorded data sets (n=54228). The percentages are collated for the target position exceeding 1mm, 3mm and 5mm in the overall treatment duration.

	Lateral Displacement (n=)	Longitudinal Displacement (n=)	Vertical Displacement (n=)
Count	54228	54228	54228
Count outside 1 mm	12039	10719	16610
(less than 1 mm)	48282	49959	47804
(less than -1 mm)	6093	4014	6450
Percent outside 1 mm	**22.2%**	**19.8%**	**30.6%**
Count outside 2 mm	6281	5808	8466
(less than 2 mm)	52284	52434	52871
(less than -2 mm)	4337	4014	4014
Percent outside 2 mm	**11.6%**	**10.7%**	**15.6%**
Count outside 3 mm	4392	4480	6596
(less than 3 mm)	53721	53465	53720
(less than -3 mm)	3885	3717	3717
Percent outside 3 mm	**8.1%**	**8.3%**	**12.3%**
Count outside 5	3665	4088	4744
(less than 5 mm)	54186	53788	54022
(less than -5 mm)	3623	3648	4538
Percent outside 5 mm	**6.7%**	**7.5%**	**8.8%**

The subsequent data review resulted in clinical outliers being removed from future calculations (removal of 2348 recorded measurements). Clinical outliers are defined as clinically improbable treatment values, large magnitude displacements as the treatment beam was interrupted at anything greater than 0.2mm or displacements occurring for extended periods. For example, longitudinal values of greater than 5cm was evident in 5 patients, upon investigation of these results it became evident from the time stamp of each recorded value that these occurred at the end of the treatment fraction when the patient was removed from the treatment position without the RayPilot® transmitter device being disconnected from the RayPilot® software system. The software therefore, continually records motion until the transmitter device is disconnected resulting in shifts of large magnitude (e.g. when a patient is moved longitudinally on the treatment couch) being recorded. Such outlier values are shown in figure 20 and highlighted in red. The graphical representation of real time motion shows large magnitude in the lateral, longitudinal and vertical direction. Attributed to a treatment couch shift by the radiographers (the patient required reassurance during the treatment fraction) the large variation in motion was accounted for and therefore classed as an outlier.



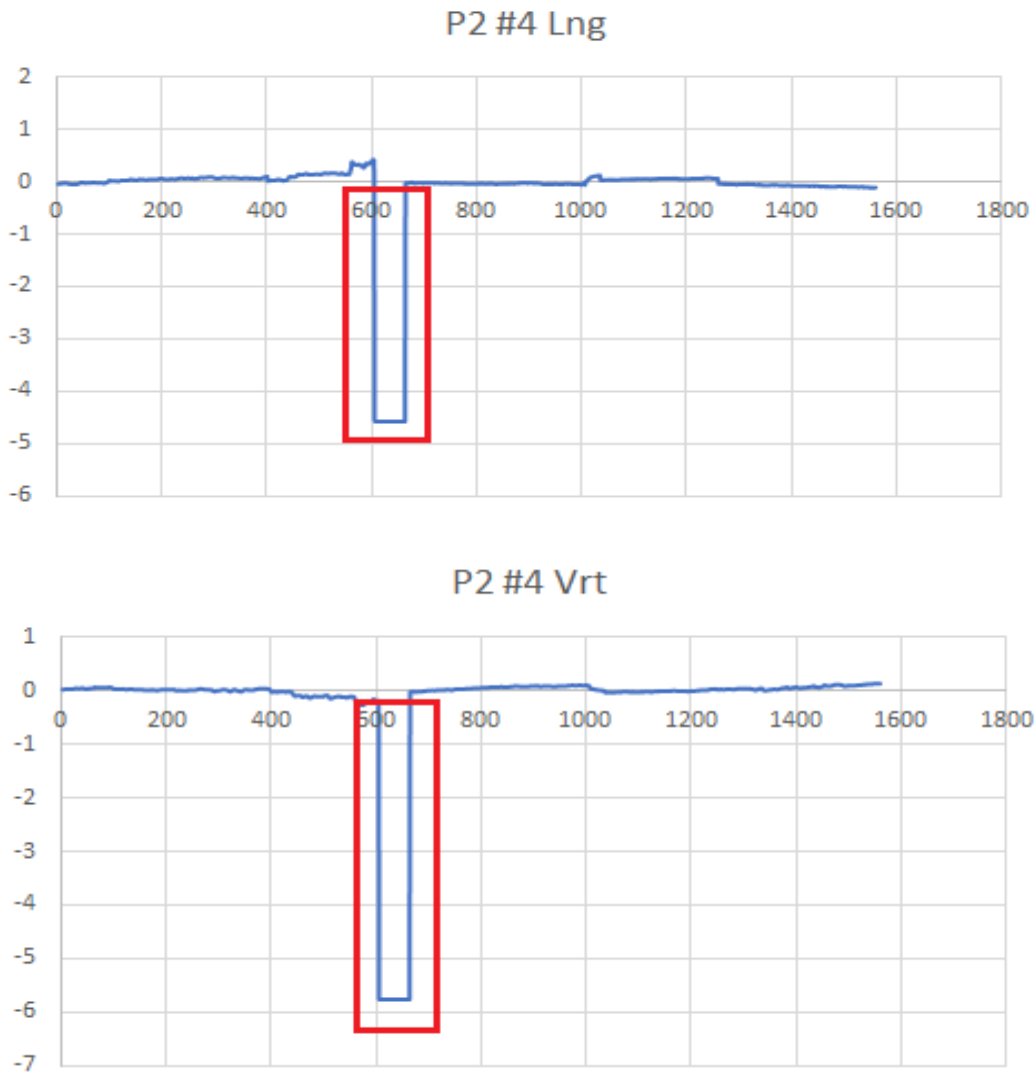


Figure 20 - Graphical example of outlier data record in the RayPilot® motion management system. The magnitude of the displacement indicate an outlier and as such, these are removed from the dataset. The time is measured in seconds and the motion value is centimetres. The outlier data is highlighted in red (this outlier was caused by the radiographers moving the treatment couch in response to patient discomfort).

Outliers of this magnitude were therefore classed as clinical outliers and removed from the data, and this can be attributed to user error and inexperience of system use, It is evident from this study that in future the RayPilot® transmitter should be connected and disconnected immediately following patient positioning at the beginning of the process and immediately after treatment completion before removing the patient from the treatment position.

The resultant values, which were corrected for outliers, were used in the VHMF to ascertain appropriate planning margins as described below.

5.6 VAN HERK MARGIN FORMULA (VHMF) RESULTS

The VHMF is: $M = 2.5\,\Sigma + 0.7\sigma$

Where Σ is the quadratic sum of all systematic errors and σ is the quadratic sum of all random errors. The systematic errors included in image-guided radiotherapy are organ delineation (OD), set up errors (SUE), organ motion (OM) and the random errors are OD, SUE and intrafraction motion (IFM) (Van Herk, 2004) (Equation 1).

Therefore, in this study the margin formula is then expanded to become:

Equation 1 The Van Herk Margin Formula. M = 2.5 times the quadratic sum of all systematic errors (Σ) + 0.7 times the quadratic sum of all random errors (σ).

$$M = 2.5\sqrt{(OD)^2 + (SUE)^2 + (OM)^2} \; + \; 0.7\sqrt{(OD)^2 + (SUE)^2 + (IFM)^2}$$

Within the research, the VHMF was used to calculate the required margins using the RayPilot® data prior to removal of the clinical outliers using the mean intrafraction motion in all vectors. The margin formula was then repeated using the filtered clinical data for comparison. As noted previously, the RayPilot® system records measurements to six decimal places, to ensure accuracy of the VHMF calculations and results these values were used in all VHMF calculations. It was then reduced to one decimal place to align with clinical applications. All resulting values are in cm. The calculations are illustrated in equations 2-4.

Lateral required margin including outliers;

Equation 2 - VHMF lateral margins required when outlier data is included. The resulting planning margin required on the lateral (LT/RT) dimension of the prostate is 0.8cm

$$M = 2.5\sqrt{(OD)^2 + (SUE)^2 + (OM)^2} + 0.7\sqrt{(OD)^2 + (SUE)^2 + (IFM)^2}$$

$$= 2.5\sqrt{(0.25)^2 + (0)^2 + (0)^2} + 0.7\sqrt{(0)^2 + (0)^2 + (0.17)^2}$$

$$= 2.5\sqrt{0.0625} + 0.7\sqrt{0.0289}$$

$$= 0.63 + 0.12$$

$$= 0.8\text{cm}$$

Longitudinal required margin including outliers;

Equation 3 - VHMF longitudinal margins required when outlier data is included. The resulting planning margin required on the longitudinal (SUP/INF) dimension of the prostate is 0.9cm

$$M = 2.5\sqrt{(OD)^2 + (SUE)^2 + (OM)^2} + 0.7\sqrt{(OD)^2 + (SUE)^2 + (IFM)^2}$$

$$= 2.5\sqrt{(0.25)^2 + (0)^2 + (0)^2} + 0.7\sqrt{(0)^2 + (0)^2 + (0.32)^2}$$

$$= 2.5\sqrt{0.0625} + 0.7\sqrt{0.1024}$$

$$= 0.63 + 0.22$$

$$= 0.9\text{cm}$$

Vertical required margin including outliers;

Equation 4 - VHMF vertical margins required when outlier data is included. The resulting planning margin required on the vertical (ANT/POST) dimension of the prostate is 0.9cm.

$$M = 2.5\sqrt{(OD)^2 + (SUE)^2 + (OM)^2} + 0.7\sqrt{(OD)^2 + (SUE)^2 + (IFM)^2}$$

$$= 2.5\sqrt{(0.25)^2 + (0)^2 + (0)^2} + 0.7\sqrt{(0)^2 + (0)^2 + (0.42)^2}$$

$$= 2.5\sqrt{0.0625} + 0.7\sqrt{0.1764}$$

$$= 0.63 + 0.29$$

$$= 0.9\text{cm}$$

Resulting required margins including outliers are concurrent with current clinical planning margins in use clinically of 1cm, 1cm and 0.8cm in the lateral, longitudinal and vertical directions respectively. These values are stated in the departmental planning protocol and have been adopted from the previously mentioned CHHiP trial results (Dearnaley et al., 2012). However, the use of the RayPilot® motion management software reduces the risk of geometric uncertainty and therefore, results in reduced required planning margins and tighter tolerance levels. In this clinical audit, the tolerance level for intrafraction motion is 0.21mm, at which point treatment delivery is halted. Treatment was not delivered unless the isocentre was positioned within the 2mm tolerance. Therefore, all measurements over 3mm were removed from the RayPilot® data (Table 12). This decision was based on all motion over the tolerance value is clinically negligible as the treatment was not delivered at these values as patient was repositioned to the isocentre. Due to the RayPilot® software not being interfaced to the linear accelerator, the operator must manually halt the beam and allowances must be made to account for this.

Table 12 - Mean and standard deviation of motion displacement in all patients (n=7) over all treatment fractions (n=35) from 0-0.3cm following the removal of outliers greater than this value. These results are used in the VHMF assessing the feasibility of planning margin reduction.

ALL	MEAN (cm)	S.D. (cm)
LATERAL	0.1	0.1
LONGITUDINAL	0.1	0.1
VERTICAL	0.1	0.1

The VHMF was then used to recalculate required planning margins including the reduced RayPilot® intrafraction motion data. The results are included in Equations 5-7.

Lateral required margins with filtered data (0-0.3cm)

Equation 5 - VHMF lateral margin requirements for filtered data (motion of 0-0.3cm). The equation was repeated with filtered intrafraction motion data to evaluate the potential of margin reduction.

$$M = 2.5\sqrt{(OD)^2 + (SUE)^2 + (OM)^2} + 0.7\sqrt{(OD)^2 + (SUE)^2 + (IFM)^2}$$

$$= 2.5\sqrt{(0.25)^2 + (0)^2 + (0)^2} + 0.7\sqrt{(0)^2 + (0)^2 + (0.06)^2}$$

$$= 2.5\sqrt{0.0625} + 0.7\sqrt{0.0036}$$

$$= 0.63 + 0.042$$

$$= 0.7\text{cm}$$

Longitudinal required margins with filtered data (0-0.3cm)

Equation 6 – VHMF longitudinal margin requirements for filtered data (motion of 0-0.3cm). The equation was repeated with filtered intrafraction motion data to evaluate the potential of margin reduction.

$$M = 2.5\sqrt{(OD)^2 + (SUE)^2 + (OM)^2} + 0.7\sqrt{(OD)^2 + (SUE)^2 + (IFM)^2}$$

$$= 2.5\sqrt{(0.25)^2 + (0)^2 + (0)^2} + 0.7\sqrt{(0)^2 + (0)^2 + (0.06)^2}$$

$$= 2.5\sqrt{0.0625} + 0.7\sqrt{0.0036}$$

$$= 0.63 + 0.042$$

$$= 0.7\text{cm}$$

Vertical required margins for filtered data (0-0.3cm)

Equation 7 – VHMF Equation 8 - VHMF vertical margin requirements for filtered data (motion of 0-0.3cm). The equation was repeated with filtered intrafraction motion data to evaluate the potential of margin reduction.

$$M = 2.5\sqrt{(OD)^2 + (SUE)^2 + (OM)^2} + 0.7\sqrt{(OD)^2 + (SUE)^2 + (IFM)^2}$$

$$= 2.5\sqrt{(0.25)^2 + (0)^2 + (0)^2} + 0.7\sqrt{(0)^2 + (0)^2 + (0.08)^2}$$

$$= 2.5\sqrt{0.0625} + 0.7\sqrt{0.0064}$$

$$= 0.63 + 0.56$$

$$= 0.7\text{cm}$$

The results conclude that RayPilot® can be used to monitor the real time motion of the prostate gland and allows for reduction of the planning target volumes when used

concurrently with fiducial markers. The RayPilot® real time motion management system allows for greater monitoring and correction of intrafraction motion and therefore allows for a reduction in planning target margins as recorded in the VHMF calculations above.

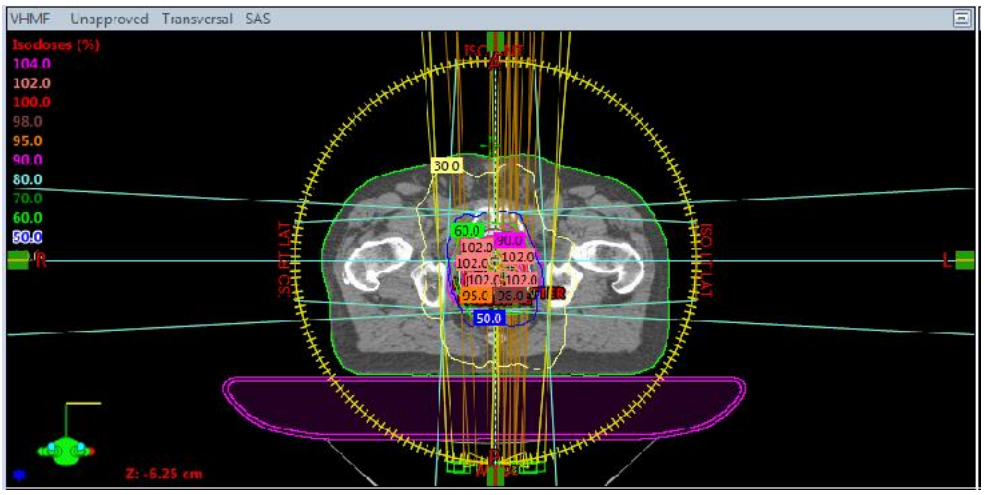
Using the VHMF required margin data, the original treatment plan for each participant was then re-planned using the resultant margins in all directions using the external beam planning software in the Eclipse planning system. The Eclipse planning system is an inverse planning system that allows constraints to be pre-allocated to organs at risk and surrounding structure prior to plan optimisation. The plans were optimised to ensure that any reduction in CTV-PTV planning margins would not have a detrimental impact on the dose constraints requirements of the research in relation to the OARs. The dose constraints are detailed in Table 13.

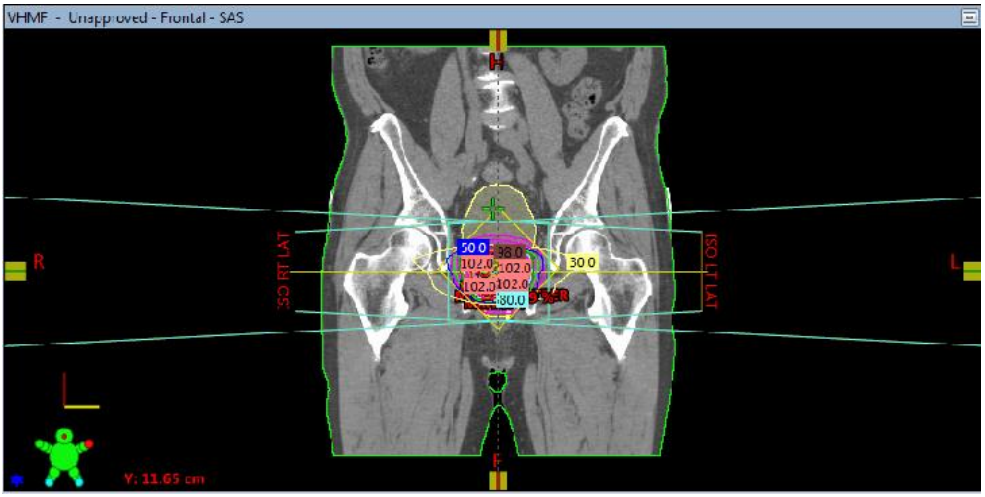
Table 13 - Dose constraints required for inverse planning of prostate SBRT treatment plans. The organs at risk as stated along with the dosimetric limits ensuring minimal toxicity to the organs at risk and surrounding structures. The V value is the volume that receives the stated dose and it must be < than the stated value e.g. rectum V18.1Gy<50% means that less than 50% of the rectum has to receive less than 18.1Gy.

OAR	Dose Constraint
Rectum	V18.1Gy <50% (i.e. less than 50% of rectum <18.1Gy) V29Gy <20% (i.e. less than 20% of rectum receiving 29Gy) V36Gy <1cc
Bladder	V18.1Gy <40% V37Gy < 10cc (optimal V37Gy <5cc)
Prostatic urethra	V42Gy <50% (optimal not mandatory)
Femoral head	V14.5Gy < 5%
Penile bulb	V29.5Gy < 50%
Testes	Blocking structure
Bowel	V18.1Gy <5cc V30Gy <1cc

Resulting reductions in CTV-PTV margins did not affect compliance of any of the replans in relation to the organ at risk dose constraints. All participants (n=7), met the dose constraints following treatment planning with reduced margins of 0.7cm

following the implementation of RayPilot®. Figure 21 illustrates the amended treatment plans for participants using the recommended reduced margins. Included in the figure are the treatment beam arrangements and the isodose dose distribution for the high dose volume. It also shows the dose volume histogram (DVH) for the organs at risk as mentioned in table 13 documenting that all dose constraints for each organ at risk and surrounding structure are within planning protocol dose constraints.





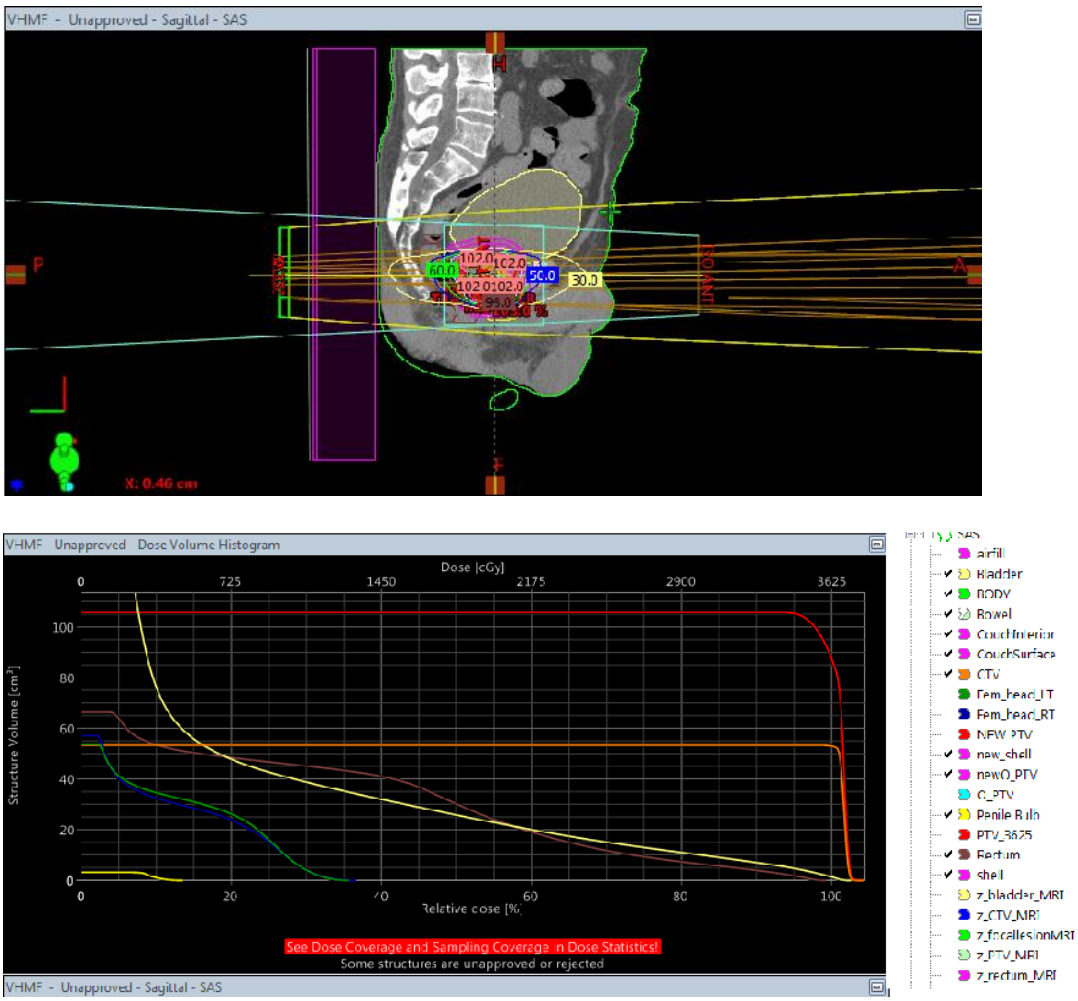


Figure 21 - An example of a patient re-plan using the reduced planning target margins. The first three images show the treatment beam arrangement (treatment arcs) and the isodose distribution within the patient using the CT planning scan. The last image is the dose volume histogram illustrating the dose constraints for the OAR's and structures defined in the list on the right hand side and confirms compliance with the predetermined dose constraints.

The reduction in planning margins creates a reduced planning target volume, in this case the prostate PTV and therefore a reduction in total irradiated volume. Table 14 demonstrates the reduction in irradiated PTV volumes for all seven participants.

Table 14 - Reduction in overall irradiated volume following implementation of feasibility calculated planning target margins. The median reduction in irradiated volume was 37.5% with an IQR of 35.2-39.3). This is a significant reduction in irradiated volume.

Patient	**Original Vol (cm^3)**	New Margin Vol (cm^3)	Percentage Reduction (%)
	(median = 105.7, IQR 91.1 – 125.7)	(median = 66.3 IQR 56.6 – 81.4)	(median = 37.5 IQR 35.2 – 39.3)
1	125.7	81.4	35.2
2	125.7	78.5	37.5
3	76.7	46.1	39.9
4	141.2	95.5	32.4
5	105.7	66.3	37.3
6	98.3	59.7	39.3
7	91.1	56.6	37.9

Table 15 outlines the mandatory and optimal planning constraints for both planning volumes and the organs at risk, however departmental policy requires further dose constraints to be achieved for the organs at risk of greater concern for toxicity, specifically the bladder and rectum. The evidence in Table 15 evidences the further dose constraint regulations for prostate SBRT and that all optimum values have been achieved using the reduced planning margins.

Table 15 - Dose and OAR dose constraints for feasibility plan using the calculated reduced planning target margins and using the inverse planning system. All dose constraints were met

for all patients following creation of a new treatment plan using the reduced planning margins as described and a dose of 3625cGy in 5 treatment fractions.

DOSE AND OAR CONSTRAINTS NEW MARGIN PLAN										
Structure	Parameter	Mandatory	Achieved	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
PTV CONSTRAINTS										
PlanPTV3625	V95.0%	99%	✓	99.8	100	99.5	100.3	99.9	100.1	99.1
CTV	V100.0%	99%	✓	99.9	99.7	101.3	100.8	99.8	100.8	100.1
OAR CONSTRAINTS										
Bladder	V100.0%	<5%	✓	2.24	1.56	0.51	5.1	1.35	4.19	0.88
	V81.0%	<25%	✓	10.12	5.48	2.38	24.96	10.68	17.03	4.69
	V68.0%	<50%	✓	22.91	922	4.26	43.2	16.03	25.23	19.95
Rectum	V100.0%	<3%	✓	0.28	1.56	1.66	0.13	0	0.23	1.76
	V95.0%	<15.0%	✓	1.8	3.03	2.45	5.72	2.26	3.71	1.66
	V88.0%	<30.0%	✓	4.62	5.89	3.92	10.34	4.73	6.38	5.72
	V81.0%	<50%	✓	9.13	8.46	5.53	14.25	6.99	9.08	8.53
	V68.0%	<60%	✓	23.22	17.85	9.53	23.96	13.03	15.4	16.14
	V54.0%	<70%	✓	37.78	34.75	14.01	37.58	23.44	23.63	26.44
	V41.0%	<80%	✓	36.21	54.69	15.44	49.6	40.39	31.2	31.31

The reduction in planning margins and consequently the reduction in irradiated volume did not have a detrimental effect on the concurrence with the regulated dose constraints and 100% of all subsequent plans achieved all of the aforementioned OAR dose constraints.

The research and resultant figures allowed for further re-planning of the participants to assess the viability of further hypofractionation using 800cGy dose per fraction, as opposed to the current 725cGy dose per fraction. The prescription assumption for this hypofractionated regime would be 2400cGy in three fractions. Due to the increased daily dose, it would follow that the OARs are at higher risk of acute toxicity and therefore, the plans required to be recreated to ensure the dose constraints mentioned are clinically achievable. Consequently, all treatment plans were recreated as mentioned previously, following the same protocols and steps using the reduced resultant margins and the resultant irradiated volumes, and a CTV dose of 2400cGy instead of the previous dose of 3625cGy. The results are as shown in Table 16.

Table 16 - Dose and OAR dose constraints for feasibility plan using the calculated reduced planning target margins and using the inverse planning system. All dose constraints were met

for all patients following creation of a new treatment plan using the reduced planning margins as described and a dose of 2400cGy in 3 treatment fractions.

DOSE AND OAR CONSTRAINTS WITH NEW MARGINS AND 2400cGY IN 3 FRACTION PLAN										
Structure	Parameter	Mandatory	Achieved	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
PTV CONSTRAINTS										
PlanPTV3625	V95.0%	99%	✓	100	100	99.8	100	99.9	100.1	100.3
CTV	V100.0%	99%	✓	99.8	100	100.5	100	99.7	100.8	99.9
OAR CONSTRAINTS										
Bladder	V100.0%	<5%	✓	0.35	0.36	0.26	3.53	0.46	2.9	0
	V81.0%	<25%	✓	1.23	0.91	1.27	8.01	2.15	6.88	0.66
	V68.0%	<50%	✓	2.55	1.47	2.37	11.9	3.2	10.14	1.65
Rectum	V100.0%	<3%	✓	0.84	0.74	0.95	4.6	0	4.08	0
	V95.0%	<15.0%	✓	1.83	1.46	1.81	9.78	1.43	8.89	0.21
	V88.0%	<30.0%	✓	3.56	2.41	2.91	13.8	6.9	13.54	1.37
	V81.0%	<50%	✓	6.01	4.01	4.49	18.04	12.21	18.73	4.43
	V68.0%	<60%	✓	13.96	9.24	8.97	29.67	26.89	32.62	13.07
	V54.0%	<70%	✓	33.09	20.81	18.18	47.06	48.87	52.7	30.01
	V41.0%	<80%	✓	42.53	37.84	33.09	58.28	66.28	56.95	51.87

5.7 OUTCOMES (DISEASE RESPONSE AND TOXICITY).

Following treatment, the participants had post radiotherapy follow up consultations at 6 weeks, 3 months, 6 months, 12 months and 18 months after completion. The outcome measure of disease response is the PSA level and this was taken at each review.

Table 17 and figure 22, show the completed follow-up assessment of PSA values. The maximum reduction in PSA was 93% and a minimum reduction of 56%; however, this was in patient 003 who did not complete the follow up process. The mean reduction in PSA following treatment was 84%.

All patients treated with the RayPilot® device in situ have shown a gradual reduction in PSA levels, indicating that ultra-hypofractionated external beam radiotherapy is comparable in success to standard fractionations.

Table 17 - PSA reduction during follow up duration (24 months) quantified through biochemical blood test results. All results measured in ng/ml.

PARTICIPANT	001	002	003	004	005	006	007
BASELINE	9.1	12.9	6.4	10.7	9.1	7.3	18

PSA 6/52	6.0	2.8	3	10.2	4.1	4.7	3.3
PSA 3/12	6.1	2.0	2.6	9.8	2.5	3.0	2.7
PSA 6/12	5	1.7	2.8	8.2	1.8	1.6	1.6
PSA 12/12	1.7	2.2	*	7.8	1.2	0.9	1.9
PSA 18/12	1.3	2.6	*	4.6	0.8	0.6	1.1
PSA 24/12	0.7	2.4	*	2.0	0.8	0.5	1.2

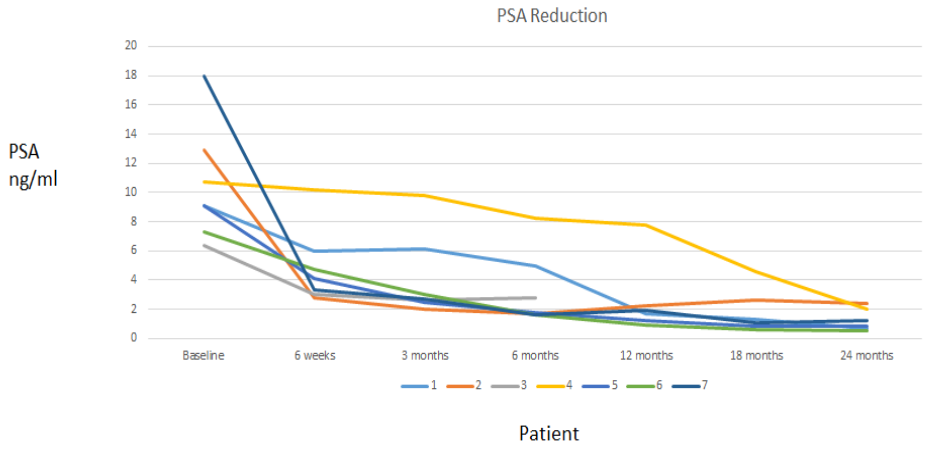


Figure 22 - Graphical illustration of reduction in PSA values during follow up duration (24 months) for all patients (n=7). Illustrates the gradual decrease of PSA detected by biochemistry blood analysis over time.

Patient toxicity was also recorded at post radiotherapy follow up consultations using the RTOG grading system. The results are show in Table 18. RTOG grades are 1-4 with severity increasing with each grade. Commonly, an increase in toxicity is evident acutely following completion of radiotherapy, which subsides and improves with time after completion. In regards to patient outcome measures in prostate radiotherapy, the principal concerns are in relation to genitourinary toxicity, lower gastrointestinal toxicity and erectile dysfunction (ED).

At the initial 6 week follow up 28.5% (n=2) of participants recorded genitourinary symptoms at RTOG 2, 28.5% (n=2) at RTOG 1 and 43% (n=3) at RTOG 0. The recorded outcomes are comparable with patients having standard fractionated radiotherapy, with RTOG 0-2 showing no or minimal changes to genitourinary

symptoms in relation to the pre-treatment baseline. At 3 months' post-radiotherapy 85% (n=6) recorded RTOG 0, meaning that genitourinary symptoms had reduced to pre-treatment levels. One patient (15%) recorded RTOG 1 symptoms; however, this had reduced from their recorded RTOG 2 level at the previous follow up. At 6 months 2 participants recorded RTOG 1, however, one of these had suffered from frequent urinary tract infections and the increase was attributed to symptoms of this rather than to the radiotherapy. By 12 month follow up, and subsequently 18 month follow up n=6 participants reported GU toxicity of RTOG 0; meaning that all participants had seen a reduction in acute toxicity to pre-treatment levels (Table 18).

Resultant gastrointestinal toxicity, at 6 week follow up recorded toxicity mirrored the GI toxicity with RTOG 2 of 28.5% (n=2), RTOG 1 of 28.5% (n=2) and RTOG 0 of 43% (n=3). At 3 months' post-radiotherapy there was a significant reduction in all reported toxicity with RTOG 1 of 15% (n=1) and RTOG 0 in all other participants. Six monthly follow up also showed a reduction to RTOG 0 for all participants and this remained stable at the subsequent follow up consultations.

Sexual function is also a concern for toxicity following prostate radiotherapy and was also included in the follow up. Four participants (57%) recorded RTOG 1 for erectile dysfunction with the remaining participants at RTOG 0. At 3 months, one participant exhibited RTOG 2 levels who had previously recorded RTOG 0. Two participants reported RTOG 1 which remained stable from their previous follow up and four participants reported RTOG 0. At 6 months 57% (n=4) reported RTOG 0, two participants were RTOG 1 and one participant recorded RTOG 2, which was an increase in sexual function toxicity. At twelve months post-radiotherapy, the participant who had reported RTOG 2 was still at this level, one participant had recorded RTOG 1 as previously reported and the remaining participants were RTOG 0.

Table 18 - Treatment outcome toxicity measures for all patients (n=7). The RTOG toxicity scoring system was used at every follow up consultation and assesses genitourinary (GU), gastrointestinal (GI) and erectile dysfunction (ED) toxicity, both acute and long-term post treatment.

PARTICIPANT	001	002	003	004	005	006	007
FU 6/52							
GU	2	1	1	0	2	0	0
GI	2	1	0	0	2	1	0
ED	1	1	0	0	1	1	0
FU 3/12							
GU	0	0	0	1	0	0	0
GI	0	0	0	0	1	0	0
ED	1	0	0	2	0	1	0
FU 6/12							
GU	0	1	0	0	0	1	0
GI	0	0	0	0	0	0	0
ED	2	0	0	1	0	1	0
FU 12/12							
GU	0	0	*	1	0	1	0
GI	0	0	*	0	0	0	0
ED	2	0	*	1	0	1	0
FU 18/12							
GU	0	0	*	0	0	0	0
GI	0	0	*	0	0	0	0
ED	2	0	*	1	0	1	0
FU 24/12							
GU	0		*	0	0	0	0
GI	0		*	0	0	0	0
ED	2		*	1	0	1	0

5.8 CHAPTER SUMMARY.

The results chapter provides the main findings of the clinical audit to address its aim. The results show that the RayPilot® real time motion management system is efficient in monitoring and allowing correction for intrafraction motion when used in conjunction with fiducial markers. The aim of the clinical trial was to assess the efficiency of the

RayPilot® system and to investigate whether it could be used to reduce planning target margins leading to further dose escalation and a reduction in the number of fractions required to deliver the treatment. The final data recorded by the RayPilot® real time motion management system was used to 'replan' the patients treatment plans using dose escalation of 800cGy per fraction and a reduced fractionation of three fractions. The data suggests that this is clinically achievable whilst maintaining current levels of toxicity and outcome.

The following discussion chapter discusses the results and the future applications of the findings in more detail.

6 DISCUSSION CHAPTER

6.1 CHAPTER SYNOPSIS

This discussion chapter will interpret and position the findings in the context of existing knowledge and will present conclusions based on the clinical audit findings detailed in the preceding chapters. It includes a comparison of the findings with the existing literature, an interpretation and explanation of the findings, acknowledgements of limitations and potential biases in the audit and the implications and applications for future recommendations for future research of the topic and the clinical application of the findings.

The aim of the clinical audit was to review and assess the efficiency of RayPilot® as a motion management device and investigate the impact this would have planning target margins in hypofractionated radiotherapy to the prostate and whether this technology would allow for planning target margin reductions and further dose escalation.

To fully assess the impact of RayPilot® real time motion management system on hypofractionated prostate cancer radiotherapy treatment, many multifaceted and complex themes had to be addressed (critical reviews of these are covered in the literature review chapter). As such, the discussion section will aim to look at these as separate entities and discuss how each process is influenced by the use of RayPilot® and the clinical impact this then has on the process that follows.

6.2 INTRAFRACTION MOTION MANAGEMENT DETECTED BY THE RAYPILOT® SYSTEM.

The intrafraction motion data results of this study are reported in Table 10 and 12 in the results chapter.

Prior to discussing these values, it is an important point of note that the tolerance for reviewing the real time motion data from RayPilot® was 2mm, in accordance with the wider PRINToUT trial protocol and the previously cited PACE trial data (Brand et al., 2019). As RayPilot® is not directly interfaced with the linear accelerator; the treatment radiographers are responsible for monitoring the intrafraction motion and manually interrupting the beam if the motion exceeds 2mm in any direction. Therefore, all

treatment delivery was halted at 2.1mm and not resumed until the prostate regressed back into tolerance or the patient was repositioned. As the device continually monitors motion until it is disconnected, the larger displacements were still recorded even though treatment was terminated. No patients were ever treated whilst the prostate was displaced over 2mm in accordance with the PRINToUT trial protocol, therefore, further justifying the filtering of data to exclude outliers of greater than 3mm. The assumption that no participant was irradiated whilst showing intrafraction motion larger than this magnitude, allowed for the removal of outliers. The tolerance of 3mm was assumed to give adequate time for the radiographers to manually halt the beam and accounts for any further motion in the time taken to halt treatment. A pilot study was undertaken by the LGR to assess reaction times of radiographers using the treatment console and the average time from the instruction to halt the beam and the beam being terminated was 1 second. The pilot study was undertaken to aid in protocol development and ensure validity in the methods of halting treatment delivery and assessing the impact this would have on intrafraction motion in the time required to halt treatment, however this was not part of the clinical audit, and it was purely a data gathering exercise. Although this pilot study was included in the initial commissioning of the system and data gathering for the implementation of the RayPilot® system, it was not included as an integral part of this research project. It is evident that due to the treatment having to be manually stopped by the radiographers, that this incorporates a further opportunity for human error in the pathway. Literature regarding operator response times and beam interruption yielded no results, however an audit conducted on the time taken for the treatment beam to be interrupted automatically using the auto beam hold technology on a Varian linear accelerator stated that beam off time was 34 ± 25ms (milliseconds) (Chen et al., 2020). In comparison to the pilot assessing reaction time of the radiographers operating the beam interruption, although the radiographers responded quickly, this is evidently not as quickly as the auto beam hold function on the linear accelerator. A future advancement of RayPilot® is to create an interface for the RayPilot® software with the Varian TrueBeam Linacs.

An interesting further analysis of data provided evidence that in 92% (n=22) of beam interruptions in treatment delivery, the patient motion continued to increase further justifying interruption of treatment, thus, concurring with previous literature that intrafraction motion is progressive and increases with duration (Jackson et al., 2018; Pang et al., 2020). Treatment delivery was interrupted 24 times (22.8%) throughout the total number of fractions (n=35) which resulted in 105 treatment arcs. Two

occurrences did not require repositioning in accordance with protocol as the prostate returned to the planned position, however, 22 instances of motion did not return to within the planned position tolerance concurring with the theory of prostate motion occurring as a gradual drift in motion rather than a sporadic systematic change. This correlates with a similar audit using the RayPilot® system of 56 treatment fractions which recorded that in 25 sessions (45%) the prostate exceeded the tolerance after the initial CBCT verification. In 10 cases (18%), a non-re-entering prostate shift (a shift that occurs where the prostate does not return to the PTV) occurred during the treatment delivery, requiring a beam interruption and a new CBCT (Panizza et al., 2022). This study was similar in design and protocol to the monitoring protocol used in the clinical audit. Within the audit if the intrafraction motion exceeded the predefined tolerance it was monitored for 20 seconds to assess whether the motion was sporadic or gradual, in the cited study this was done for 15 seconds prior to patient re-positioning. Although the cited article and the clinical audit shared similar methods, e.g. bladder filling protocols, micro-enema administration prior to treatment delivery the discrepancy in the ratio of beam interruptions and re-positioning required vary. The beam method delivery was different in the cited article that used flattening filter free (FFF) beam delivery. For the case of linear accelerators fitted with a flattening filter an attenuator is located between the primary collimator and the monitor chamber and its main role is to make the photon beam dose distribution uniform at reference depth within the allowed variations. The flat dose profiles with a homogenous dose variation across the beam provide the ease in patient dose calculation during treatment planning. Flattening filters require lower dose rates and are typically used for IMRT or IGRT treatment delivery. However, modern linear accelerators have the option to use flattening filter free beam delivery. The removal of the flattening filter results in less variation of the total scatter factor with field size; and less variation of the shape of lateral dose profiles with depth which can lead to lower doses to normal tissues and organs (D'Agostino et al., 2016). Importantly in the context of SBRT treatments which tend to have larger doses per treatment arc or an increased number of treatment arcs, the dose rate can be higher in FFF beam delivery by a factor of 2.2 – 5.5 times depending on the beam energy being used (Sharma, 2011). Therefore, by increasing the dose rate, the overall treatment time is shortened considerably. This would account for the discrepancy in the audit data and the results cited in the study of beam interruptions and required repositioning. If the treatment time was reduced, the likelihood of intrafraction motion, and the corrections required, is reduced.

The results found in this study concur with findings in previous studies that although prostate motion occurs in all directions (Poli et al., 2016), the greatest intrafraction motion displacements occur in the longitudinal (superior/inferior) and vertical directions (anterior/posterior). Intrafraction motion was less in the lateral (left/right) direction. Intrafraction motion studies have been shown to share comparable methodologies to increase efficacy of results, the main variation between studies is the imaging modality used to assess the intrafraction motion, for example kV imaging, CBCT or ultrasound (Baker and Behrens, 2016; Hunt et al., 2016; Dang et al., 2018; Jackson et al., 2019). The importance of these findings is relevant to the use of anisotropic planning margins e.g. larger planning margins used for the longitudinal and vertical directions to account for greater variations with smaller planning margins being used for the lateral directions due to smaller variations. This would then reduce the overall irradiated volume. Greater motion in the anterior/posterior direction, closely followed by the superior/inferior direction is widely reported in the literature (Frank et al., 2008; Poli et al., 2016; Pang et al., 2018; Ghaffari et al., 2019; Richter et al., 2020). The larger vectors of motion are recorded in the vertical and longitudinal direction due to the variations in rectal volume and the natural travel of gas and air in the rectum, rectal matter or gas follows a downward trajectory and as it fills the rectum the rectal volume fills like a tube from anterior to posterior. As the prostate is located immediately in front of the rectum, this attributes the vertical and longitudinal measurements to the passage of rectal gas and intrafraction motion (Tondel et al., 2019). Gas in the rectum does not expel laterally therefore, the prostate lateral motion will be less than that of the other directions. Frank et al. (2008) reported for 15 patients, the mean systematic internal prostate variation was 0.1 +/- 4.1 mm and 1.2 +/- 7.3 mm in the anterior/posterior axis, -0.5 +/- 2.9 mm and -0.7 +/- 4.5 mm in the superior/inferior axis, and 0.2 +/- 0.9 mm and -0.9 +/- 1.9 mm in the lateral axis, respectively. The mean magnitude of the three-dimensional displacement vector was 4.6 +/- 3.5 mm for the prostate. Within this clinical audit, the results were mean lateral, longitudinal and vertical motion of 0.1cm (SD± 0.51cm), 0.3cm (SD± 1.32cm) and 0.45cm (SD ± 1.62cm). However, this included all outliers. This accounts for the large variation between the results of the clinical audit and the above literature. The outliers in this audit are discussed further in this chapter; however, the large outliers were attributed to movement of the treatment couch. When the outliers are removed, the mean motion values in the lateral, longitudinal and vertical directions were 0.1cm (SD± 0.1cm). This is more comparable to the literature and the small value corresponds to the outlier measurement being set at 0.3cm. Pang et al. (2018)

assessed the intrafraction motion in 20 patients using 486 pre-treatment CBCTs and reported that the mean prostate motion of 5.8 ± 3.1 mm for all treatment fractions, with a maximum variation of 20 mm. This resulted in a dosimetric impact of approximately 5% of the treatment fractions, the prostate volume receiving 100% of the prescription dose decreased dramatically (15-20%) compared with its intended dose. These results clearly demonstrate the relationship between intrafraction motion and the dosimetric impact on perceived target dose.

However, clinical oncology is a fast-evolving discipline and as time and clinical techniques advance, for example the use of fiducial markers, pre-determined bladder and rectal preparation techniques and treatment planning constraints, there has been a shift in the literature evidencing smaller intrafraction motion displacements. A later subsequent study from Ghaffari et al. (2019) reported that overall mean values of shifts were 0.22 mm, 0.23 mm and -0.43 mm in the vertical, longitudinal and lateral directions, respectively. Richter et al. (2020) recorded that intrafraction monitoring resulted in a mean prostate displacement of (-0.06 ± 0.49) mm, (-0.09 ± 0.61) mm and (-0.01 ± 0.78) mm in the SI, LR and AP directions, respectively. The motion recorded by RayPilot® within this clinical audit is concurrent in the lateral, longitudinal and vertical directions. The unfiltered data shows larger magnitude of directional motion in all vectors, with the mean lateral, longitudinal and vertical displacement of 0.1cm, 0.3cm, and 0.4cm respectively. This is attributed to the device continually monitoring patient motion which also take into account patient motion out with beam delivery, for instance when the device is attached to the recording system it was not always in the treatment position for beam delivery. The larger vectors of motion were seen prior to or post beam delivery which relates to when the patient is being positioned. In context, the results obtained in this study are comparable to the more recent studies conducted into prostate intrafraction motion. In part, this can be attributed to a more global approach to treatment techniques and planning preparation. Using evidence-based practice approach, for example WHO guidelines, National Institute for Clinical Excellence (NICE) guidelines and current literature, treatment delivery is more uniform and targeted, and standardised bladder filling protocols allows for the collation of robust multi-centre data. Many clinical sites employ the use of fiducial markers in situ to aid in prostate visualisation and verification.

The software identifies the fiducial markers and the required shifts are populated using a 2D/2D algorithm. The resultant shifts are applied prior to treatment accounting for

interfractional positional changes prior to treatment delivery. Typically, when using IGRT, radiographers match and align the daily images with the original treatment planning images, sometimes with the help of computer-assisted registration software, the alignment should be based on imaged target volumes and other anatomical structures. The process in this form is subjective due to the correct alignment of anatomical structure, image registration quality, target volume or anatomical changes, which could potentially lead to incorrect patient set-up. Therefore, the use of fiducial markers and image registration and matching software can reduce the potential for human error due to its objective nature (Handsfield et al., 2012). However, radiographers will always be required to carry out a physical sense check of the match result to ensure the software had correctly identified the fiducial markers. A recent study collated retrospective imaging and used a produced phantom to assess the precision of the software in identifying implanted fiducial markers (Korpics et al., 2019). Fiducial marker positions were found to be reproducible with 0.5 mm of precision. In addition, fiducial markers were identified correctly within 3mm of actual position in 60% of instances, not identified in 33% and not found in 7% of instances. Within the clinical audit, there were no instances of fiducial markers not being identified on CBCT or kV imaging. The process of fiducial marker matching in the audit was done using the auto-match software on the linear accelerator OBI system. The reduction of human error in matching the placement of the fiducial markers has clinically reduced the magnitude of intrafraction motion and has been an integral component of many recent research studies such as those cited. The auto matching software records the position of the fiducial markers, and therefore the prostate, and this was then matched automatically by the OBI system to the treatment digitally reconstructed radiograph (DRR). DRRs are reference images generated from the 3D CT data set used for set up verification. The DRRs are created on the lateral and anterior planes to allow for verification in all dimensions. Once the orthogonal kV images were acquired, the auto match process was carried out. The auto match locates the fiducial markers and then gives displacement values and the shifts required to the treatment isocentre to allow for online correction prior to treatment delivery. Following the auto match, radiographers assess and review the auto match to ensure that all fiducial markers were detected and the match is correct. If the auto match process failed to detect a fiducial marker correctly, this was then done manually be the treatment radiographers. Detection of the fiducial markers can be affected by artefacts in either the initial DRR or the acquired online images, for example calcifications within the prostate, which would then require correction by the

radiographers. Within the clinical audit, although markers were detected in all patients and all acquired imaging, manual amendment of the marker match was required in some cases. As this is a common occurrence in IGRT for prostate radiotherapy, this is not recorded. For the purpose of the audit aims, this is not a detrimental limitation; however, it would have been of interest to record the variations in fiducial marker detection to assess whether manual matching of some fiducial markers had any impact on the recorded intra-fraction motion. However, the literature and current clinical practice concludes that implanted fiducial markers greatly reduce interfraction uncertainties in prostate radiotherapy and could be used to reduced and monitor intrafraction motion with the possibility of fiducial markers being used to aid in margin reduction.

In this clinical audit, fiducial markers were used as the primary 'matching' modality. The three fiducial markers were matched and a shift to the treatment isocentre was done from these matched co-ordinates. The RayPilot® transmitter position was also matched; however, this was for data collection purposes rather than treatment position verification. The main function of the RayPilot® transmitter device is as a real time motion monitor and although the manufacturers suggest that it could be used independently of fiducial makers, this was deemed unreasonable until experience and competence had been gained in the system in the clinical application and setting. At present, no literature has been found to suggest that any department using RayPilot® use the transmitter as an independent isocentre positioning modality. Future developments may allow for progression towards this but as yet, this has not been achieved in the clinical setting.

For contextual clarification, intrafraction motion is the motion that occurs in the target volume during treatment delivery. Primarily intrafraction motion is attributed to changes in rectal volume, intrafraction bladder filling and patient motion. Erratic motion of the prostate, including rotation, was also reported in several studies (Kupelian et al., 2007; Ng et al., 2012; Hunt et al., 2016; Chi et al., 2017), again primarily attributed to bladder and rectal variations. To mitigate this the clinical audit implemented a bladder and bowel preparation regime for all patients. As described in the methodology chapter and justified in the literature review chapter, the participants were advised to drink a predetermined volume of water (300ml) approximately 30 minutes prior to treatment delivery, thus ensuring comparable bladder volumes throughout each treatment. This approach used in the clinical trial concurs with the results of a meta-analysis and systematic review of 417 patients in

ten cohort studies and one randomised controlled trial. The results of which state that bladder filling volumes of 300-400ml is optimum for prostate SBRT. It also suggests that the higher the volume of water consumption, the greater the variation observed in treatment versus planning CT bladder volume (Chen et al., 2021). This could be attributed to patient comfort, as volumes over 400ml would be time consuming for patients and this volume of water in the bladder for an extended period of time would lead to patient discomfort, especially if bladder control is compromised by urinary symptoms. Although the methodology of the meta-analysis is sound, the variations in methodology of the relevant literature used in the meta-analysis was not comprehensively explained or quantified. It was stated that differing modalities of assessing bladder volume e.g. US or CT and that patients must be undergoing prostate radiotherapy. The inclusion criteria and the results did not distinguish between the treatment modalities. This would suggest that on the evidence and literature assessed, optimum bladder volume is independent of the treatment technique, dose and fractionation. Each participant also administered a micro-enema prior to bladder filling to attempt to mitigate rectal variations. There is vast literature on the standardisation of bladder filling and bladder filling protocols. The consensus throughout the literature is that as long as the volume of the bladder is consistent throughout treatment, the method of achieving this will be department dependent, e.g. a designated volume of water to be ingested prior to SBRT, a comfortably full bladder based on the patient's perception or volumetric assessment using CBCT. Commonly, the literature suggests water intake for the patient to be between 150ml and 300ml (Kole et al., 2015; Byun et al., 2016; Tsang and Hoskin, 2017; Nasser et al., 2021) which the clinical audit complies with. Although there are varying approaches to achieving standardised bladder filling throughout treatment such as catheterisation, patients following departmental guidelines is the least clinically invasive method of doing so.

Throughout the duration of the clinical audit, it became apparent that the approach to bladder filling relied heavily on patient compliance. Patients were asked to inform the radiographers of the time that they completed drinking the determined amount of water. This was recorded and treatment was timed to begin within 30 minutes of this. On a number of occasions, patients failed to record accurate timings for this and could give an estimate of within five or ten minutes. Although this was not overly detrimental to the treatment bladder volume due to bladder filling time, an exact record could not be made. The occurrence of patient deviation is a common problem within prostate SBRT. Smith et al. (2020) reported that in the cohort of 200 fractions, bladder-filling

guidelines were followed on 91 occasions. For the remaining 101 fractions, volume of water and/or wait time was altered to meet optimal bladder volume or provide patient comfort. Within the clinical audit patients were made aware of the importance of following the bladder filling and bowel preparation requirements however, this could not be assessed until the first CBCT was acquired and bladder volume was compared to that in the initial CT planning scan. Variations were seen which resulted in patients having to abandon that treatment attempt to drink more water or to expel rectal gas. If this was a continual pattern with a specific patient, the bladder filling protocol could be amended, for example, the waiting time from drinking to treatment could be shortened if patient comfort was a concern, or the volume of water to be consumed could be amended as long as this still achieved comparable volumes to the CBCT. In all circumstances, any amendments to bladder preparation protocols were recorded on the patient's radiotherapy prescription sheet. In the clinical audit, this was required for two patients. One patient was suffering with bladder control and could not hold the required volume of water for longer than twenty minutes, in this case the wait time was reduced and volumetric comparison of the CBCT did not show any significant variations to that of the treatment plan ensuring that the bladder dose constraints were still clinically achievable. The other patient required to drink a greater volume of water than stated to achieve comparable bladder volumes between treatment CBCTs and the treatment plan. Although there was no clinical reason for this, some patients do not fully void their bladder prior to the initial planning scan leaving a residual amount of fluid, so therefore, when they drink the stated amount the volume is larger. As the treatment conditions have to recreate the initial planning scan conditions, and essentially bladder volume, this is routinely amended on treatment. Recent literature reported assessing the bladder volume on the pre-treatment CBCT of ten patients undergoing prostate SBRT that the CBCT bladder volumes ranged from 78% smaller to 163% larger than that outlined on the initial CT planning scan over the course of the treatment fractions (Gorovets et al., 2018). However, the variation in bladder volume over the whole course of treatment did not negatively affect the dosimetric outcome of the treatment plan and met the stated dose constraints of the treatment plan. The occurrence of this coincided with patients starting to experience lower urinary tract symptoms (LUTS) such as bladder irritation, leading to them not complying or being unable to comply with the drinking protocol. Byun et al (2020) analysed 85 patients throughout the course of five fractions of SBRT and also found that bladder volume was significantly decreased, up to 19%, by the final fraction. This was again attributed to the evidence of LUTS. One patient in the clinical audit

struggled with compliance, not due to LUTS but due to the fact that they perceived the treatment duration to be too lengthy so there were frequent discrepancies with the patient reported volume drank and the timeframe in which this was done for this patient.

Patient compliance is a clinical issue that is hard to mitigate in radiotherapy treatment. The patient cohort were all given written information along with verbal instructions regarding bowel and bladder preparation both prior to and during the radiotherapy treatment. The importance of following the devised preparation requirements in terms of minimising dose to surrounding structures and the consequences in terms of side effects and late toxicity that they could experience is also made abundantly clear to the patient to aid in compliance. Clinically as much as possible was done to increase patient compliance and education in the hope that they will follow the required protocols.

Clinically, patients could undergo a bladder scan prior to treatment delivery to ensure consistency in bladder volume. Although this is not a time-consuming task, it would have an impact on staffing resources as it has to be carried out by an entitled member of staff, it would require either extra time in the treatment room or the use of a clinic room within the department. Another consideration must be given to the inclusion of unnecessary procedures for the patient. A bladder scan requires the use of ultrasound technology, which is not governed by ionising radiation regulations (IRMER), however, as the imaging protocol for the audit states the patient requires a pre-treatment CBCT daily, on which bladder volume can be assessed, this would mean that the bladder ultrasound would be an unnecessary medical procedure. Conversely, the argument could be made that if the bladder was scanned prior to the pre-treatment CBCT and deemed unacceptable, the patient would then not require a further pre-treatment CBCT if they have been removed from the treatment couch to further fill their bladder, leading to a smaller exposure to ionising radiation. Although bladder scanning provides details of the bladder volume it does not give any further volumetric detail e.g. bladder position or shape after filling which would still require to be assessed prior to treatment delivery. A retrospective study on twenty patients, compared pre-treatment bladder ultrasound scans to pre-treatment CBCT in 390 CBCT data sets and concluded that on average, the bladder ultrasound scan underestimated the bladder volume on CBCT by 28.3% ± 14.3%, but a limitation of this study was the time from bladder ultrasound measurements to CBCT was not recorded (Reilly et al., 2020). In a validation study comparing bladder volumes

recorded using ultrasound bladder scanning compared to CT assessment of the bladder volume found that there was a mean increase of 28 ± 30 ml between the ultrasound estimate and the CT estimate, which was deemed as a clinically acceptable difference. They concluded that bladder scanning was a feasible option for prostate SBRT patients and that based on the findings that bladder volumes assessed on pre-treatment CBCT should be at least 50% of the planned volume to avoid a detrimental effect to the dosimetry of the treatment plan (Smith et al., 2022). The study was carried out on a relatively small cohort of 19 patients however, to minimise intraobserver variability each patient has three bladder scans acquired and the mean was used for analysis. Using the mean reduced the observer variability as these scan were reported by one observer reduces observer variability. The study would have been enhanced if this study included interobserver variability in the clinical setting. The study also highlighted the time difference between the bladder scan and the CT scan as less than three minutes which is a contributing factor to the small variations in bladder volume recorded, 28±30ml). In clinical practice, this is something that would require monitoring. In the clinical setting, this may be difficult to achieve due to availability of the treatment room or clinic rooms, trained staff availability, equipment failures or breakdowns. An increased time scale between bladder scanning and the acquiring of the pre-treatment CBCT could lead to an increase in recorded measurement variation. Therefore, in the current clinical setting, until a pathway has been determined, it would be necessary to still use both bladder volume scanning modalities in conjunction. In terms of future clinical audit of the process, it would be of great interest to compare the bladder scanning data to that of the pre-treatment CBCT and investigate the correlation of both to determine the best bladder assessment modality prior to treatment or whether both are required to be used in conjunction.

It is also widely reported that treatment duration adversely affects intrafraction motion. Shelton et al. (2011) found that observed intrafraction prostate motion during radiotherapy is greater with increasing session time. A further study agreed that VMAT, due to shorter treatment sessions, resulted in significant reduction (30%-40%) in intrafraction displacements and therefore the intrafraction motion of the prostate (Ballhausen et al., 2015). They also anecdotally suggested that "*prostate intrafraction motion was a random walk and neither static (like inter-fraction setup errors) nor stationary (like a cyclic motion such as breathing, for example). The prostate tends to drift away from the isocentre during a fraction, and this variance increases with time, therefore, shorter fractions are beneficial to the problem of intrafraction motion*."

"Consequently, online tracking and position correction should be considered as the preferred approach to counter intrafraction motion". (Shelton et al., 2011; Bellhausen et al., 2015; Tong et al., 2015; Pang et al., 2018). When evaluating intrafraction motion it is imperative to address the correlation of treatment delivery time and the effect on intrafraction motion. It is inherently obvious that the longer a patient is in the treatment position the likelihood of intrafraction motion increases. A retrospective analysis of 38 patients equating to 770 monitoring sessions reported that at 60 s, a prostate displacement >2 mm was present in 0.67% of the data. The percentage increased to 2.42%, 6.14%, and 9.35% at 120 s, 180 s, and 240 s, respectively. The mean monitoring session was 254 s. However, they also state that with increased treatment time, larger prostate displacements up to 18.30 mm could be observed. The study did not highlight the rationale for the mean monitoring time or whether this was from the initiation of treatment or time from the acquisition of pre-treatment imaging. It would be assumed from the data that the monitoring time would be from the initiation of the treatment delivery due to the 240 s timeframe (this would equate to beam delivery); however greater clarification would be beneficial to the findings (Sihono et al., 2018). A Swedish single-centre retrospective analysis of nine patients undergoing SBRT used intrafraction motion data to assess the required PTV margins dependent on treatment duration. The treatment time was between 1500s and 6000s. Imaging was performed with an average interval of 19–92 s during treatment. The study reported that prostate shifts are time-dependent and resulted in correction margins (PTV) of 0.5–1 mm at 40 s, 0.9–1.55 mm at 60 s, 1.5–2.6 mm at 100 s, 1.9–3.6 mm at 150 s, 2.2–4.2 mm at 200 s, and 2.6–5.6 mm at 300 s. This depicts the increased change in prostate position during increasing treatment duration. Although the methodology of the study was sound, the intrafraction motion values were represented in a table format making it difficult to interpret the mean intrafraction motion used in the calculations of the PTV requirements to ensure optimal dosimetric coverage of the target volume (Oehler et al., 2022).

Prostate intrafraction motion is variable and will alter in all vectors at unknown magnitudes, therefore intrafraction motion is not a linear process, and the prostate may move away from the designated target volume but may return to position and then move again. Therefore, prostate motion is difficult to predict as it may sporadically move but return to its original position. Patients become uncomfortable and therefore are more likely to move. In relation to treatment delivery, RayPilot® does not have any effect on the planned execution time of the treatment beams. RayPilot® does however; produce real time tracking which can lead to the beam being

terminated and repositioning may have to be carried out. Patient repositioning required further orthogonal kV imaging to be acquired and this can add on time to the treatment delivery. In this study, the median treatment time was 17.2 minutes (IQR 15.1 – 18.5 minutes) with the minimum treatment time being 13.3 minutes and the maximum treatment time of 99.2 minutes as shown in Figure 18. In this clinical audit, these values represent the overall duration of treatment from initiation of the pre-treatment imaging until completion of the final post-treatment CBCT. Patients that had to have additional imaging were on the treatment couch longer which would have influenced the overall intrafraction motion displacement values as evidenced in the above literature. The treatment duration of this clinical audit is comparable to a recent study of 13 patients and 56 treatment fractions, using the HypoCath® electromagnetic transmitter stated that treatment times averaged ten minutes. However, this study did not provide the minimum, maximum or standard deviation of this value (Faccenda et al., 2023). The variation from ten minutes in the cited study and the mean 17.2 minutes calculated in this study can be attributed to the cited study using the FFF method of beam delivery described previously in the chapter. The maximum treatment duration of 99.2 minutes in this clinical audit occurred on the first patient treated using the RayPilot® system. As stated, this was the time from the initiation of the first pre-treatment CBCT until the completion of the post-treatment CBCT. In this fraction, the patient was removed from the treatment couch on three occasions to empty and refill their bladder due to patient comfort. This accounts for the extended treatment duration as the system was recording as being active during this whole time period. This may have been due to inexperience with the system as the patient remained active on the RayPilot® VDU. If a patient has been opened on the system and is then removed, even before treatment delivery is completed, it makes this treatment session inactive. To remedy this, the patient information data must be amended to add another treatment fraction, for example changing the total fractions for the patient record from 6 (day zero plus five treatment fractions) to 7 (or more if required for subsequent fractions). If the audit was to be repeated it would be a recommendation that the calculation of overall treatment duration was carried out using the treatment time stamp data from the linear accelerator software. The linear accelerator software clearly states imaging time stamps, beam on and off timestamps and this would clearly indicate the actual overall time the patient was on the treatment couch for which would provide a more accurate representation of overall treatment duration.

The overall treatment duration also reduced throughout the timeframe of the clinical audit as shown in the collected data. The main factor believed to attribute to this was the increasing experience and confidence of the trained treatment radiographers not only in the process itself but also in the equipment and image requisition and clinical decision making in relation to image verification and matching. Although the process of image matching, verification and repositioning is the same as current clinical protocols in the department, the number of images required is much greater, especially if the patient requires repositioning during treatment. Due to the increased daily dose the planning target margins are much 'tighter' than standard prostate treatments and can therefore, be more detrimental to toxicity outcomes. This was seen to extend the time that the radiographers required to assess the initial CBCT in comparison to the treatment plan. Over time, the treatment radiographers became more confident in what would be an acceptable variation prior to delivering treatment.

As the training of the treatment radiographers required to be executed and established on patients actively on treatment, it was crucial that this did not affect treatment duration for the reasons outlined above. As such, training for treatment radiographers was carried out in a 'staged' manner. The radiographer would do each component of treatment delivery following one specific patient. For example, on day one, they would be responsible for co-ordinate entry, day two they would focus on monitoring the RayPilot® real time motion data and then subsequent treatments they would be responsible for image verification and treatment. By ensuring competence in each component of the system, this meant that any increase in treatment duration was only incurred in one stage of the process.

Increasingly, researchers are accounting for treatment duration by reporting the results of intrafraction motion studies contextualised as the duration of overall treatment time that the target volume was displaced. Tong et al. (2015) conducted one of the largest and most recent studies investigating intrafraction motion using a real time tracking system (8660 treatment fractions). The American based study looked at not only the displacement values but also the percentage of the treatment fraction that the prostate position had altered. The study tracked intrafraction motion of the prostate during 8,660 treatment fractions for a total 236 patients. The results showed that the percentage of fractions in which the prostate shifted by > 2, 3, 5, and 7 mm off the baseline in any direction for > 30 s was 56.8%, 27.2%, 4.6%, and 0.7% respectively. The percentage of tracking time during which the prostate shifted > 2, 3, 5, and 7 mm was 27.8%, 10.7%, 1.6%, and 0.3%, respectively. Sihono et al., (2018),

in their previously cited study, concluded that the percentage of treatments for which prostate displacement was ≤2 mm was 97.01%, 92.24%, and 95.77% in the LR, AP, and SI directions, respectively. At 60 s, a vector length of prostate displacement >2 mm was present in 0.67% of the data. The percentage increased to 2.42%, 6.14%, and 9.35% at 120 s, 180 s, and 240 s, respectively. The data collated in this study, not only concurs with the results in the literature, but also evidences the correlation of time and intrafraction motion.

The results of this clinical audit show that the RayPilot® data collated showed comparable results to previous literature (Tong et al., 2105; Sihono et al., 2018). The percentage of tracking time during which the prostate displacement ≤3mm was 91.9%, 91.7% and 87.7% in the LR, SI and AP directions, suggesting that when using the stipulated tolerance of 2mm, the prostate would have been in an acceptable position in all directions for the majority of the treatment. It is worth noting that these values are from the raw data and were calculated prior to the outliers being removed as described previously, to provide a robust measurement of variation and an accurate representation of variations without manipulated data being used, increasing the validity of the measurements. Lateral displacement values for >2mm, >3mm and >5mm were 11.6%, 8.1% and 6.7% respectively. Longitudinal displacement values for >2mm, >3mm and >5mm were 10.7%, 8.3% and 7.5% respectively. Vertical displacement values for >2mm, >3mm and >5mm were 15.6%, 12.3% and 8.8% respectively. These results are comparable with the studies cited in this chapter and the previous literature review (Kupelian et al., 2007; Hunt et al., 2016; Chi et al., 2017; Koike et al., 2018; Roch et al., 2019). Critically within the audit, treatment delivery was interrupted when intrafraction motion breached the threshold of >2mm. Therefore, although ultimately irrelevant to the margin calculations, motion >3mm and >5mm was collected for further research purposes. The proportion of time the intrafraction motion was >2mm was used and reviewed to assess whether beam interruption was warranted at the time of execution.

The main outliers for all vectors occurred on fraction four of the treatment schedule. At this point, the majority of patients had reported an increase in urinary symptoms following treatment. This was established through oral information only through daily discussions with the patients throughout the treatment fractions. As with all patients undergoing radiotherapy treatment, their general well-being and any changes in symptoms or concerns are reviewed and assed by radiographers through conversation and further multi-disciplinary opinion is sought if required. These

discussions are not recorded and therefore evidence of occurrences of changes in symptoms, such as the LUTS experienced by patients towards the end of the fractionation schedule becomes anecdotal. A recommendation if the audit was to be repeated would be to record these instances and grade them in accordance with the RTOG toxicity grading system. As the patients in the clinical audit do not complete toxicity assessments until the first follow up six weeks after completion of SBRT, this would provide conclusive information on the onset of symptoms along with the duration of the symptoms experienced. Urinary toxicity is experienced by patients in an accumulative fashion and it is common for patients to report symptoms approximately two thirds of the way through treatment schedules especially when exposed to higher daily doses (Wang et al., 2021). Lower Urinary Tract Symptoms include urinary retentive symptoms, incomplete emptying, frequency and urgency, poor flow, and radiation cystitis. The three patients who had the highest variations in displacements, all reported urgency at the time of that fraction causing them to tense and move on the treatment couch. The patient who exhibited the greatest displacements in the study discussed the fact that he had lifted himself off the treatment couch to try and reposition himself due to discomfort caused by urgency, thus, explaining the variations of over 7cm, the incidence of which also seen in the results of previous studies (Su et al., (2011); De Leon et al., (2019).

The RayPilot® software records an overall treatment time, from instigation of the first set of imaging until the completion of the post treatment CBCT, so this includes the time that a patient may have been removed from the treatment room. For example, the maximum time of 99.2 minutes occurred in the patient who had to repeat the treatment process, including bladder filling and reimaging, and was therefore, out of the treatment room for a minimum of 15 minutes. Outliers could also have been a consequence of radiographers re-entering the treatment room. Patients commonly move to address the radiographers or assume that because they have entered the room treatment has been halted and that it is safe to move if they need to. For example, the largest motion value recorded of > 7cm was verified to be at the end of treatment by reviewing the recorded time stamp. It was concluded that the value was due to the treatment couch being moved to address the patient without disconnection of the RayPilot® transmitter. The software continuously monitors and records motion until the device is disconnected regardless if it is during treatment delivery or patient set-up. For future comparisons, it is now an essential step that the transmitter is disconnected prior to moving the patient immediately at the end of treatment. Regrettably, this was not discovered prior to the study, if it had been an independent

time check could have been employed giving validity to the effect of overall time on the intrafraction motion results. For future research and development of the technique and process current departmental protocols have been amended to address this and increase rigour and validity of the resultant findings.

The findings of the clinical audit concur that RayPilot® is an effective and accurate method of quantifying real time motion of the prostate providing valid, effective and clinically expected results.

The evidence and literature supports and reiterates the use of real time tracking to quantify intrafraction motion. It is also evident that real time intrafraction motion management can have an impact on the correct use of dosimetric margins. It also alludes to real time intrafraction motion monitoring allowing for reduction in dosimetric margins and therefore allows for dose escalation.

6.3 VAN HERK MARGIN FORMULA.

The intrafraction motion values have been discussed previously in this chapter and in the results section. As such, the mean intrafraction motion was used to calculate the resultant required planning margins in the anterior/posterior, left/right and superior/inferior directions.

The margin formula used in this study was the Van Herk Margin Formula. As previously discussed, the VHMF ensures that 90% of patients in the population receive a minimum cumulative CTV dose of at least 95% of the prescribed dose. The VHMF is $M = 2.5\ \Sigma + 0.7\ \delta$ (Equation 1). Where Σ represents the quadratic sum of systematic uncertainties in treatment set up and δ represents the quadratic sum of random uncertainties in treatment execution. It states the contribution of systematic errors is approximately 1.5 times greater than that of the random error component ($2.5\Sigma + 0.7\delta$). Therefore, systematic errors contribute to a larger portion of the PTV than random errors, suggesting that reducing the overall Σ value results in a better shrinkage effect on the required PTV margin. However, random errors such as intrafraction motion have to be taken into account when deducing target margins as their contribution is not clinically negligent.

Equations 5-7 evidence the results of the VHMF calculations using the resultant intrafraction motion data collated from the RayPilot® software records. The resultant

margin requirements are 0.7cm in the lateral direction (left/right), 0.7cm in the longitudinal direction (superior/inferior) and 0.7cm in the vertical direction (anterior/posterior). The uniformity of these values is expected given the similarity on intrafraction motion data for all vectors and directions.

A limitation of the VHMF is that it assumes the target volume is homogenous and clinically this is not the case. The formula assumes that the dose distributions created in the plan conform exactly to the previously derived PTV. The recipe does not take into account the target size, variations in tissue density along the path of the treatment beams or the type of treatment being used, for example IGRT or VMAT techniques (Witte et al., 2017). McKenzie et al. (2000) firstly suggested that the appropriate size of PTV margins is inversely proportionate to the number of radiotherapy treatment beams present in the treatment plan. The number of treatment arcs utilised in planning for VMAT prostate radiotherapy is normally less than that required for past conformal techniques. In VMAT or IGRT the beam modification is such that the shielding of multi-leaf collimation reduces the penumbra of the beam. The VHMF is based on the assumption that the dose distribution falls away at the edge like a normal cumulative distribution function, however this does not happen. The effect of more beams is to “spread out” the exit dose around the target, resulting in a smaller σ coefficient than in the original VHMF. This is relevant in the application of the margin recipe in relation to the techniques used in clinical departments, and with advances in technology and treatment techniques. However, the formula has not evolved to consider this.

The VHMF considers systematic and random errors devised at time of calculation (PTV margin = 2.5Σ + 0.7σ (where Σ = quadratic sum of systematic deviation of systematic errors and σ = quadratic sum of systematic displacement of random errors. Van Herk 2004). Included in the calculation used are organ delineation errors, set-up errors, organ motion and intrafraction motion. Due to the advances in treatment techniques and technology, systematic errors have greatly been reduced and organ motion is accounted for and corrected prior to treatment (Ferrara et al., 2020). Therefore, the value of organ motion in the systematic component of the calculation becomes zero due to all systematic errors being corrected for using isocentre repositioning prior to treatment delivery. It has been suggested that with increased image guidance frequency the systematic error for organ motion can be decreased therefore allowing for the decrease of CTV-PTV margins without compromise on the coverage of the high dose volume (Gupta et al., 2018). The study analysed 2700 pre-

treatment set up images and the dataset was used to recreate planning margins using the resultant set-up error data. Although this is a justified methodology, the use of pre-treatment CBCT's only does not take into account intrafraction motion or intrafraction variations in bladder or rectal filling which could affect the dosimetric volumes of the PTV. If the study used pre-treatment and post-treatment CBCT to assess intrafraction volumetric variances this would have led to more robust results concluding that the high dose coverage was not compromised throughout the treatment duration. Pramanik et al. (2020) also concluded that IGRT reduced set-up errors to effectively zero, but the data collected was anatomically multi-site therefore, reducing their pelvic sample data meaning that the results may not be representative of the whole population. However, even with perfect IGRT conditions factors of organ delineation and intrafraction motion continue to have a significant impact on the margin calculation. Clinically the host institution employs a daily reposition to isocentre IGRT technique and thus, the value of zero was used in the VHMF for all systematic errors.

A further important and fundamental systematic error within the margin formula is organ delineation. Organ delineation in radiotherapy planning is the outlining or contouring of the volumes using the CT planning scan and the planning system software, in this case the Varian Eclipse contouring workspace. Contouring or outlining of the target volume and surrounding organs at risk is a time-consuming task and is normally carried out by consultant oncologists. This procedure is mostly done manually in two-dimensional slices using simple drawing tools on the computer software. Due to the large variations in organ shape and internal structures, this must be done individually for each patient. As such, organ delineation can be a source of significant error as inter-and intra-observer variation in delineating regions of interest (ROIs) occurs due to differences in expertise level and preferences of the radiation oncologists. It is from these contours that the CTV and PTV are grown and therefore, organ delineation has a significant impact on margins. There are numerous studies evaluating organ delineation in pelvic radiotherapy, however, they are highly variable with different numbers of observers, datasets, and methods of comparison. Comparison between studies is therefore difficult due to the variance in methodology.

Alasti et al. (2017) conducted an observational study requiring five clinical oncologists to delineate organs at risk and the high dose volume, the prostate, using CT planning scans. It concluded that the mean ± SD inter-observer variability is 2.0 ± 0.6mm. This work did not show significant differences between organ delineation variability in an

earlier similar study (White et al., 2009) who stated the mean standard deviations for left–right; anterior–posterior and superior–inferior boundary displacements were, respectively, 1.8, 2.1 and 3.6 mm. The authors did not report SD in this study. Both studies had a similar methodology and used five clinical oncologists to assess the intraobserver variability. However, neither study reported the experience of the clinical oncologists undertaking the outlining; this could affect the outcome of intraobserver variability. The study by White et al, had five clinical oncologists delineating structures on five patients, whereas the study by Alasti et al, the clinical oncologists (n=5) used three CT data sets on ten patients which was assessing the delineation on 320 slice CT scans. Khoo et al. (2012) also evidenced inter and intra observational variability of prostate delineation, but this study reported the outcomes as variations in delineated volumes. The study used three datasets and five clinical oncologists for assessment of volumetric variations in the delineation of the prostate gland. The reported intraobserver variation was 9%. However, the results of this study were reported as variation in volume ratio, where the mean (range) volume ratio was 1.58 (1.47–1.69) which was deemed clinically acceptable. The reporting of the results in this way make direct comparison to other literature challenging. As organ delineation has a major impact within the systematic error component of the VHMF, the reduction in variation can lead to the reduction in margins. One of the limitations of this study is that an inclusive inter observational of organ delineation was not carried out as part of the clinical audit. As such, it is justified to use a known value of variability of organ delineation previously used in departmental construction of planning margins. A historical departmental audit of prostate organ delineation and the use of fiducial markers to assess planning margins applied to fiducial markers, of which all the current clinical oncologists were participants, resulted in an organ delineation value of 2.5mm, the assumption being that planning and outlining techniques and software have not altered since the previous audit and at that time all participation clinical oncologists had extensive experience in contouring, therefore educational factors were negligible. To ensure direct comparison with previous work within the department, and time constraints it was decided and justified to use this value in the VHMF used in this clinical audit. It would be appropriate to readdress this in future departmental studies. If the time constraints and consultant availability allowed, the inter and intra observational variations in organ delineation could have been assessed to provide a mean inter observational error with standard deviation to provide more robust evidence and justification of the delineation value used in the department. It could be assumed that changes in clinical practices, protocols, and

staff experience or skillset could affect the inter observer variations. For example, modern planning systems allow for auto contouring of the structures, which is then sense checked by the clinicians and amendments can be made in required. The system also allows for auto segmentation, where the clinician can outline the structures on a number of the CT slices but not all of them and the system then auto segments the structures on the slices that have not been contoured. This shortens the time taken for outlining. However, not all clinicians use this method, some outline the structures on every data set. It would be a valuable study to undertake in future to determine the organ delineation value for both auto segmentation and manual contouring and also clinician experience to compare the mean and standard deviation of both. This could then be used to provide evidence of changes in historically assumed organ delineation values and amendments could be made in the clinical application if required.

6.4 DOSIMETRIC MARGINS.

Currently in the department hosting the research study, of which the clinical audit is a sub-study of, the margins used follow the CHHiP protocol as previously cited (Dearnaley et al., 2012). Protocol recommendations stipulate that CTV to PTV growth margins are 0.5cm in all directions, apart from the posterior margin, which should be reduced to 0.3cm with the aim of reducing rectal toxicity. Within the host centre, the genito-urinary medical team adhered to recommendations with the department protocol using a posterior margin to 0.3cm to increase confidence of target coverage. This results in a total margin of 1.0cm longitudinally (0.5cm on each longitudinal axis), a total of 1.0cm laterally (0.5cm on each lateral axis) and 0.8cm vertically (0.5cm anteriorly and 0.3cm posteriorly).

Data from this clinical audit, and the resultant VHMF suggests that planning margins of 0.7cm in the lateral direction (left/right), 0.7cm in the longitudinal direction (superior/inferior) and 0.7cm in the vertical direction (anterior/posterior) would be clinically adequate to ensure sufficient coverage of the CTV, including accounting for inter and intra fraction motion. Table 13 illustrates the relationship between reduction in planning margins and a reduction in the overall irradiated volume with a mean reduction of 37.1% (min 32.4% and max 39.9%). Proving to be a pivotal, significant finding within the study, this was the basis of the margin reduction and increasing dose theory. Reducing the irradiated volume allows for increased dose without

increasing toxicity to the high dose target area, but more importantly clinically, it allows for this increase without the probability of increased toxicity to surrounding tissue, therefore reducing overall treatment toxicity for the patient.

The plans of each participant were then reconfigured using the reduced margins using the Varian Eclipse planning system. Each plan was then reviewed and assessed against the required dose constraints to ensure plan compliance. Compliance with dose constraints ensures sparing of the OARs when using VMAT. This involved optimisation of the plan to ensure adequate target coverage and the creation of dose volume histograms to ensure that the organs at risk were not clinically compromised by the new margins failing to meet the organ dose constraints. All patients in the audit achieved the required dose constraints previously mentioned. In one case the bladder constraint was breached however, the clinical oncologist approved the plan to ensure adequate high dose target coverage.

RapidPlan® (RP), which is the integrated optimisation tool in the Varian Eclipse planning system, is a knowledge-based planning tool. The concept of RP is to standardize plan quality by using knowledge-based models to optimise clinically acceptable VMAT plans with minimal workflow. Good et al. (2013) stated that knowledge-based planning was superior or equivalent to the original plan in 95% of cases concluding that using knowledge-based systems allows for homogenising plan quality by transferring planning expertise from more experienced to less experienced institutions and individual planners. The research created a knowledge-based database which was created from 132 treatment plans. Fifty-five independent data sets were then re-planned using the knowledge based database. The results stated that the knowledge-based plan had a significantly more homogeneous dose to the planning target volume and a significantly lower maximum dose. The volumes of the rectum, bladder, and femoral heads were nominally lower for the knowledge-based plan. In 40% of cases, the knowledge-based plan had overall superior (lower) dose–volume histograms for rectum and bladder. The system estimates achievable dose volume histograms for OARs and provides optimisation objectives based on each individual patient. Individual anatomical factors contributing to OAR dose sparing in prostate have been identified as the median distance between OAR and PTV, the portion of OAR volume within an OAR specific distance range, and the volumetric factors: the fraction of OAR volume which overlaps with PTV and the portion of OAR volume outside the primary treatment field (Yuan et al., 2012). Kubo et al. (2017) also concurred that the RP system was able to produce IMRT & VMAT pelvic treatment

plans, in a single optimisation, that had comparable sparing and comparable or better conformity than the original clinically acceptable plans. The optimisation software allows for pre-determined dose constraint templates to be used to create optimum planning constraints with a minimum and maximum optimised target range, otherwise known as inverse planning. In this case, the pre-defined OAR constraints are as discussed in the methodology section. RP also allows for multiple constraint optimisation (MCO). Therefore, multiple OAR constraints can be applied at the same time, for example bladder and rectum.

In all cases, the plans produced using the reduced margins achieved all OAR limits proving that the reduction in planning margins was a feasible and viable option for prostate hypofractionated regimes. The aim of this clinical audit was to assess the impact of RayPilot® on planning margins. In this circumstance, the implementation of RayPilot® had proven to be an efficient method of reducing planning margins whilst ensuring current clinical dose constraints are not compromised. The clinical audit aim includes the feasibility of dose escalation and treatment fraction reduction using the RayPilot® system as a future treatment development. As such, the plans were then recalculated and optimised incorporating a further hypofractionated regime of 2400cGy in three fractions. This is an increase to 800cGy fractions, which is deemed to be clinically achievable and not detrimental to OAR toxicity.

The RapidPlan® optimisation process was repeated and again, produced favourable results for the amendment of dose and fractionation. All dose constraints were achieved for all OARs including the expanded rectal and bladder constraints.

6.5 OUTCOMES (DISEASE RESPONSE AND TOXICITY).

Table 17 and figure 22 represent the long-term PSA levels in the participants. PSA is used as a disease marker in prostate cancer treatments and is an indicator of disease response following treatment. The PSA value is a critical tool in assessing disease free survival statistics. Evidently, all patients exhibited a decrease in PSA levels following completion of treatment producing favourable results for the trial.

The median (IQR) reduction in PSA levels was 86.8% (IQR 56.3-92.3, IQR = 40). Reduction of PSA appears to be gradual in this cohort of patients. The gradual decrease in PSA values is attributed to the fact that this group of patients did not have neo-adjuvant or adjuvant hormone therapy (Garcia-Albeniz et al., 2015; Harshman et

al., 2018; Crawford et al., 2019). Hormone therapy reduces PSA due to the mechanism of blocking androgen reducing the production of testosterone, which results in lowered PSA. PSA rapidly reduces in 90% of patients following the addition of hormone therapy (Spratt et al., 2021). However, analysing the collated data in the clinical audit it is assumed that the PSA levels will continue to reduce, and therefore the PSA reduction mean value would increase, due to the omission of ADT. These results are a fundamental finding within the study by evidencing that the current hypofractionated regime results in the regression of disease and its control.

Assuming the dose constraints used for the initial research and the participants in the PRINToUT trial are achieved using the resultant planning margins and suggested hypofractionated treatment regime in this study, it is presumed that the toxicity outcomes will be comparable.

Rectal and bladder toxicity are the most common acute and late side effects for prostate cancer patients receiving radiotherapy. Although these have been reduced due to treatment advances such as VMAT, IGRT and continuous motion management, many patients still report toxicity. A systemic reviewed of 26 previously completed studies concerned with toxicity including over 70 patients with a mean follow up of five years and concluded that IMRT is associated with decreased toxicity compared to conventional radiotherapy treatments (Zaorsky et al., 2016). Following on to conclude that late GU and GI toxicities are similar between conventionally fractionated radiotherapy and hypofractionated radiotherapy with long-term toxicities, were rare (<5%).

Reassuringly, the data in Table 18 evidences acute side effects which reduce over time from completion of hypofractionated radiotherapy until scheduled follow up. Due to the radiobiological effects of radiotherapy it is common that patients will exhibit urinary and rectal toxicity towards the end of the treatment prescription and immediately after for a period of weeks which subsides following a period of repair. RTOG scoring is used to provide an objective record of toxicity in the follow up consultations. Each recorded consultation was conducted by the same clinical oncology consultant therefore reducing inter-observational error and bias. The scoring system is graded from RTOG 0 to RTOG 4 with severity of toxicity increasing with each value. The toxicity assessment was done in correlation with RTOG and a devised Lent Soma questionnaire.

GU and GI toxicity appears to reduce significantly with time following treatment (Nakamura et al., 2019). However, it is evident that sexual function can be affected

on a longer term basis than acutely, therefore the effects of EBRT on ED are not apparent immediately after completion of treatment but can become apparent some time later. Biologically ED is more common as men age and can be attributed to other medical co-morbidities, for example diabetes, obesity and hypertension.

The participant in this study who reported increasing ED was also diagnosed with myasthenia gravis (MG) upon completion of treatment, however the patient confirmed that the symptoms had been longstanding prior to the diagnosis of prostate cancer. MG is an autoimmune neurological disorder that effects the neuromuscular junction (Dresser et al., 2021). The clinical manifestation of MG includes fluctuating weakness of striated muscles, peripheral and central fatigue. Peripheral fatigue is a direct result of muscle fatigability due to disorders of the muscle or neuromuscular junction. Central fatigue is an experienced lack of energy and feeling of tiredness not related to muscle weakness or pain, and interferes with mental or physical activities (Ruiter et al., 2020). As with many neurological disorders, MG has periods of remission. However, a diagnosis of MG can greatly affect the patients overall quality of life, not just physically but also psychologically (Farmakidis et al., 2018). It is therefore difficult to ascertain if the side effects experienced can be attributed solely to post-radiotherapy toxicity, or more likely his muscle weakening condition (Sanders et al., 2018; Mantegazza and Cavalcante, 2019).

The follow up protocol for both the PRINToUT trial and the clinical audit was 2 years post treatment completion. Patient reported toxicity and clinically graded toxicity was reviewed by the lead radiographer for the purpose of the audit. Although the main focus of toxicity was assessed against common and expected treatment related toxicities, both acute and long-term side effects, it became apparent that further investigation and acknowledgement of any other relevant new diagnoses or co-morbidities should also be given consideration. For example, as recorded in the results section, one patient passed away during the follow up period. The cause of death was unknown but not associated with prostate cancer. The only recorded co-morbidity for this patient was diabetes mellitus type 2. Again, as a metabolic disorder, diabetes mellitus type 2 can cause erectile dysfunction, which could inadvertently be attributed to post radiotherapy toxicity rather than due to a long-standing diagnosis of diabetes mellitus type two. A meta-analysis study reported that 56.5% of the diabetes mellitus patients included in the study had mild to severe erectile dysfunction (Bajaj et al., 2021). Another possible complication of relevance with diabetes mellitus type 2 is that of diabetic bladder dysfunction which can result in a triad of decreased

bladder sensation, increased bladder compliance and capacity, and impaired detrusor contractility and had been reported to be present in 50% of patients with diabetes mellitus type 2 (Witting et al., 2019). The presence of diabetic bladder dysfunction could therefore mask or exacerbate the post treatment urinary toxicity experienced by these patients.

To mitigate the possibility of confusion between post treatment toxicity and long-standing conditions that may attribute to the toxicity reported, the lead radiographer and clinicians undertaking follow up consultations were advised to remind patients that both the patient reported, and clinician reported toxicity scores were from the patient's baseline or normal function. To do this patient were reminded that the toxicity scoring was relevant to post treatment only and that when completing questionnaires or consultations that the answers were to be based on the month prior to commencing treatment and the changes that they had experienced since then.

These findings are an integral part of the clinical audit aims to ensure that changes to dose and fractionation and the clinical implementation of hypofractionated or ultra-hypofractionated treatment regimes do not result in detrimental toxicity or reduction in QOL of patients. The fundamental principle in clinical research is “can we implement clinical changes for disease control or cure without causing detrimental effects to the patient above which they would experience with current interventions?” In this clinical audit, the results of acute and long-term toxicity are comparable with standard fractionation treatments and in context to previous literature on the subject.

Brand et al. (2019) published a comprehensive (n=874) and most recent multi-centre trial assessing the toxicity outcome of the PACE B trial of IMRT versus ultrahypofractionated SBRT. The results are of particular interest in relation to this research as the dose and fractionation comparison is identical to the regimes used in this research (the conventional fractionation of 7800cGy in 39 fractions, moderated hypofractionation of 6200cGy in 20 fractions and SBRT of 3625cGy in 5 fractions). The study concluded that substantially shorter treatment regimes did not increase GU or GI toxicity. Worst acute RTOG gastrointestinal toxic effect proportions were as follows: grade two or more severe toxic events in 53 (12%) of 432 patients in the conventionally fractionated or moderately hypofractionated radiotherapy group versus 43 (10%) of 415 patients in the stereotactic body radiotherapy group. Worst acute RTOG genitourinary toxicity proportions were as follows: grade two or worse toxicity in 118 (27%) of 432 patients in the conventionally fractionated or moderately hypofractionated radiotherapy group versus 96 (23%) of 415 patients in the

stereotactic body radiotherapy group. The results of the undertaken clinical audit showed comparable toxicity to the cited studies. A similar systematic review and meta-analysis of previous studies and found that substantial evidence exists for the efficacy of ultra-hypofractionation, with over 6000 patients treated in prospective studies and excellent 5-year biochemical progression-free survival in a recent meta-analysis (95·3%) (Jackson et al., 2019).

The clinical audit conducted for this study provided essential information in relation to the reduction of margins, the reduction of fractionation and the increase in daily dose. Clinically this could prove influential in the treatment regimes utilised for prostate cancer patients and service delivery. The author also reported no significant differences between conventionally fractionated or moderately hypofractionated radiotherapy and stereotactic body radiotherapy for the comparison of toxicity. This was derived through analysing the toxicity outcome reported in the clinical trial data with the current literature as discussed previously in this chapter (Yu et al., 2014; Zelefsky et al., 2020; Tree et al, 2022). The standard treatment used currently within the department is a 20-fraction schedule using 200cGy fractions. The implementation of a hypofractionated regime would, therefore, reduce the current fractionation by 15 (using the current trial fractionation of five fractions) or by 17 fractions (using the further research suggestion of three fractions) per patient. Service implications of this reduction would result in reduction in treatment costs, increased availability of machine time and reduced waiting times for patients. These will be discussed further in the future development section of this chapter.

6.6 LIMITATIONS AND POTENTIAL BIASES

6.6.1 PATIENT COHORT

The obvious limitation of this clinical audit is the small patient cohort (n=7). The intended patient recruitment level was 1-2 patients per month over an initial 18-month period, which would have resulted in 18-36 patients in total. Unfortunately, this was not achieved and resulted in 11 patients undertaking the study with a resulting cohort of 7 patients in the clinical audit. As explained in the previous chapters, four patients were removed from the audit following enrolment to the PRINToUT study and the reasons outlined. The small sample size subsequently made it unrealistic to apply inferential analysis and would probably have yielded inaccurate, unreliable results

(Marino, 2018). As the clinical audit required quantitative data for extraction and insertion into mathematical formulae, the descriptive statistics were deemed appropriate for use as set out in the methodology chapter. If the study were to be repeated, a recommendation would be to recruit a larger sample to allow for inferential statistical analysis. A larger sample size would provide more information in relation to whether the data collected would be normally distributed to determine appropriate inferential statistical analysis, with a sample size as small as the one in this clinical audit this cannot be confidently determined, which would reduce the validity and rigour of the audit. For example, the outcome measures and values of the RayPilot® sample and outcome measures from standard prostate radiotherapy patients could be compared using a t-test to allow comparison of the two groups of values. If the data is normally distributed a correlation a Pearsons r test could be used, however another option would be to use a Spearmans r test if the data did not follow a normal distribution. In relation to the ability to reduce planning target margins and the feasibility of clinical application the confidence interval would be set at P=0.05 to ensure confidence in the results.

However, the main mitigating circumstances in the failure to obtain the desired patient cohort were as follows:

6.6.2 Patient Pathway

Within the research design, and the implementation of a 'one-day' planning methodology, co-ordination of appointments for five different departments was required (MRI, theatre, day bed suite, radiotherapy department and Wellcome Research Facility), which proved problematic.

Access to theatre lists and radiologist availability were the main contributing factors in lack of patient throughput. It was extremely problematic to co-ordinate radiologist participation and availability of theatre access throughout the study timeline. Due to the small numbers of intended patients, it was not feasible to procure a protected theatre scheduled session for the implantation of the RayPilot® device. The theatre requirements are dependent on patient recruitment which could not be guaranteed, therefore providing scheduled theatre time would be detrimental to the urology services as a whole due to the demands of the surgical procedures required for routine patient such as prostate biopsies, template biopsies and fiducial marker insertions and would potentially impact waiting lists if available theatre space was

obtained and not used. Therefore, the surgical implantation aspect was on an 'ad-hoc' basis relying on available theatre sessions and radiologist availability.

Only two clinicians were trained and competent in surgical implantation of the device – the lead radiographer and one senior radiologist. Although this was deemed suitable for the number of patients indicated at the beginning of the trial, in clinical practice this became difficult to sustain. As the available theatre time had to be compatible with the availability of the radiologist and the lead radiographer along with the other clinical departments involved.

Repeated attempts were made to amend the pathway to mitigate this being a recurring theme, however, they were not successful and the booking of theatre slots remained on an ad hoc basis. Conversely, the remainder of the pathway for the 'one-day' planning methodology was less problematic. To ensure appointment availability the radiology department allocated two MRI appointments per month for RayPilot® patients on the basis that if these were not required the department would be informed within two weeks of the allocated appointments so that these could then be made available for patients, therefore not having a detrimental effect on the departmental workload, patient waiting times or emergency requirements. The radiotherapy department mirrored this. CT planning appointments and subsequent treatment appointments were allocated to 1-2 RayPilot® patients and again, if these were not required they would be released.

6.6.3 Technology Issues.

Another delay in recruitment was incurred due to a technological issue with the RayPilot® couch top, which resulted in the equipment being out of commission for four months for repair and re-commissioning. Unfortunately, the equipment remains to be a concern in relation to repairs due to the host department being the only department in the UK to have the technology system, which means that, logistically if it requires work the Micropos team must travel from Sweden to repair and recommission the equipment before it can be used clinically.

The RayPilot® couchtop receiver was procured for research purposes therefore; there is only one RayPilot® receiver in the department. They are also commissioned for use and compatible for use on one specific linear accelerator. In the clinical setting, this means there is no 'back-up' system available for use if any equipment faults occur. In normal circumstances if there is an equipment failure or linear accelerator breakdown patient can be treated on another machine to ensure that there are no

unscheduled gaps in treatment, however for patients using the RayPilot® system this was not the case. This resulted in clinical decision making in relation to going ahead with treatment without the use of the RayPilot® technology as allowed within the PRINToUT trial protocol or delaying the start of the patients treatment until the issue is resolved. Further acknowledgement and contingency planning in relation to the technology is given in the future developments section.

6.6.4 Covid-19 Pandemic.

During the timeframe for the clinical audit, the Covid-19 pandemic occurred. At this time, NHS Scotland halted all non-essential research. Rightly, so, this was to allow for research facilities and resources to be made available for Covid-19 research. Essential research was allowed to continue, for example drug trials where there were patients already 'on drug' and receiving active treatment. However, all other research trials were paused at this time. The overall impact on the patient recruitment was a period of 13months of where no patients were recruited to the PRINToUT trial and therefore the clinical audit patient cohort was affected. However, patient recruitment recommenced when the research guidelines and policies were updated. As this was a globally unprecedented occurrence, this delay was obviously unavoidable.

6.6.5 RayPilot® Motion Management System Equipment Upgrades.

Towards the end of the clinical audit, when data had already been collated and analysis had begun, Micropos released a change to the method of real time tracking. The implanted device was being replaced and upgraded to the new HypoCath® system. The patient identifiable transmitter chip was to be contained within an indwelling catheter (the HypoCath®) rather than the surgically implanted transmitter. In the clinical setting this was advantageous as a catheter was only required for CT planning for displacement purposes and then the HypoCath® was inserted for the 5 day treatment duration. Not only was this a more favourable option for the patient it is also advantageous for the service as it only requires a competent and adequately trained professional to introduce the catheter, therefore removing the requirement for theatre and associated resources, for example radiologist time and recovery ward availability. Further acknowledgement to this change will be discussed further in the future developments section. However, this negatively affected the resultant patient cohort. As data analysis had already begun, the decision was made to complete the clinical audit using the available patient cohort at the time, n=7.

Due to the amendments in the RayPilot® system components (the retirement of the surgically implanted device and the introduction of the HypoCath® transmitter) the patient cohort could not be increased as the results would be invalid and detrimentally impacted by comparing different methods of real time tracking, leading to invalid conclusions.

However, following multiple discussions and forums with not only the clinical oncology consultants, departmental physicists and supervisory colleagues it was deemed unfeasible to continue with the clinical audit as a change in technology would not allow for direct comparison or undisrupted data collection. At this point, the lead radiographer in this clinical audit, following clinical and academic guidance, halted the data collection. In consultation with the professional doctorate supervisors it was concluded that the research and the results obtained would be used to complete the professional doctorate thesis in its entirety. Therefore, the results and conclusions from this clinical audit are complete at a natural point of conclusion in relation to research methodology and design as stated previously.

A further limitation of the clinical audit is that it was a single centre study based on the experience of a single UK centre. Although this is not necessarily a limiting factor, it would have been beneficial to the validity of the findings and robustness of the methodology of this clinical audit to compare the findings to another centres implementing the system. At the time of conducting the clinical audit such studies were not available, however this would be an interesting future development between centres, both in the UK if RayPilot® becomes available in other centres and internationally.

As such, a further limitation to the research study was the lack of literature in relation to the RayPilot® system. As the system is relatively new in conception there is a lack of literature in relation to it. It also follows that there is a distinct lack of follow up data available for patients who were treated with the device. Scant literature and use of the system made direct comparison of study results with previous experiences of other clinical users. The aim of the lead radiographer and this clinical audit was to fill this void in literature.

For the clinical outcomes of the trial to be robust and valid, it is essential that all areas of bias be reduced in the reporting of treatment outcomes and associated toxicity. The principal investigator, a senior clinical oncologist, for the PRINToUT trial was also the lead clinician in the GU medical team. The principal investigator was therefore involved in patient recruitment and subsequent follow up and this could have been a

potential area for bias to occur. Similarly, the LGR was also involved in the follow up of this patient cohort. Professionally there is no question that bias would be shown, to mitigate this as a potential limitation to the research study and the clinical audit, toxicity outcomes were not only clinician reported they were also patient reported in the form of questionnaires. Although the principal investigator was involved in patient recruitment this was also conducted by the wider GU team of five further clinical oncologists who selected eligible patients at the new patient clinic. The team as a whole were also involved in follow up consultations and toxicity scoring which limits bias. The patient reported outcomes and clinician reported outcomes were also recorded using the RTOG definitions mentioned previously in the discussion, therefore, there is a clear description and definition of toxicity to ensure uniformity and accuracy of results.

6.7 FUTURE DEVELOPMENT.

The clinical audit focused on the clinical application and efficiency of the RayPilot® real time motion management system and the potential that it could be used to further hypofractionate prostate SBRT by allowing further planning target margin reductions. This could be reducing fractionation and increasing the daily dose to the target volume, however, conversely the fractionation could remain the same but the overall treatment dose could be increased. By replicating the planning processes of the study, it could be investigated as to how much the target dose could be increased to gain optimum tumour control without increasing presumed toxicity to the surrounding tissues. Although primarily the end point was to assess efficiency at dose escalation and fractionation reduction, it would be an interesting direction to take the study in to see if potentially higher dose escalation in current plans could be achieved.

The host department are considering replicating the research study methodology using the Hypocath® technology and comparing the results of both. Due to the fact that the new system uses a transmitter housed in a catheter the variation in intrafraction motion data would make for interesting comparison. It would also be of benefit to assess patient compliance and satisfaction with the two devices, as long as both remain currently clinically available. However, if not then a multi-centre study could be conducted as long as the methodology was robust and replicable. Although the surgically implanted RayPilot® device was well tolerated by the participants, it would be of interest to compare the reactions and experiences of participants using a catheter system and as such, due to it being in constant use would migration of the

transmitter and motion of the device be more problematic than the surgically implanted option.

Due to the impact of the halting of research, the host department then considered the use of other options available clinically to achieve motion monitoring using technology already installed in the Varian TrueBeam linacs in situ in the department. Triggered imaging was being considered as a contender for the RayPilot® method. The linacs have the capability to take in beam treatment images at triggered points and assess the positioning of the prostate fiducial markers in relation to a pre-defined search area. If the fiducial markers migrate from the specified area, the beam is interrupted and isocentre positioning can be repeated. However, the pre-defined trigger intervals do not equate to the accuracy of the RayPilot® technology of recording motion 30 times per second. Therefore, the host department is considering a comparison trial between the efficiency of the RayPilot® system and the implementation of a triggered imaging protocol. The primary researcher will be the lead radiographer on the comparison study and will have input at clinician level to collate and review the data to then aid in the making of an informed decision on whether RayPilot® or triggered imaging should be the method of choice within the host department for monitoring intrafraction motion.

6.8 CLINICAL APPLICATIONS OF THE FINDINGS.

Principally, the main focus of undertaking professional doctorate research is to assess and review the impact that the chosen field of study has on the clinical environment and the development of clinical practice.

Prostate SBRT is fast becoming a treatment option of choice for both patients and in the clinical setting. As such, the number of prostate SBRT patient's is increasing in the clinical setting. Patients will receive 3625cGy in five fractions as stated and evidenced in the PACE trials. Consideration must be given to the motion management system required for treatment. Currently, it is suggested that the RayPilot® system could be used for all prostate SBRT patients in the department. A feasible option given that the department has an increasing amount of experience in using the system, however the implications for the service must be considered. For example, although the HypoCath® transmitter does not require as many resources as the surgically implanted transmitter, it does require competent and entitled staff to perform catheterisations. Currently, three radiographers are entitled to do this procedure. This is something that requires to be addressed to ensure that there are

no external resources required for the process, as this was one of the main areas of difficulty. If RayPilot® is used as the motion tracking system for prostate SBRT then it would be advantageous to the service if another receiver board could be procured so that the protocol could be delivered on more than one linear accelerator in the clinical setting. However, the expense of procurement must be balanced by the benefits to the service e.g. the reduction in resources required and the advantages to capacity and the outcomes for the patients.

Upon completion of this clinical audit, it was apparent that real time tracking was a reliable and efficient method of delivering hypofractionated prostate radiotherapy and could be used as a method of altering current treatment prescriptions and techniques. In the context of the clinical setting this can be utilised to make changes to fractionation schedules and to put that into context, patients who would have the standard fractionation of 20 fractions could then have a reduction of 15 fractions if using the current trial protocol, or a reduction of 17 fractions if the proposed 3 fraction treatment was given clinical approval. However, RayPilot® patients would require a day zero appointment, which has previously been discussed in the methodology chapter. Including this day zero appointment, the actual reduction in overall treatment appointments is 14 fractions if the standard 20 fraction treatment was required and 16 fractions if the proposed three fraction regime was implemented. Although this reduction seems advantageous, the benefit of fractionation reduction must be correlated to overall linear accelerator time saved to assess whether this is a viable option for the service.

Standard prostate radiotherapy fractions using IGRT and fiducial markers are currently given an arbitory 15 minute appointment per patient. The overall linear accelerator time required for a standard prostate radiotherapy patient is therefore, approximately 300 minutes or 5 hours. If RayPilot® is used; the current radiotherapy appointment time is 45minutes. Therefore, the total linear accelerator time required for each patient, including the day zero appointment is 270 minutes or 4.5 hours. This suggests that although RayPilot® does save treatment fractions, there is not a great deal of benefit in terms of overall linear accelerator time required. To put this into context the 30 minutes difference would allow for two extra fractions of standard pelvic radiotherapy per RayPilot® patient as discussed, the change of technology to the HypoCath® system requires for the patient to have 150ml of sterile water introduced into the bladder prior to treatment being delivered. This method of standardising bladder filling reduces the time that the patient has to be in the department, however

currently this is done in the linear accelerator treatment room, which requires additional time. Moving forward the process of pre-filling the bladder could be done in an external environment, e.g. a peripheral clinic room leading to a reduction in the allocated treatment appointment. Implementing this change could lead to a reduction in the treatment appointment to 30 minutes per patient, saving a further 15 minutes per appointment, which would be a favourable outcome in terms of linear accelerator time and capacity. However, in reality, the ratio of RayPilot® patients to standard prostate radiotherapy patients is 1.6:1.

When evaluating a significant change in technique and the equipment required, it is essential that the service forecast the overall cost of such a change and whether this is not only beneficial, but also feasible for the service to deliver. The planning of IGRT and SBRT including preparation, imaging and dosimetry is costed at £706. Each radiotherapy fraction is costed at £109 (NHS England, 2020). Standard prostate radiotherapy fractionations of 20 fractions is costed at a total of £2,886. For prostate SBRT patients using the RayPilot® technology is costed at a total of £1,251, however this is for radiotherapy treatment only. For RayPilot® patients the additional HypoCath® would be an additional cost. Each HypoCath® unit is costed at £2150 per patient (Micropos, 2020). As such, this is in addition to the per fraction treatment cost, making the total cost for RayPilot® patients is £3401. Additional cost is incurred with the use of fiducial markers; however, these are also required for RayPilot® patients, therefore, and the cost is balanced and negligible.

Obviously, the initial outlay for the RayPilot® motion management system has to be given consideration. In this case, the original system was procured at a cost of £215,490 however; this was procured within the PRINToUT research budget. As discussed previously a second system within the department would allow for more RayPilot® or prostate SBRT patients to be treated. However, this cost would be an outlay from the radiotherapy department equipment budget. Without further investigation and long-term planning it has yet to be determined whether this would be financially viable and a beneficial addition to the service.

One major positive aspect of the implementation of this study has allowed for a cohesive relationship to be formed with the company responsible for its conception, Micropos. From this, the host centre has been allowed unprecedented opportunity

for development of the devices and protocols for its use. As a forward thinking collaboration, the host department and the company are not only progressing the use of its devices within prostate radiotherapy but are also looking as to how the device could be adapted for use in bladder cancer. Not only has this relationship enhanced the reputation of Micropos but has also promoted and enhanced the reputation of the host department by allowing the showcasing of the results, not only in the UK, but in the international oncology community by publishing data and information sessions for multiple oncology conferences.

Following the implementation of the clinical audit, staff training has been increased and instead of there only being a core team of entitled radiographers, pyramid training has been implemented to ensure that all radiographers rotating on the linear accelerator used for RayPilot® patients are adequately trained in using the technology. As such, the RayPilot® real time motion management system is becoming a routine technology and treatment option within the clinical setting.

6.9 CHAPTER SUMMARY

This chapter has discussed the findings of the clinical audit in relation to previous literature and acknowledged the limitations and recommendations for further studies on this topic and aimed to fill some gaps within previous knowledge. The discussion chapter has compared the experience of the use of RayPilot® in the clinical setting and the results show comparable results to previous literature. It has also shown that it would be feasible to further develop the use of the system to allow for further hypofractionation in prostate SBRT. Although discussion and acknowledgement of limitations within the study show some reflection, further reflections on learning will be further discussed in the reflections of learning and experience chapter which follows on from the conclusion chapter.

7 CONCLUSION.

The aim of this clinical audit was to assess and evaluate the the efficiency of the RayPilot® real time motion management system and the effect on dosimetric margins and treatment delivery in hypofractionated prostate radiotherapy and to assess whether this could lead to a further dose escalated regime and reduction in treatment fractionation of prostate SBRT using a retrospective approach of seven patients who completed five fractions of prostate SBRT with the device in situ.

The clinical audit found that the RayPilot® real time motion management system is an effective method of tracking prostate motion during treatment delivery. Reviewing and correcting for intrafraction motion of the prostate allows for enhanced optimum dose delivery to the high dose target volume whilst reducing toxicity to surrounding tissues. Furthermore, the accuracy of the software allows smaller planning target margins to be applied clinically, which in turn, allows for dose escalation in hypofractionated prostate radiotherapy. The RayPilot® motion management system facilitates either dose escalation using the current clinical fractionation or the reduction in fractionation utilizing a larger daily dose.

Future developments based on the results of this clinical audit should progress to larger studies on the feasibility of implementing a further hypofractionated regime in the clinical setting. As the RayPilot® system was used in conjunction with implanted fiducial markers, it would be advantageous to carry out further research to assess and review the efficiency of RayPilot® as a stand-alone modality for intrafractional positional verification.

8 REFLECTIONS ON LEARNING AND THE DOCTORAL EXPERIENCE.

8.1 CHAPTER SYNOPSIS.

This chapter will discuss the research skills developed, challenges faced and personal growth throughout the process of undertaking a professional doctorate. It will explore how the doctoral experience has contributed to the intellectual and academic journey.

8.2 THE PROFESSIONAL JOURNEY.

Therapeutic radiography is an extremely rewarding profession and one that I have been proud to be part of in the twenty years since qualification. It is a fast-evolving discipline, which is multifaceted providing opportunity for professional progression and development. For the past twelve years I have been the advanced practitioner for genitourinary cancers and this role has allowed me to not only use my transferrable skills to take on roles traditionally taken on by other disciplines but to also promote the role of the radiographer out with the radiotherapy department. As a relatively small professional cohort within the wider NHS, it is important that we continually take the opportunity to progress and enhance the roles within the department, and increase knowledge of my scope of practice amongst other health professionals.

As my career has progressed, I like many others have reached a plateau of progression and looked for other areas of opportunity to improve and enhance our expertise not only in our professional practice but personal development. In my case, this was to expand my knowledge of research within the therapeutic radiographer role. My clinical role is extremely important to me and as a therapeutic radiographer, we use evidence-based practice in our everyday duties, and this lead to my desire to be a researching professional in practice. I wanted to follow on from gaining my MSc (master of science) to expand my level of study by undertaking the professional doctorate. The professional progression from advanced practitioner would be to that of the consultant radiographer. The main roles of the consultant radiographer are to provide expert clinical practice, professional leadership and consultancy, education, training development, service development and research and evaluation. This links to the four pillars of practice defined in the NHS Education for Scotland Pillars of

Practice Guidance (2019). The completion of the professional doctorate evidences the Scottish Credit and Qualifications Framework (SCQF) level 12 attributes required for the role of the consultant radiographer. Level 12 attributes require the professional to exhibit a high level of autonomy, initiative and leadership in professional activities (Appendix 12). The professional should be making a significant development of change within the sector by identifying, conceptualising and offering expert insights into new and developing concepts, along with planning and executing research to generate new knowledge. The professional is required to use a range of complex professional skills and techniques at the forefront of developments in the sector to critically assess current and emerging processes and treatments. This level of expert knowledge allows the professional to critically evaluate the sector and also identify areas that affect its development whilst reflecting critically on their role and responsibilities and using these for positive change. The Society of Radiographers (SOR) state that at this level the post holder should be working toward doctoral level study. However, this is not always an essential characteristic and varies within clinical departments. These roles are not as common as that of the advanced practitioner and whilst contemplating my professional progression I decided to undertake the professional doctorate qualification to aid on my career progression when the opportunity for this arose.

The Professional Doctorate allows for work-based learning focusing on clinical practice, and through the process of robust research, leads to positive change that will enhance and develop that particular practice. For clinicians who have already developed expertise in specific areas, for example, advanced practitioner site specialists in radiotherapy, the Professional Doctorate allows for further clinical autonomy and enhanced professional identity in their chosen field. This was why the Professional Doctorate was the next step in my professional development. Although I wanted to extend my academic knowledge, I wanted to do this in a way that would benefit the clinical environment and not involve a permanent move from the clinical setting towards the academic setting. Doctoral level study requires perseverance, commitment and resilience and transferable skills, which can be used to problem solve and communicate effectively (Sverdlik and Hall, 2020). This is of benefit to the individual and the department as a whole. Having practitioners in the clinical setting that have advanced to this level of study benefits the service in many ways. Not only does it show a commitment by the management to career long learning and development, it promotes a culture of peer support. For example, practitioners that have completed doctoral level research can mentor and support peers looking to

advance their own careers, and thus advance the profession as a whole. It also widens the AHP (Allied Health Professional) and clinical educator relationships on a multi-disciplinary level which in itself, creates further opportunities for role development and inter-professional interaction.

8.3 RESEARCH SKILLS DEVELOPED.

Research skills involve the ability to gather, evaluate, and synthesis information from various sources to address the study aim. These skills include searching for relevant materials, critically analyzing sources, organising findings, and effectively citing information. Developing strong research skills can help make informed decisions, support arguments with evidence, and contribute to a deeper understanding of a subject. These broad skills provide an overarching description of gained research skill, which can then be further developed. Becoming proficient in information gathering provides the ability to efficiently search for and locate the relevant information from various sources for example journals, articles, books, databases, online sources and through the use of reported outcome measures. This is something that I have gained confidence in following this process. For example, fully appreciating the hierarchy of evidence and the effect and consequences that this has on the validity, rigor, robustness and credibility of the literature and the evidence reported within it. This was extremely pertinent in this clinical audit. As RayPilot® is an emerging technology; the majority of the literature was experienced-based case studies. However, the underpinning theory and the clinical considerations that the clinical application of the system is designed to mitigate produced vast amounts of literature including randomized controlled trials, meta-analysis and retrospective research. A major reflection whilst undertaking this process was that in some instances the information that is left out of a study or a piece of research can be just as important as the information reported in it. For example, one piece of research assessed QOL of prostate patients under various topics such as urinary symptoms or colo-rectal symptoms, but the study did not divulge how this was assessed; the patients were simply asked how these symptoms affect their quality of life. However, it would have been more beneficial to the reader and to the overall results if this were broken down into further subsections to gain an understanding of all the issues that played a part into their results, especially in the arena of improving patient care. Along with the hierarchy of evidence it is essential to give consideration to the reflexivity of the authors, for instance - are there any conflicts of interest or are the authors

showcasing positive results to fit an agenda dependent on their involvement within the research for example the funding or location of the study or research being carried out. This was something that I was conscious of in the initial and latter part of this study. Initially, we were the only cancer Centre in the UK using this technology. The majority of the information we had regarding the system and evidence of its efficiency came from Micropos, the company that devised the system. Although they were very open and honest about the clinical capabilities of the system there was not much published or independent literature to confirm this. This was where the visits to two European Centre's (Orebro in Sweden and Lyon) which had already implemented the system became invaluable. However, again much of the information received was anecdotal or based on experience of using the system. Many of the clinicians involved were still in the process of publicizing their findings at this point. The clinician involved in this audit and the larger PRINToUT clinical trial has suggested that with the clinical implementation of the HypoCath® use in the RayPilot® system that this is the method of motion management that should be used clinically for all prostate SBRT patients moving forward. However, there is varying thought within the department that triggered imaging may also be a viable option given that this is available on all linear accelerators within the department. I was extremely conscious that the future use of the RayPilot® system within the department, which had already procured the system, would have to be a separate decision to the results and aim of this clinical audit. Especially with such a small patient cohort and the fact that the methodology of this clinical audit used a different RayPilot® transmitter device to the one which will be used moving forward. Although the method of device implantation differ (surgically implanted into the prostate as in the clinical audit or in an indwelling catheter), the evaluation of the efficiency and the process of the real time motion monitoring would be the same. In addition, the overall results of this clinical audit may have been seen to be a deciding factor in the method of motion management going forward or may have influenced the future recommendations of the author. There were no conflicts of interest within the clinical audit and the author's involvement and therefore the reflexivity of the author was not an issue and I believe this is apparent in the balanced review and collection of appropriate and relevant literature.

At the beginning of this process, I completed the certification of learning in Good Clinical Practice (GCP). This was an invaluable experience as it strengthened my knowledge and insight into the research process. Having completed a number of internal audits as a lead auditor and completing an MSc in Radiation and Oncology, it was assumed that I had a grasp on the paperwork and protocols required for

implementing a research project as I had demonstrated skills in this area. In theory, this was the case, but in more of an 'it is required' rather than 'why is it required' sense. The paperwork and protocol information required for submitting and implementing a research trial is vast and repetitive and at times can seem like a lesson in administrative paperwork. We all know about morals and ethics, as medical professionals we make ethical judgements and decisions every day. However, as a lead or primary researcher it is imperative that the trial design and implementation is held to impeccable professional standards and that the justifications for the decision made by the lead researcher are made with sound, robust intent both medically, personally and in the evidence the research provides.

"Just because we can, doesn't mean we should" – this is a phrase I personally have used countless times in my career when talking about future developments within the profession or even in an ethical sense in end of life care in the cancer setting. If the research does not provide benefit over standard available treatments, then it does not have a purpose. The purpose of the research needs to be clearly defined along with the benefit to each stakeholder group, for example, clinical benefit to the patient and clinical benefit in the healthcare setting. It is essential to question the research in the wider setting to assess and review the impact on the patient population and therefore, the efficacy of the research in clinical practice. In reviewing the research there needs to be a robust critique of not only the research being presented but also the literature upon which it is based. By rigorously critiquing the literature and methodologies used in the research, investigators can identify gaps in the research or service and devise further research in order to fill these gaps in knowledge. These skills take time to develop, I am still in the process of doing this effectively, but in using these skills effectively, the limitations in the research become apparent. These can then be considered in the construction and implementation of your own research.

The foundations of the good clinical practice course are to obtain the skills required to create robust trial documentation and protocols which focus on transparency, accountability (both ethically and medically) and provide a structured and detailed explanation of the research that is to be carried out. Assuming the role of primary researcher required a far larger commitment in relation to ownership and autonomy than many of the audits and service development that I had undertaken prior to the professional doctorate. Previously, I had been working within defined protocols or creating protocols in accordance with defined boundaries of the clinical setting. However, in terms of being a primary researcher and implementing a project, I was

defining the boundaries. All outcomes of the study or all the pitfalls of the study were my responsibility e.g. adverse events, patient compliance, trust approved protocols and training plans. The GCP module provided an insight into managing all aspects of trial construction and documentation. It also increased my awareness and instigated further research into the Declaration of Helsinki, which was first introduced in 1964. This is widely believed and understood to be the corner stone of ethical research by providing ethical principles in relation to human experimentation in the medical community.

Upon reflection, the ethical approval request I had submitted to the QIT would have been greatly improved if I had completed the course prior to seeking approval. Although the submission was granted approval without changes required, having completed the GCP module I would have included further information supporting not only the methodologies, but also the consequences and management of issues such as adverse effects and training timelines etc. Reflection and being responsive are two of the skills that I feel I have greatly enhanced since starting this journey and becoming responsive in adapting to changing situations, results in greater understanding and outcomes than being reactive to them.

Data analysis is also an essential research skill in the doctoral experience. Collecting, organising and interpreting the data to draw meaningful conclusions and insights is a primary focus of all research or audits. At the beginning of the larger PRINTOUT study, we made the decision to use the implementation as an opportunity for maximum data collection. For example, although a post CBCT is not clinically required this was in the protocol to allow us to assess intrafraction bladder filling and the consequences of this on prostate motion and the volumetric dose constraints from instigation to completion of treatment. There were three methods of assessing toxicity outcomes as discussed in previous chapters. If the study were to be repeated, a recommendation would be to reduce this as a lot of the information gained was repetitive for both patients and clinicians. However, this was seen as an opportunity to ensure maximum data collection. An imperative research skill is knowing what data is relevant to the aim of the study and what this brings to not only the results, but also the credibility and robustness of the piece of work. As we had collected so much data form various sources, patients, radiographers and the RayPilot® system recorded data it was crucial that the right information was included in the audit to address the aims. Whilst completing this audit and the write up of results and discussion, it was apparent that there are areas where evidence or points are anecdotal. In daily clinical practice,

we assess patient condition and discuss any issues or concerns that they have in including symptom control. These conversations were not recorded or annotated unless further multi-disciplinary input was required. For example, in the discussion chapter reference is made to patients exhibiting an increase in LUTS at fraction four. All this is oral information from conversations with the radiographers and the patients and obviously this occurred in too many incidences to be considered coincidence and therefore the inference was made that this is a common occurrence. However, there is no recorded data to definitively evidence this. If the study were repeated, it would be a sensible recommendation that any reporting of symptom variations should be recorded either on an approved audit document or the patients radiotherapy prescription sheet. In terms of data collection this is something that I would address in future practice to ensure there was robust evidence to use in the discussion of results. This aligns with a further research skill of attention to detail. Again, in clinical practice, this is something that you do subconsciously and at points, this has shown in the data analysis or collection within the audit. There has to be an awareness shown, that just because we do things, such as use abbreviated terminology or know the process, this has to disseminated appropriately in audits or research. An example of this was in writing the work instructions for the use of the RayPilot® system. One of the radiographers involved in the end-to-end testing noted that there was no instruction that stated “turn on the RayPilot® computer”. At the time this seemed extremely pedantic however, upon reflection, if you are using documentation within an audit or research this is the level of detail required to validate the methodology used and in turn the findings and results. This was something I tried to focus on throughout the rest of the experience.

Adaptability is an essential skill within research. Being open to adjusting research strategies and methodologies based on new insights or unexpected challenges is a crucial skill. At the beginning of this process, it was assumed that the patient cohort would potentially have been large enough to used inferential statistics. However, due to a number of factors discussed the resulting patient cohort was extremely small at n=7. This required a rethink and redirection of statistical analysis, and the acknowledgement that the audit may not be as impactful in terms of power or generalisation to the population. The most impactful unexpected challenges were that of Covid 19 and the update from Micropos outlining a change in the method of device implantation from the surgically implanted device to the use of the HypoCath® system. The decision had to be made whether to complete the audit on the patient cohort of seven or to repeat the audit once the new system was in place. Due to the

time constraints of the doctoral protocol this would not be a feasible option as at the time of this change in technology, Covid restrictions on research were still in place and the issues of clinical implementation of the new technology would have encountered further delays. For example, staff training on the new technology and gaining competency in the procedure of insertion of an indwelling catheter. This was a period of great frustration as the benefits and disadvantages of both options needed to be considered carefully. This was an example of how this process aligns with the level 12 SCQF descriptors. By using communication skills and expert knowledge to make decisions in a complex and unpredictable situation when information is incomplete or inconclusive, is exhibiting a high level of autonomy. As data collection had already been started on the seven patients, I decided in conjunction with clinicians and academic supervisors to continue the process with the available patient cohort. The process was the same, however, it was disappointing to realise and conceptualise that the audit would not reach full potential on correlation due to small numbers.

Dissemination of findings was a research skill that I lacked prior to this experience. As radiographers we are involved in research projects routinely, however, we are rarely included in the dissemination of findings. Along with this, we routinely do research and implement service changes but we are extremely underrepresented in the research arena. Appropriate dissemination of information and findings is crucial in medical research and the sharing of information culminates in collaborative evidence based practice for the wider radiotherapy community. However, it is essential that departmental information sharing is also a priority to ensure that patients are not only receiving the right information but that colleagues directly involved in the research are also given a comprehensive overview of the trial but also to ensure that they are competent in the processes and have the ability to problem solve any issues that arrive. It is essential that colleagues are educated in the importance of documentation in the trial environment and the role that they play in this.

Initially the department and I decided to enrol a small team of therapeutic radiographers to undergo training in the use of the RayPilot® system and then complete a training plan, which would then be signed off to ensure consistent compliance with training. This included detailed descriptions of all the components of the RayPilot® system and software, transmitter device management and initial problem solving tasks. The training plan is included as Appendix 8. At its inception, it was decided that only senior radiographers were recruited to the team, the rationale

for this being that at their experienced level the further training required would be purely in relation to the use of RayPilot® and the software, whereas less experienced staff may not have completed the required competencies in other areas e.g. 3 dimensional imaging, or have limited experience in clinical judgement. It is essential that training plans ensure the knowledge and experience gained warrants the radiographer being classed as competent in that technique. It is therefore imperative that consideration is given to the magnitude of learning required and the complexity of the task along with the notion of radiographers possessing appropriate transferable skills. The training plans had clear outcomes from the outset. Initial tasks included an overview of the system, an observational period including five patients or phantom set ups, and then the radiographers taking the clinical lead in three patients including rationalising their decision-making.

I composed a presentation for this team and this was used for information sessions for other therapeutic radiographers and nursing staff. This is alignment with SCQF level 12 recommendations of managing and communicating complex material to a varied audience. An inclusive approach was taken to ensure consistency in patient care from all stakeholders e.g. treatment floor nurses who may be required to assess patients during radiotherapy treatment and the clinical nurse specialists for post radiotherapy care and enquiries. It was also available for registrars who joined the team on a rotational basis and the new Clinical Consultant Oncologists who took up new posts within the GU team. It was also used as a method of updating the RTMG on the development and progress of the project for which they had granted ethical approval (Appendix 13).

The method of dissemination and interpretation of findings within an audit or research is obviously a fundamental component to a thesis or report; however, we need to consider dissemination of findings out with this context. Due to the department being the first to use this in the UK, the lead clinician requested the involvement of the BBC (British Broadcasting Corporation) news. This proved to be an area of contention with the departmental managers. The lead clinician is passionate about promoting the research and developments within the department and to the GU service and as such wanted to televise the first patient in this pivotal trial. The radiotherapy management team had reservations that this would be disruptive and increase stress in an uncharted procedure. After much consideration, they agreed. All persons involved were asked to sign consent forms allowing video footage to be recorded and used in three news bulletins for that day, this included the patient. The footage was recorded

and the first treatment with RayPilot® went without any incident. Of the back of this, many patients requested information regarding the trial and, contrary to my expectations, many men were interested in the development due to the far-reaching potential of the national news. Upon reflection, this was a pivotal moment in the dissemination of information to a wider reaching audience. It also highlighted that patients, as major stakeholders of the service, are also interested in future developments and research in relation to their condition that leads to increased informed decision making in their patient pathway.

Previously in my career, I have been reluctant to publish work in peer review journals due to a feeling of my work not being of interest or a high enough standard to do so. However, as I progressed in the Professional Doctorate journey, I have seen an improvement in my confidence and ability to convey the findings of my work. Again, this may be due to personal growth following self-reflection. In an attempt to engage the wider oncology community, I have had successful submissions to a number of conferences relating to my research. It is essential to see the benefits and impacts from all stakeholder perspectives and as such, I submitted a poster presentation to the UKIO (UK Imaging and Oncology Congress) 2020 conference entitled RayPilot®: The Patient Experience (Appendix 14) (Adamson, 2020). This shares qualitative data collected from a number of face-to-face interviews with the patients where they were asked a number of questions but also given time to describe their own thoughts on the experience following implantation and treatment delivery. This was a new skill acquired within the process and as such, moving forward I would try and include more qualitative data in the future as a researching professional.

Our regulatory body, the SOR, conducts an annual conference displaying the research and development of radiographers in their chosen field. An abstract entitled 'Implementing research in to clinical practice; a report of the implementation of the printout trial at the Edinburgh Cancer Centre' (Mitchell et al., 2020) was offered as a proffered paper abstract. The paper was submitted in collaboration with the radiographers working on the PRINToUT study with each radiographer constructing a section on their area of expertise (Appendix 15). This was also included in the SOR monthly peer reviewed journal, Radiography. Following on from the submission of this proffered paper, we were given the opportunity to present our research at the conference. It was decided that for continuity, one member of the team would present, but again, we all contributed to the presentation and were named authors in all aspects. This was a defining moment in my own journey into publication as the impact

of having accepted submissions reviewed and presented to your professional peers created a great sense of pride and excitement.

Most recently, I have collaborated with one of the lead physicists in the department to submit an abstract for the American Society for Radiation Oncology (ASTRO) annual meeting (Appendix 16). The paper was written in regards to dosimetric impact of the RayPilot® data and is entitled 'Analysis of the intrafraction motion of the prostate during SBRT using an EM (electromagnetic) transmitter' (Trainer et al., 2020). The results of which have been described in both the results and discussion section of this thesis. Unfortunately, due to the global COVID crisis, this meeting was cancelled but submissions were available to download online.

8.4 CHALLENGES FACED.

One of the greatest challenges in this process was the availability of peer support. It was essential before embarking on this process that agreement and support was gained from the departmental management. Research is a fundamental part of clinical practice and as such, the SOR have recently implemented a research strategy to highlight the importance of research within the profession. However, research is still seen in some departments as an 'add on' to professional practice, not a fundamental part of it. As such, it was important to get the approval from the radiotherapy manager before embarking on this endeavour. At that time, I was the only person attempting doctorate level study and this was a new process to my manager and myself. Following discussions, it was agreed that I could start the process and that we would have follow discussions regarding support required. Unfortunately, this did not transpire and support within the radiotherapy team was difficult to obtain. For example, throughout the whole process the study had to carried out in my own time, I was not allocated any time in my workload for carrying out the study. This was a large barrier to overcome. I think this came from a lack of knowledge and understanding of what this process entailed and again, the opinion that research is considered as a 'bonus' participation rather than an embedded element of the professional role. Following completion of this professional doctorate journey, this is something that I am passionate about challenging and changing in the clinical setting. It was also difficult to engage peer support as the only radiographer studying at this level. At times this was quite an isolating experience; however, coincidently a physicist was also undertaking the professional doctorate, which gave

some support at varying times throughout the process. This however, highlighted the difference in managerial support. As a different sub-section of the radiotherapy department, this person had a different line manager who appeared to value research. As such, they were allocated protected time to carry out their study. I think it would be beneficial for all managers to provide, where possible, an integrated approach to providing support. Recently, a further member of staff has started the doctoral journey and had been provided with allocated time for completing the process at two days per week. After completing the process, there is no question as to how beneficial this would have been in terms of support. I think that this is something that requires to be addressed if we want to inspire more radiographers to undertake this level of study in line with the SOR research strategy. With more members of staff concluding this level of study hopefully, we can be seen as a source of support and encouragement for future radiographers attempting further study. It would be beneficial to the department to have members of varying levels of study to use as a resource for others.

An encouraging development within the department's approach to research was the implementation of the two research radiographers and a principal research radiographer thereafter. The concept of having a cohesive team to ensure that all research projects within the department are disseminated to the wider team, ensure compliance with research guidelines such as GCP , complete eligibility assessments and other research required tasks, shows a level of commitment towards research within the department. However, it is worthy to note that the PRINToUT study was the first major research study conducted as a UK first in the Edinburgh Cancer Centre so the input of the principal and the research radiographers was focused on the research trial and neither had any input into the clinical audit of this thesis. The department has a vast number of clinical trials ongoing currently and this is the main workload and focus of the principal research radiographer. However, upon reflection, it would have been beneficial if part of that role included advocating for staff members completing studies for further qualification, for example, allocated protected time as previously mentioned or regular meetings to review the needs of the researching professional to offer advice or sign post support. Again, this aligns to the fact that doctoral level research does not only benefit the individual but the department as a whole and provides enhancement to service delivery and the patient journey.

This aligns with the perception of the radiographer's role and the promotion of transferable skills, which allow site specialists to take on other roles that would have traditionally been carried out by other disciplines. This was an area of contention

during the implantation process. Initially a senior clinical radiologist and I were trained in the surgical trans-perineal implantation of the transmitter device. This included a visit to Orebro in Sweden where we were trained by the clinical oncologist who patented the device and implantation method. This proved to be an invaluable experience, which was followed up by a visit to Lyon to observe implantations. Following this, the clinical oncologist from Sweden attended our department to offer further training and to be on hand for the first patient. There is no question that the clinical radiologist had vastly more experience in trans-perineal procedures, however it became apparent early on that this was going to be deemed a radiologist led procedure. As mentioned previously this had quite an impact on the patient pathway and therefore our ability to book patients. If the training of both members of staff had been utilized then this could have been mitigated. It also meant that, with no experience of carrying out the process, this gained skill was effectively wasted in the clinical setting. This made it apparent that although multi-disciplinary working has greatly increased within the NHS, more work is required to highlight the transferable skills that disciplines can use effectively to increase workflow and implement effective patient pathways. As such, a small discipline within the allied health professions, it is essential to career progression, recruitment and retention that radiographers are given the opportunities to promote the profession whilst gaining new skills. This is something I am extremely passionate about following completion of this process.

8.5 PERSONAL GROWTH.

Clinically the advanced practitioner radiographer is not only the department lead for their speciality area, but also provides leadership on a daily basis in the effective running of the treatment units providing support and advice for colleagues, ensuring protocols are adhered to, aiding in staff training and skills development, organising patient workload, dealing with conflict and general management of the high paced, dynamic environment. However, experience in this role can lead to ‘prescriptive’ forms of leadership e.g. working within and leading peers in a regulated fashion in relation to protocols already in place. In my opinion, taking responsibility for leadership in the implementation of a research project or clinical audit requires a completely new and different set of leadership skills. The outcomes of the project, not just clinically but professionally and personally, are reliant on you providing motivation and engagement from other members of the multi-disciplinary team. It is therefore, essential that you develop leadership skills in which you can not only lead

but also support your team. It is also imperative that researching professionals make use of specialists in other fields to ensure robust inter-professional input, and if appropriate, the researcher can delegate tasks to other specialists that may have a greater understanding of the subject knowledge. Providing support is a critical role of not only the person leading the project but also from team members. When seeking or giving help it is important for the support to come without removing ownership of the task as this is how we learn and develop our roles.

It is essential that effective leaders have a forward thinking and flexible approach to leading a project. Seminal research will not follow a simple path from instigation to completion. There will be failures and hurdles in the research journey trajectory and it is imperative that the lead can come up with novel solutions to these issues whilst maintaining engagement and trust from their colleagues. I have enhanced this level 12 SCQF skill throughout this journey. I feel that I am now more confident in offering original and creative insights into addressing issues and development programmes. A good leader must remain flexible in their approach to achieve their goals. In saying this, a good leader will also know when they are required to ask for support or help in order to do so.

Good leadership is reliant on self-awareness and reflection. This is something that I have researched and given greater attention to since starting this project. Effective leaders learn to take feedback from a variety of sources and pay attention to a balance of so-called “positive” and “negative” feedback which they then evaluate it in a way that supports and helps them make decisions and take action. However, all the skills mentioned to be an effective leader require an understanding of your learning and personality style.

I undertook the Myers-Briggs type indicator (MBTI) personality assessment following implementation of the first patient and found that I am classified as an INJF (introverted, intuitive, feeling, and judging) personality type. INFJ types in the working environment are described as focused on the task of bettering the human condition. INFJs are dedicated, helpful, and principled workers who can be relied on to envision, plan, and carry out complex projects for humanitarian causes. Although they are typically driven by lofty ideals, they gain the most satisfaction from their work when they can turn their ideas into reality, creating constructive change for other people. INFJs are typically organized and prefer work that allows them to complete projects in an orderly manner. They are often independent and tend to prefer a quiet

environment that allows them the opportunity to fully develop their own thoughts and ideas.

The ideal work environment for an INFJ is harmonious, industrious, and oriented to a humanitarian mission, with co-workers who are similarly committed to positive change. INFJs are creative solvers of people problems, and bring innovative ideas for fostering human potential. They are usually perceptive in observing the talents of others, and good at encouraging teammates to contribute their skills. They are mindful of group process, listening attentively to the opinions of others and synthesizing varied priorities to create a unified vision. Because they prefer to accommodate all points of view, INJFs may have trouble on very competitive or conflictual teams.

In leadership positions, INFJs motivate others by sharing a positive vision. INJF leaders are often quiet and unassuming, but win other's dedication through their own hard work, strong principles, and inspiring ideas. They are at their best when guiding a team to commit to a common vision, and when creating organizational goals to benefit people. They are insightful and creative, and bring a sense of confidence and commitment to projects they believe in.

Much of this resonates with me in relation to how I like to work or what is important to me at work. One of my main priorities is to develop the service to improve the patient journey. The patient is the main stakeholder in all that we do and service evaluation and development should always have the patient at the heart of it. I do hate conflict and do not deal with it well in any environment; however, I especially avoid it in the workplace. I am also averse to the assumed hierarchy and superiority of some colleagues in the workplace – I am a strong believer that you should not need to make others feel inadequate, less, or reduce their self-esteem to make yourself feel important or superior. Unfortunately, I have experienced this first hand, even during this project, and it can be an issue of extreme stress and emotional turmoil.

Having self-reflected on how I see myself and how I see an effective leader, before I put that into practice I wanted to evaluate how other peers and colleagues see me in the workplace. This could give an insight into further strengths and weaknesses that could require work. To do this I gave a number of colleagues that I have worked with for a period of time a 360° feedback questionnaire (Appendix 17). I decided on a multi-disciplinary approach to participation to ensure a broad spectrum of opinion, I included a senior clinical oncologist, the clinical nurse specialist team that I work closely with, a medical secretary, a senior radiographer, an advanced specialist radiographer, a band five radiographer, a medical physicist and the chairman of the

prostate support group. The cross section of peers included an advanced specialist radiographer who trained me not only as a student but also throughout my career; it is safe to say that in that time we have had a number of professional disagreements and differences of opinion. The band five radiographer had the least amount of experience and I have been a mentor to them since qualification. The inclusion of the chairperson of the prostate support group was to receive feedback on my performance out with the clinical setting. For feedback to be honest and valuable to self-reflection, it is important that it is not just sought from peers that you assume would give you positive answers, but that includes peers that you have differing opinions and interactions with to ensure open, honest, robust feedback allowing you to contextualise the responses. It was completed anonymously and provided favourable positive results. I was deemed as a valuable member of the team, inspiring in my methods of teaching and support and described by all respondents as a person centred character. Having self-reflected, I was aware of being reactive to situations and extremely self-critical. This was echoed in a reply that stated that although responsive to feedback I could respond defensively. If I am passionate about something, in this case the project, I can find constructive criticism a personal attack. I believe this comes from my own insecurities and self-esteem. In part, this is due to previous experiences with interactions from senior members of staff and in part from the notion that I am the expert and the need to convey this appropriately. This was also apparent in one response that reiterated the point that I seem to be uncomfortable when receiving compliments and positive feedback. When receiving feedback, I have acknowledged that perhaps I do not consider that my reaction to positive feedback can influence the person giving it. This could conversely result in them not providing positive feedback in general terms as I convey the impression that I do not believe it or feel deserving of it, which can lead to a self-fulfilling prophecy of thinking that I only receive feedback if I have done something wrong or that feedback is reserved for criticism.

Moving forward in my self-development, my aim is to receive both negative and positive feedback in the manner it was given. I will try to take the emotion and the connotations I perceive, in a non-emotional way and use it to constructively adapt and develop my practice. The aim of doing so is to address feedback objectively and learn from it to adjust my behaviours in dealing with colleagues.

I have improved my communication style greatly and use this daily in the clinical setting. Unfortunately, during this experience I have personally been faced with

conflict from a colleague who was given a senior role. I strive to maintain good working relationships with all the people I work with however, in this instance this was not possible. It made implementing my methods quite challenging and at times, I felt like my autonomy was being jeopardised. The particular issue was the way in which we communicated. I perceive that there was a consistent pattern of belittlement and negativity in the communication and this had a cumulative effect of my professional confidence and motivation being chipped away. I addressed this with them directly however, this did not achieve the hoped for outcome. Rationally, I reflected upon this as not a personal issue as this was common practice from this individual to a number of specialists. In this situation, I can only control my reaction to it. Previously, I would become defensive in my interactions and my decision-making rationale when questioned. However, as I have gained experience in the process I have realised that I am the expert in this subject and deserve to be respected as such. I have also learned that there will always be outside factors that can affect your direction, motivation and work, however, these are all emotional aspects that will fluctuate through the journey and it is our commitment that matters. Commitment is constant, motivation and learning from failures is not.

Having completed this process, I am extremely passionate about promoting and advancing the role of the therapeutic radiographer. This has now crossed over into the realm of academia. I am now a lecturer in radiotherapy and oncology at a local university. This role in conjunction with my clinical role allows for transferable knowledge and a link between the clinical centre and the new generation of radiographers joining the profession. I enjoy this role immensely and aim to instil knowledge and values that will aid in the transition from student to clinical professional. In this role I have recently lead on the interprofessional research modules and having completed this process, feel very well placed to do so. It is essential that the new generation of professionals realise the potential or the role and the part that research can play in a profession that relies on lifelong learning. In the long term, this is something that can aid in retention in the profession. Role progression can sometimes be a barrier in relation to retention, so preparing members of the team in terms of what they can add to their remit and professional qualifications can provide a good opportunity of keeping staff motivated in their career journey.

Within this role, I am also gaining further study and qualification by undertaking the PgCAP (Post Graduate Certificate Academic Practice). This will give me a greater

understanding of the theory and practical knowledge to enhance my academic teaching. However, these skills will transfer to the clinical setting.

Following completion of this process, I will strive to use the knowledge and skills gained to advance my career, clinically and academically. Acquiring this qualification would allow me to have the desirable criteria stated by the SOR to enquire about a consultant radiographer role if the opportunity arose. Undertaking the professional doctorate has changed my attitude to academic learning due to the autonomy of research – initiating research into a topic that you are passionate about ignites a fire within you to push forward in your sector, make a tangible difference to the clinical landscape, your role in the service and the difference it can make to patient outcomes.

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10 APPENDICES

10.1 APPENDIX 1 – PRINToUT PROTOCOL

PRINToUT

Using breath analysis to PRedIct Normal TissUe and Tumour response during prostate cancer SBRT

	The University of Edinburgh and/or Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
Protocol authors	**Dr Duncan McLaren**
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Amendment classification and number:	**Summary of change(s)**

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CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

INTRODUCTION

BACKGROUND

Prostate Cancer is the commonest male cancer in the UK and its incidence is growing (1). Technological advances in the delivery of external beam radiotherapy has led to the development of Stereotactic Body Radiotherapy (SBRT) where curative doses of radiotherapy are given in only 3-7 large (5-8Gy) fractions of radiotherapy compared to conventionally fractionated 2Gy doses over 40 fractions (2). Accumulating evidence suggests that prostate cancer has a low alpha beta ratio and will particularly benefit from the hypofractionation used in SBRT (3).

In delivering this treatment, attention must be given to ensuring that the Clinical Target Volume (CTV) to Planned Target Volume (PTV) margins are 5mm or less (frequently 3mm posteriorly) to limit the dose to the critical surrounding normal tissues (4). Importantly any errors in hypofractionated treatment delivery are magnified by the lack of fractions which can smooth out systematic or random errors during a more prolonged course of treatment (5). This may result in a significantly reduced dose to the tumour and perhaps more importantly a higher dose than expected to the normal tissue

In addition to inter-fraction error there is also the potential for intra-fraction treatment error due to prostatic motion during the relatively prolonged treatment time of an SBRT fraction (6). Delivering prostate SBRT with Filter Flattening Free (FFF) protocols can shorten treatment time but can potentiate the effects of treatment errors due to the large amount of radiation dose delivered each second. Prostate motion management systems, which track the position of the prostate in real-time, can greatly reduce this risk with several commercially available systems already in use (7-9). In this study the implantable system developed by Micropos Medical, RayPilot® will be used (7).

Increasing radiotherapy dose to the prostate can improve PSA relapse free survival (RFS) and in effect cure more patients (10). It does however also lead to a potential increase in acute and cumulative late radiation effects which can impact on QoL (11). Traditional prostate dose escalation has been achieved by adding extra fractions of radiotherapy of 2 Gy per day, resulting in protracted treatment over 8 weeks (10). Prostate SBRT can provide dose escalation to a biologically equivalent dose of 78Gy in 39 fractions in only 1-2 weeks by using much larger 5-8 Gy fractions. Prostate cancer is particularly sensitive to the larger dose per fraction schedules used in SBRT with equivalent PSA control and treatment related toxicity reported in single centre cohort studies (12). Important longer-term randomised controlled trial data from the Swedish Hypo-RT trial has recently been presented (13). 1200 men with intermediate risk prostate cancer were treated with 78Gy in 39 fractions over 8 weeks or with 42.7Gy in 7 fractions over 2.5 weeks. After a median of 5 years of follow up there was no difference in the side effects of therapy or in the PSA control between the 2 groups. Patients who receive prostate SBRT benefitted from resultant gains in terms of patient convenience without added toxicity while the radiotherapy departments benefited from the greater through put of patients and linear accelerator capacity.

Despite meticulous radiotherapy delivery and carefully worked out Equivalent Dose in 2Gy (EDQ2) schedules a proportion of patients will continue to fail treatment and develop treatment related toxicity. One reason for this is the inherent heterogeneity of each individual patient's normal tissue and tumour sensitivity to radiotherapy (14). The prediction of radiation normal tissue sensitivity using a clinically useful and practical assay has so far been elusive. The RAPPER study may well demonstrate single nucleotide polymorphisms (SNP'S) in a patient's genome that may be predictive, and the data is awaited (15). Patients who are predicted to be sensitive to radiotherapy could receive a lower total radiation dose while those thought to be less sensitive, the dose may be increased to try and improve tumour control for the same level of toxicity. Trying to optimise this therapeutic ratio is clearly worthwhile, however having the ability to adapt radiotherapy dose during a course of treatment based on the actual normal tissue response would adapt and personalise the radiotherapy to a higher level.

Understanding of how the normal tissue is reacting to treatment is important for treatment related toxicity and quality of life, however to improve local control and survival by eradicating more tumours we need to understand the complex individual tumour biology (16). Tumour heterogeneity is likely to be greater than normal tissue due to the mutational drive that tumours possess (17). The effects of treatment will have dynamic effects on the tumour biology and we need to be able to measure these effects in real-time.

We have experience with using Gas Chromatography, Ion Mobility Spectroscopy (GC-IMS) breath analysis as part of the Toxi-Triage Horizon 20:20 European Grant 653409. We have irradiated cancer patients with Prostate, Breast and Lung cancer and detected volatile organic compounds released into the breath relating to radiotherapy normal tissue and tumour damage using GC-IMS breath analysis. Exciting preliminary data also suggests that the pattern of breath analysis volatile organic compounds (VOC's) changes over time, between patients with the same tumour type and between patients with different tumours (unpublished data). Development of these rapidly measured breath biomarkers may provide real-time information on tumour and normal tissue heterogeneity of response to the dose of radiation delivered raising the possibility of reducing the dose to those patients predicted to be sensitive to therapy while increasing dose to those thought to be more resistant.

RATIONALE FOR STUDY

Hypothesis

Individual prostate cancer patient heterogeneity in normal tissue and tumour response to radiotherapy can be rapidly detected via volatile alkane release (VOC) during high dose per fraction stereotactic body radiotherapy (SBRT). These data can then be used to adapt the dose or fractionation schedule during a course of prostate SBRT to optimise outcome.

The ability to adapt the radiotherapy delivery to the patient's own response to that treatment would be transformative. Personalisation of the radiotherapy dose and schedule would maximise the chance of cure and minimise the long-term post treatment toxicity, impacting on quality of life.

STUDY OBJECTIVES

OBJECTIVES

Primary Objective

- To establish biomarkers of normal tissue and tumour response through the measurement of VOC's released in the breath following high dose per fraction prostate SBRT.

Secondary Objectives

- To compare the VOC biomarkers to quantitative analysis of the free circulating tumour and normal tissue DNA in blood and in urine
- To analyse the specific gene mutations detected within the free circulating tumour and normal tissue DNA
- To assess the pre-radiotherapy RNA gene signature profiles of the original prostate biopsies
- To assess the acquired mutations with the germline mutations

- To compare patient reported outcome measures and clinical radiotherapy toxicity measures with the VOC and genetic data

ENDPOINTS

Primary Endpoint

- To establish sufficient pilot data to explore the hypothesis
- To assess the ease of recruitment to the study
- To assess the optimal data collection time points for analysis

Secondary Endpoints

- To compare the VOC biomarker data with patient and clinician reported outcome measures of treatment related toxicity
- To compare the VOC biomarker data with blood and urine free circulating tumour and normal tissue DNA analysis
- To compare the VOC biomarker data with pre-treatment prostate biopsy RNA gene profile analysis.

STUDY DESIGN

This is a non-randomised cohort observational study.

STUDY POPULATION

NUMBER OF PARTICIPANTS

We will aim to recruit 1-2 patients per month over a 12-month period. On completion of radiotherapy patients will be followed up in the outpatient clinical trials clinic for 2 years. The study will close once the last patient has completed 2 years of follow up or withdrawn from the study after approximately 3 years.

INCLUSION CRITERIA

- Low risk prostate cancer T1-2, PSA<10ng/ml Gleason score of 3+3=6
- Intermediate risk prostate cancer with 1 or more of T1-T2, PSA10-20ng/ml, Gleason score ≤7 (3 +4 only)
- WHO performance status 0-2
- Prostate volume ≤90cc (no androgen deprivation therapy will be given in the study or for downsizing the prostate)
- IPSS Score ≤20
- Q-max>10cc/sec
- Urinary residual <250mls total
- No prior TURP
- Medically fit for radical radiotherapy
- No contradiction to receiving radiotherapy such as inflammatory bowel disease
- No previous pelvic radiotherapy

- Able to give informed consent
- Aged between 40-80 years of age

EXCLUSION CRITERIA

- T3/T4 disease
- WHO performance status >2
- PSA >20ng/ml
- Gleason grade 4+3= 7, 8-10
- Prior Androgen deprivation therapy
- Previous TURP
- Prostate volume >90cc
- IPSS score >20
- Q-max <10cc per second
- Urinary residual >250mls
- Unsuitable for radical radiotherapy due to inflammatory bowel disease
- Previous pelvic radiotherapy
- Medically unfit for treatment
- Unable to give informed consent
- Under 40 or over 80 years of age

CO-ENROLMENT

Co-enrolment will not be permitted within this study.

PARTICIPANT SELECTION AND ENROLMENT

IDENTIFYING PARTICIPANTS

Patients thought to be potentially suitable for the study will be identified through the weekly multidisciplinary team meeting (MDT) or within the weekly GU Oncology clinics when seen as a new patient.

CONSENTING PARTICIPANTS

The research nurses within the Team 4 SCRN trials team will provide the patient with the patient information leaflet after initial clinic discussion. The research nurses will also check eligibility criteria. After at least 24 hours the research nurse will contact the patient to answer any questions and organise a follow up appointment in the Monday afternoon trials clinic if the patient is considering joining the study. At this visit consent will be taken after answering any outstanding issues.

Withdrawal of Study Participants

A patient may withdraw from the study at any time by removing consent or by the investigator if medically unfit to continue. Any data already obtained will be held within the study unless explicitly expressed by the patient not to do so.

STUDY ASSESSMENTS

STUDY ASSESSMENTS

Prior to treatment a standard 30-minute multi-parametric prostate MRI scan will be undertaken. Following the MRI scan the patient will be taken to the Daybed Outpatient Theatre Unit for ultrasound guided trans-perineal insertion of 3 gold fiducial markers and the RayPilot® device into the prostate under local anaesthetic (a pre-planned short general anaesthetic may be used in selected cases if required). Patients will receive 3 days of oral antibiotics as per standard procedure. On completion of this procedure the patient will be taken to the Oncology Department for a standard radiotherapy planning CT scan to be performed. The patient will empty their rectum of gas using a small rectal suppository, empty their bladder and then drink 300mls of water as per standard Departmental policy. The CT planning scan will be performed with the patient supine and feet in standard foot stocks at 1mm slice thickness. This single day visit will minimise patient visits and provide a smooth workflow. If the CT planning scan cannot be completed as planned, or excessive haemorrhage or fiducial marker migration is noted at the time of the planning CT resulting in poor MRI to CT fusion, then CT planning scan will be performed within 7 (+/- 3) days of the RayPilot® insertion.

The planning CT scan and the MRI scan will be fused together using the Eclipse™ treatment planning system (Varian Medical Systems Inc.) with non-rigid and rigid mapping of the two scans. The patient's treatment plan will then be created by the oncologist and medical physicist. The radiotherapy protocol has been taken from the from the PACE trial (https://doi.org/10.1186/ISRCTN17627211) incorporating an identical dose and fractionation schedule. Standard dose volume constraints will be met as per the PACE trial for the plan to be acceptable. Each treatment plan will have peer review with a second oncologist and medical physicist to ensure concordance.

On the day of their radiotherapy treatment the patient will report to the Clinical Research Facility at the Wellcome Institute at the Western General Hospital. A cannula will be inserted into a peripheral vein in the arm and baseline blood (10mls EDTA tube, centrifuged and plasma isolated and frozen at -80 C), urine (10mls centrifuged and frozen at -80 C) and base line breath analysis will be taken by the CRF research nurses. Standard operating procedures are already in place as part of the Toxi-triage protocol currently being undertaken in Edinburgh (Eddelston local PI grant number 653409 H2020 European Grant). Breath analysis will be performed using the portable GC-IMS device BreathSpec® device (GAS Dortmund). A saliva sample will be collected for germline DNA analysis.

Patients will then be taken to the Department of Oncology for their prostate radiotherapy. Each fraction of treatment will last approximately 30-40 minutes from entering the linear accelerator room to leaving it once more. Immediately on completion of radiotherapy the patient will perform a further breath analysis and then return to the Wellcome CRF for repeat breath analysis at 30-minute intervals (+/- 10 minutes) for 3 hours post radiotherapy. If a patient does not manage to complete a given breath analysis within the allocated time frame then this will not be considered a protocol deviation, however every attempt will be made to continue to collect samples for future time points. Repeat urine samples and blood samples will be taken post treatment as above at 1 hours and 3 hours post radiotherapy (+/- 15 minutes). The patient will leave the department after the 3-hour breath analysis. Each breath analysis requires a patient to exhale a single breath through the mouth into a collecting tube with a side syringe connected. On completion of a full exhaled breath the air sample is drawn off by the syringe and connected to the GC-IMS for analysis. A full GC-IMS scan result is available within 11 minutes.

Radiotherapy will be started on a Wednesday and the procedures repeated on Thursday and Friday before a weekend treatment break and completing the last 2 days of treatment on Monday and Tuesday. On completion of treatment the Raypilot® device is removed by simply applying pressure on the system to release it from the prostate and pressure applied to the perineal skin until any bleeding is stopped. No stiches are required. Baseline patient reported outcome measures (EPIC-CP) and acute RTOG and CTCAE_V5.0 acute toxicity scores are taken on Day 1 and 5. Medical clinic follow up will be a week's 6, and 12 and months 6, 12, 18 and 24.

LONG TERM FOLLOW UP ASSESSMENTS

Patients will be followed up in clinic at weeks 6 and 12 and then months 6, 12, 18 and 24. On each occasion a PSA and acute RTOG & CTCAE_5 toxicity score will be assessed. For month 6 onwards a late RTOG score together a CTCAE_5.0 score will be used. Patient reported outcome measures will be undertaken at each visit via the EPIC-CP form. After 2 years post completion of radiotherapy, patients will enter standard Departmental postal follow up.

STORAGE AND ANALYSIS OF SAMPLES

Each patient will have a unique patient identifier starting with ZC-PRINTOUT to link their data through the study. Breath samples are not retained however the data is stored as a file within the Wellcome CRF data base for transfer and analysis to the Edinburgh Oncology Physics research encrypted database. The blood and urine samples collected at each time point will be processed within the Wellcome CRF and stored for subsequent bioinformatics analysis. The original prostate biopsy samples will be stored within the Department of Pathology at the Western General Hospital or requested from the referring Hospital if required. These samples will be returned once the study has been completed to the referring Hospital.

DATA COLLECTION

Baseline quality of life EPIC-CP and RTOG and CTCAE_v5.0 scores will be taken prior to treatment. Baseline breath, urine and blood samples will be taken on each day pre-treatment. Repeat breath samples will be taken immediately on completion of radiotherapy and at 30-minute intervals (+/- 10 minutes) for 3 hours (7 samples in total). Repeat blood and urine samples will be taken post radiotherapy at 1 hour and 3 hours (+/-15 minutes). On completion of radiotherapy repeat EPIC-CP and RTOG and CTCAE_v5.0 assessments will be made and repeated at weeks 6, 12 and then months 6, 12, 18 and 24. A serum PSA will also be taken at baseline and at these time points.

Source Data Documentation

The patients' medical notes will be the source document. A proforma for the collection of the breath, blood and urine samples will be used.

Case Report Forms

Paper Case report forms will be used to collect data and stored within the source documentation. The extensive biological output data will be electronically stored and analysed. Paper versions of EPIC-CP and RTOG & CTCAE toxicity assessments will be stored in the patient's case notes as the source document.

STATISTICS AND DATA ANALYSIS

SAMPLE SIZE CALCULATION

This study has been reviewed by the Statistics division with in the Wellcome CRF (Dr Cat Graham). In this observational study there is no formal sample size calculation required. The data collected will be used to generate future power calculations in larger follow on studies.

PROPOSED ANALYSES

Observations will be made on the patterns of patient VOC response during the study to assess the optimal time points for future collection and analysis. These are pilot data and preliminary data analysis will however be undertaken looking for statistically significant correlation co-efficient of the breath analyses patterns with the patient reported outcome toxicity data and clinically assessed treatment related toxicity, together with correlation with urine and blood free normal tissue and tumour DNA qualitative release and single nucleotide polymorphism analysis. Correlation with the pre-treatment prostate biopsy tumour gene RNA signatures will also be sought. Lastly, we will look for imaging biomarkers on the pre-treatment MRI and on treatment cone beam CT scans that may correlate with VOC patterns.

ADVERSE EVENTS

Any adverse events will be recorded in the source documentation.

OVERSIGHT ARRANGEMENTS

INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

RISK ASSESSMENT

A study specific risk assessment has been performed by representatives of the sponsor NHS Lothian through ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input has been sought from the Chief Investigator. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency. Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit-plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed**.**

GOOD CLINICAL PRACTICE

ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF.

Investigator Documentation

- The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

GCP Training

The Chief investigator and all Co-investigators involved in patient contact and trail management will have up to date GCP training, confirmed on their CV.

Confidentiality

Patients entered on to the study will be identified by a unique identification number starting with ZC001, ZC002 etc. All laboratory specimens, evaluation forms, reports, and other records will be identified using this unique number to maintain participant confidentiality All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

STUDY CONDUCT RESPONSIBILITIES

PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

MANAGEMENT OF PROTOCOL NON-COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation except in the case of a missed breath sample which may occur if a patient cannot provide it at the desired time. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

Patients will enter our Departmental 6-monthly postal follow up by PSA testing and questionnaire on completion of 2 years of follow up. If any untoward PSA or symptom scores are received, then an urgent return follow up clinic appointment will be made.

INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

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Appendix 1.0 Radiotherapy planning Criteria for prostate SBRT

15.0 SBRT planning

- Insertion of 3 fiducial markers will be done 7 days before the planning MRI scan and the CT planning scan
- The RayPilot® Hypocath™ will be placed between the planning MRI scan and the planning CT scan
- Bladder volume to be maintained between scans, by draining the bladder before each scan then dinking 325mls of water 20-30 minutes before the scan is performed
- Microlax enema to be used 2 days before the MRI and CT scan and before each day of treatment
- MRI multi-parametric with flat top couch, supine, foot stocks- standard image acquisition
- CT scan supine, foot stocks, 2.5mm slices scan from L3/4 intervertebral space to 2cm below the ischial tuberosities
- Image fusion performed based on fiducials and urethral position as per the RayPilot® Hypocath™

15.1 Evaluated Structures

The Clinical Target Volume CTV

- MRI fusion is good for the apex and rectal prostate interface but less accurate superiorly at the prostate SV interface
- If there is a discrepancy, then the CT volume is used
- Low risk CTV = prostate only
- Intermediate risk CTV = prostate plus 1cm of proximal SV

The Planning target Volume PTV

- The CTV to PTV margin is defined as the CTV plus 5 mm except posteriorly where the prostate abuts the rectum, where a 3 mm margin will be applied
- PTV = CTV +5mm ant/sup/lat and inf and 3mm post
- Dose 36.25Gy in 5 fractions over 7 days

Organs at Risk OAR's

- Rectum-defined as a solid structure form anus at ischial tuberosties to recto-sigmoid junction
- Bladder-defined as a solid structure
- Urethra-defined from bladder neck to membranous urethra

- Penile bulb-defined as the bulbous spongiosum inferior to urogenital diaphragm
- Femoral heads-defined to exclude the femoral neck
- Bowel within 4cm of PTV, outline as a bowel bag volume
- Testes are to be outlined and blocked if in field

Nomenclature used in the study	
SBRT treatment volumes	
Clinical target volume: prostate +/- seminal vesicles (receives 40 Gy)	CTVp_4000 or CTVpsv_4000
Planning target volume (receives 36.25 Gy)	PTV_3625
Organs at risk	
Rectum	Rectum
Bladder	Bladder
Urethra	Urethra
Left femoral head	FemoralHead_L
Right femoral head	FemoralHead_R
Penile bulb	PenileBulb
Bowel	Bowel

15.2 Dose Specifications

- The prescribe dose is 36.25Gy given in 5 fractions over 7 days
- Treatment will start on a Wednesday with a built-in weekend break
- V36.25Gy ≥95% = prescription dose to the PTV
- V40Gy≥95% = dose to the CTV
- PTV: D98% ≥ 34.4Gy
- Dmax <48Gy
- D2% ≤ 42.8Gy if possible

Table 5: Dose Specifications for SBRT (36.25 Gy in 5 fractions)

OAR	Dose constraint
Rectum	V18.1 Gy <50% (i.e. 50% rectum <18.1 Gy) [59, 78] V29 Gy <20 % (i.e less than 20% rectum receiving 29 Gy) V36 Gy <1cc
Bladder	V18.1 Gy <40% [79] V37 Gy <10cc (optimal V37 Gy<5cc)
Prostatic urethra (if visualized)	V42Gy <50% (optimal , not mandatory)
Femoral head	V14.5 Gy <5% [79]
Penile Bulb	V29.5 Gy <50% [80]
Testicular	Blocking structure
Bowel	V18.1 Gy <5cc V30 Gy <1cc

Rectum dose

- minor variation V36Gy ≥ 1cc but <2cc
- major variation V36Gy ≥ 2cc

Bladder dose

- minor variation V37Gy ≥10cc but <20cc
- major variation V37Gy ≥20cc

Target Volume Variations

- minor variation: CTV V40Gy 90-94.9%
- major variation: CTV V40Gy <90%
- minor variation: PTV V36.25Gy 90-94.9%
- major variation: PTV V36.25Gy <90%

Inability to meet protocol dose coverage and constraints

- one minor variation allowed in EITHER primary or secondary dose prescription i.e. PTV 36.25Gy 90-95% or CTV V40Gy 90-95%
- Two minor variations or one major variation will require consent of the CI
- Minor variations are allowed in bladder and rectum OAR's
- Major variations in bladder and rectum OAR's require permission of CI

On treatment

- Fiducial markers match to 3mm tolerance
- RayPilot® patient registration to couch and observation of tracking
- Pre and post treatment daily cone beam CT
- On treatment tumour tracking and beam interruption if prostate moves outside of PTV
- Allow the prostate to settle back to treatment position before switching beam on

APPENDIX 2 – ETHICAL APPROVAL NOTICE.

10.2 APPENDIX 2 – PRINToUT PATIENT INFORMATION SHEET

Participant Information Sheet

PRINTOUT

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Contact us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

We wish to study whether the release of chemicals called volatile organic compounds (VOC's) into your breath, released from the tissues following radiotherapy to your prostate could predict for response to treatment. If we could predict the response to the treatment during the radiotherapy it may be possible in the future to alter the radiotherapy treatment dose or schedule to reduce the risk of side effects or to increase the chances of cure. This is an early exploratory study where we hope to recruit 1-2 patients per month over a 12- month period.

Why have I been invited to take part?

You have been asked to take part as you have been diagnosed with localised prostate cancer suitable for curative treatment with radiotherapy.

Do I have to take part?

No, it is up to you to decide whether or not to take part. If you decide to take part, you are still free to withdraw at any time and without giving a reason. Deciding not to take part or withdrawing from the study will not affect the healthcare that you receive, or your legal rights. Before participating you should consider if this will affect any insurance you have and seek advice if necessary

What will happen if I take part?

If you do decide to take part, you will be given this information sheet to keep and be asked

to sign a consent form. The research nurse will organise for you to come to the trials clinic

to answer any questions, you may have about the study with the Doctor in the clinic. Once

you are happy, you will be asked to sign the trial consent form, and this will be

countersigned by the Doctor. You will be likely to start the radiotherapy in approximately 4

weeks from signing this form.

In order to receive the radiotherapy a number of stages of treatment planning are

required.

Planning MRI scan

- **A Radiotherapy planning MRI scan of the prostate will be undertaken initially, that will take approximately 30 minutes. This will be very similar to the diagnostic MRI scan. A small injection of contrast is given into a vein by the radiographers to help with the scan. This can lead to some patients feeling a flushing sensation for a few minutes. This scan will be combined with the radiotherapy planning CT scan to help plan the radiotherapy treatment by accurately localising the tumour.**

Insertion of RayPilot® and fiducial markers

- **On completion of the MRI scan you will then be taken to the surgical day bed area for insertion of the 3-standard fiducial gold marker grains into the prostate under local anaesthetic. These markers are inserted through the skin between the anus and the scrotum called the perineum. The procedure is similar to your prostate biopsy. An ultrasound probe placed in the rectum visualises the prostate and guides the gold marker placement however, unlike the biopsy the needle does not pass through the rectum. The local anaesthetic is given as a small injection into the perineal skin and can sting a little before the area is numb.**
- **If you are on blood thinning drugs such as Clopidogrel, Aspirin, Apixaban or Warfarin you should have been asked to stop these drug 7 days before this procedure.**
- **Once the gold grains have been positioned the RayPilot® device is inserted into the prostate through the perineum in the same fashion as the gold grains. The ultrasound probe in the rectum being used to guide placement of the device within the prostate.**

- **Once the RayPilot® device is in place a thin plastic tube attached to the device comes out of the perineum and is attached to your leg by sticky tape. This tube is the connected to the treatment bed at the time of the radiotherapy and tracks the prostate motion. (please review images attached to this information sheet)**
- **Antibiotics for 3 days will be given post insertion of the gold markers and the RayPilot®. These are the same antibiotics that you would have been given after your biopsy.**
- **Simple pain killers such as paracetamol can be used and there may be a small amount of bruising seen a few days later.**
- **Insertion of the RayPilot® and gold grains under local anaesthetic will take approximately 30 minutes**
- **You will be given a prescription of a drug called Tamsulosin to take home and to start taking 3 days before the radiotherapy starts.**
- **Your consultant will advise you when to stop this drug on completion of the radiotherapy. This once a day tablet can help the flow of urine and decrease the need to pass urine following the radiotherapy.**

Radiotherapy planning CT scan

- **If possible, we would then like to do the radiotherapy planning CT scan on the same day before you go home.**
- **This is a standard scan taken in the Department of Oncology and will take 30 minutes**
- **Before the scan is performed any gas in the rectum is expelled using a small suppository inserted into the rectum. After only a few seconds the suppository is expelled along with any gas.**
- **The radiographer will then ask you to empty your bladder and drink 3 cups of water (300mls) to refill the bladder prior to having the CT scan**

- **The scan will take 30 minutes and some measurements of the prostate position will be taken and a few small ink marks called tattoos placed on the skin**
- **You are then free to go home**
- **The MRI and the CT scan will be used to plan the radiotherapy treatment with the Doctor and the Oncology Physics team producing your treatment plan.**
- **It is anticipated you would start the radiotherapy approximately 2 weeks after this scan on a Wednesday.**

Treatment day tests and procedures

- **On the day of treatment, you will report 1 hour before treatment to the Wellcome Research Institute to be met by the research nurses**
- **A saliva sample will be taken via spitting a small amount of saliva into a tube**
- **A baseline urine test will be done -10mls (a teaspoon of urine)**
- **A baseline breath test will be done- a single breath is exhaled into a simple plastic tube with a 10 ml syringe attached to the side of it. Towards the end of the breath a sample of the air in the tube is drawn into the syringe.**
- **The syringe is then inserted into the BreathSpec™ machine and the sample is analysed**
- **A baseline blood sample will be taken 10mls (a teaspoon of blood) through a small cannula placed into a vein.**
- **The saliva, blood and urine samples will be stored for future analysis of DNA mutations that may match patient's breath toxicity patterns. These samples are held in the Edinburgh Cancer Medicines Centre**
- **A baseline patient side effect questionnaire to fill in.**

- **You will then be taken to the Oncology Radiotherapy Department for your treatment**
- **The suppository insertion and the drinking of water as per the planning CT scan will be done in the Oncology Department under the supervision of the treatment Radiographers.**
- **Your treatment is delivered by a machine called a linear accelerator. You will lie on your back, arms by your side on the machine couch and the RayPiolot® device will be plugged into the treatment couch to tell the machine exactly where your prostate is in 3 dimensions. This device will track the movement of the prostate that occurs due to breathing, bowel gas motion or changes in bladder filling during the radiotherapy. Should this result in the prostate moving outside of the target treatment area the radiotherapy beam is stopped and you will resume the treatment once the prostate has returned to the correct position. This system allows very accurate radiation dose delivery to your prostate.**
- **A brief treatment image of the pelvis, called a cone beam CT scan, will be done by the linear accelerator prior to and just after completion of each radiotherapy treatment**
- **The total duration of each radiotherapy treatment from lying on the bed to leaving the room may take 30-40 minutes**
- **When the treatment is being delivered the radiographers leave the room, but they can see you via CC-TV. If you experience any difficulties, you raise your hand and they will stop the treatment and come to your assistance.**
- **Radiotherapy is painless, but you will hear a clicking noise as the x-rays are delivered by the machine.**
- **The machine will rotate around you as the radiotherapy is given but will not touch you**
- **The procedure is identical for each day of treatment over the 5 days in total. The treatment will start on a Wednesday and finish on the**

Tuesday of the following week having had a break from treatment over the weekend

- **Once each fraction of treatment has been completed the research nurses will take another immediate post radiotherapy breath sample and then you will be taken back to the Wellcome Institute to repeat the breath analysis at 30-minute intervals until 3 hours post completion of the radiotherapy (7 samples in total)**
- **A repeat urine sample will be taken at 1 hour and 3 hours post radiotherapy**
- **A repeat blood test will be taken at 1 hour and 3 hours post radiotherapy**
- **A repeat baseline side effects questionnaire will be taken on Day 5 after completion of treatment**
- **On completion of all of your radiotherapy treatment there will be a repeat single trans perineal post treatment biopsy performed under local anaesthesia within the Daybed unit to assess the immune response to treatment and the RayPilot® removed.**
- **No stitches are required**
- **3 more days of antibiotics will be prescribed**
- **Once all the tests are completed you are free to go home**
- **The treatment schedule will be Wednesday, Thursday and Friday, Monday and Tuesday.**

Post treatment follow up

- **You will be followed up in the oncology trials clinic at 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months**

- **Prior to each visit your GP or district nurse should check your PSA blood test at least 48 hours prior to the clinic**
- **A side effect questionnaire will be filled in at the clinic visit also**
- **A digital rectal exam would only be performed if clinically indicated and usually would not be required**
- **After 2 years of follow up you leave the study and enter our standard nurse led postal follow up system.**
- **This requires you to check your PSA with the GP every 6 months and fill in a toxicity questionnaire.**
- **If there were any concerns you would then be given a further clinic appointment.**
- **No travel expenses will be given as part of this study**

Is there anything I need to do or avoid?

- **For any patient receiving radiotherapy to their prostate standard advice is to limit alcohol and caffeine intake during and for 4-6 weeks after completion of treatment. We can advise on any changes to your diet if you experience any side effects during treatment however generally keeping a normal healthy diet is advised.**
- **It is unlikely that you will notice any pinkness of the skin during radiotherapy, but you may notice some loss of pubic hair a few weeks after completion**
- **You should not take supplements or herbal therapies during this study**

- **Please insure your Doctor or the research nurse is aware of all medications that you are taking**
- **You should stop any drugs that thin the blood, Clopidogrel, Aspirin, Apixaban or Warfarin, 7 days before the insertion of the gold grains and the RayPilot® and restart them the following morning.**

What are the possible benefits of taking part?

You may get a benefit from taking part in this study.

- **From the reduced number of radiotherapy visits required to deliver prostate SBRT compared to standard dose external beam over 4 weeks.**
- **From the use of the RayPilot® device for tumour tracking to ensure accuracy**

You will not directly benefit from the assessment of the breath, blood and urine analysis

However, the results from this study might help to improve the healthcare of patients in the future.

What are the possible disadvantages of taking part?

- **Although the number of radiotherapy treatments are significantly less, each treatment takes approximately 30-40 minutes to deliver**
- **There may be discomfort or inconvenience associated with the RayPilot®**
- **Each treatment day will be a long day of 4-5 hours in the Hospital**

- **You are ok to shower with the RayPilot® device in place but not to go swimming or have a bath.**
- **We would not recommend cycling while the RayPilot® is in place as this may be uncomfortable**
- **Should the RayPilot® come out of the prostate accidentally we would not replace it, however we would continue with the Radiotherapy as planned.**

What if there are any problems?

If you have a concern about any aspect of this study, please contact Dr Hamish Phillips Consultant Clinical Oncologist who is the independent advisor to this study. His contact details are telephone 0131 537 3092 and he will do his best to answer your questions

In the unlikely event that something goes wrong, and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against NHS Lothian, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate)

What will happen if I don't want to carry on with the study

You are free to withdraw your consent to the study at any time. We would want to complete the radiotherapy as planned if possible as not doing so would decrease the chances of cure. Any data already collected from your participation in the study would still be kept unless you expressed that you do not wish this to happen. Any future trial specific tests such as patient questionnaires etc. would not be undertaken. Ongoing follow up would be within the normal prostate cancer follow up clinic rather than the trials clinic. After 2 years you will be followed up on our nurse led postal follow up system as per our Departmental follow up protocol. Any future care would not be affected by study withdrawal.

What happens when the study is finished?

When the study has completed recruitment and each patient has had 2 years of follow up the study will close. The results of the study will be analysed and published. All data is anonymised. The tissue samples will be stored and retained in the ECMC tissue bank for possible future analysis.

Will my taking part be kept confidential?

All the information we collect during the course of the research will be kept confidential and there are strict laws which safeguard your privacy at every stage.

- **Study researchers will ask your permission to access your medical records to carry out this research project**
- **Data or samples may be included in future studies after any new study has received ethical approval.**
- **All data will be kept on secure computer systems with password protection and limited access to delegated trial personnel.**
- **The chief investigator and the trial data manager will be responsible for looking after the data.**
- **In order to monitor and audit the study we will ask your consent for responsible representatives from the sponsor (NHS Lothian and University of Edinburgh ACCORD) and NHS Institution(s) to access your medical records and data collected during the study, where it is relevant to you taking part in this research. The Sponsor(s) is responsible for overall management of the study and providing insurance and indemnity**
- **With your consent we will inform your GP that you are taking part.**

What will happen to the results of the study?

This study will be written up as a publication and may also be presented at medical conferences. You will not be identifiable in any published results. Once the results are published you can request a copy of the paper by contacting Dr McLaren

Who is organising and funding the research?

This study has been organised by Dr DB McLaren and sponsored by NHS Lothian and the

University of Edinburgh as part of ACCORD.

The study is being funded by Jamie-King Urological Cancers Research Fund

Who has reviewed the study?

The study proposal has been reviewed by the Wellcome Clinical Research Facility and the

members of the research study group and the Edinburgh Cancer Centre Radiotherapy Services Group.

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee. A favourable ethical opinion has been obtained from ACCORD REC. NHS management approval has also been given

Researcher Contact Details

If you have any further questions about the study, please contact Dr Duncan McLaren on

phone number 0131 537 2215

Independent Contact Details

If you would like to discuss this study with someone independent of the study, please

contact Dr Hamish Phillips Consultant Clinical Oncologist on 0131 537 3092

Complaints

If you wish to make a complaint about the study, please contact:

Patient Experience Team

2 – 4 Waterloo Place, Edinburgh, EH1 3EG

feedback@nhslothian.scot.nhs.uk

0131 536 3370

10.3 APPENDIX 3 – IPSS QUESTIONNAIRE.

IPSS – International Prostate Symptom Score Form

Name:	Date:

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times or more	Your score
Nocturia Over the past month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	
Total IPSS score							

Total score: 0-7 Mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic.

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed: Equally satisfied / dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

10.4 APPENDIX 4 – PATIENT INFORMATION LEAFLET.

NHS Lothian

EDINBURGH CANCER CENTRE

WESTERN GENERAL HOSPITAL

DISCHARGE INFORMATION FOR PATIENTS FOLLOWING RAYPILOT® INSERTION UNDER LOCAL ANAESTHETIC

PRE-IMPLANTATION SCANS

You will attend for a MRI scan in the morning. To ensure optimal images are obtained you will be asked to use a micro-enema prior to the scan. This is to clear out your rectum of gas and faeces. Full instructions for this are in the accompanying leaflet **Rectal Preparation for External Beam Radiotherapy for Prostate Cancer.**

You will also be asked to follow a bladder filling protocol to ensure that your bladder volume remains relatively consistent throughout your planning scans and your radiotherapy treatments. This will involve drinking 3 cups of water 30 minutes prior to the scan taking place.

THE IMPLANTATION PROCEDURE

The implantation will take place under local anaesthetic in a theatre environment.
The first part of the procedure is to implant the gold grain seeds that are required for your radiotherapy treatment. You will be given some local anaesthetic to the area and an ultrasound probe will be inserted into the back passage and the three gold grains will be implanted. This procedure may be a little uncomfortable but should not be painful and will be similar to the biopsy procedure you will already have had.

You will then change position and the Raypilot® implantation will start. Again an ultrasound probe will be used to guide the implantation.

You will be given more local anaesthetic and the Raypilot® device will be inserted through the perineum (this is the

patch of skin between your back passage and your scrotum) to the prostate. You will feel a little bit of pressure but should not be overly painful due to the anaesthesia.

The implantation site may bleed slightly however, this will be covered with a dressing.

FOLLOWING THE IMPLANTATION

The Raypilot® device has a small cable that will then hang from your perineum for the duration of the treatment. It is essential that proper attention is given to keeping the device from being damaged.

The device can be loosely taped to the groin and covered with a cotton pad to avoid irritation or discomfort. Alternatively, you may find it more comfortable to leave it loose in your underwear.

There may be a small amount of discharge from the site, this is normal and to be expected. If this occurs the use of a thin sanitary pad might be helpful.

The area might be tender so avoid tight fitting underwear; it is preferable to have a shower rather than a bath so the device is not immersed in water. Also, when drying use a soft towel and 'dab' at the area gently rather than rubbing with the towel.

In terms of toilet hygiene it is better that you wipe from front to back following a bowel motion to reduce the transfer of and bacteria to the implantation site.

Your urine may be a light pink colour or you may notice some blood in your urine for a short time, this is to be expected following the procedure.

Avoid constipation by eating plenty of fruit vegetables and fibre. You can ask your GP for medication if needed.

You must refrain from doing anything strenuous for the next 48 hours.

If you develop;

- Pain in the area
- Temperature or shivering bouts
- the urine you are passing changes from a light pink colour to dark red or you notice clots in your urine or your bowel motions

Please call the Cancer Treatment Helpline on 08009177711.

PRE-TREATMENT PLANNING

You will be monitored following the implantation for a period of time and then you will be taken for your treatment planning CT scan.

Again you will be asked to follow the same bladder filling protocol prior to the scan.

After this you will be able to leave the department.

FOLLOWING DEVICE REMOVAL

The Raypilot® device will be removed on your last day of your radiotherapy treatment.

Again you may notice slight discharge following the removal, and a little discomfort at the site for a few days. You will be asked to take an anti-inflammatory tablet and paracetamol regularly for a couple of days following the removal process.

Following the device removal it is important to continue with the advice given previously and to be gentle with the area for a few days. It will tend to heal over quite quickly, but again if you notice anything that you have concerns about please contact us or the Cancer treatment Helpline.

CONTACT INFORMATION

If you require any further information regarding your device implantation or the radiotherapy treatment please contact:

Susan Adamson, Advanced Practitioner Uro-Oncology

0131 537 2627

10.5 APPENDIX 5 – QIT APPROVAL DOCUMENT.

QUALITY IMPROVEMENT PROJECT WORKBOOK

(AUDIT, SERVICE EVALUATION AND QI IMPROVEMENT PROJECTS)

Unlike research, audit and service evaluation projects do not require ethical review, but should be approved by the appropriate Quality Improvement Team (QIT) and must conform to governance requirements.

The simple project proposal /registration form at the front of the workbook should be completed and sent to the appropriate QIT for approval before starting the project - the workbook will guide you through the issues you need to consider and give examples at each section.

Please also refer to the additional resources on the Intranet for more information and contact details.

A feedback form is also provided for you to report very briefly on how the work has gone and help close the loop on NHS Lothian's quality improvement initiatives.

If you need help in completing the workbook or in planning the project, advice is available from the Quality Improvement Support Team (QIST) at:
Pentland House Tel: 0131 537 (8) 8565 or 8613
RIE Tel: 0131 242 6856 (26856)
St. John's Tel: 01506 523585 (53122)

QIST, Ground Floor, Pentland House, 47 Robb's Loan, Edinburgh, EH14 1TY

CONTENTS

PROJECT PROPOSAL AND REGISTRATION FORM

Please see sections in the workbook for guidance on completion of the form.
Please note - your form will be returned if any section is blank.

Project Title:

Implications on planning margins using Raypilot for hypofractionated radiotherapy in prostate cancer.

Why was the project selected?

Implementation of the Raypilot motion management system and the implementation of prostate stereotactic radiotherapy protocol. This is the only Raypilot system in the UK so it is imperative that we research the benefits of this system for both patients and the service. Can the motion management system lead to tighter planning margins being used and therefore reduce the toxicity to the patient? If the device resulted in a reduction in planning margins, it would follow that a dose escalation/ ultra-hypofractionated treatment schedule could be adopted. Also the treatment regime is over 5 days not 20 so the benefit would also encroach on cost cutting and the patient through put within the service.

Objective(s): *(Why are you doing the project and what do you hope to achieve – see section E)*

The aim of the project is to assess the efficiency of the Raypilot device and then use this to assess intrafraction motion of the prostate and subsequently the planning target margins that we currently use clinically. If these can be reduced this would result in less bladder and rectal toxicity for the patients but also allow us to escalate the current treatment dose. In conclusion the use of Raypilot in stereotactic prostate treatment will be analysed and assessed to investigate whether we can increase the dose per treatment leading to an ultra-hypofractionated treatment regime with comparable side effects.

Appropriate Quality Improvement Team *(see section I)* Cancer, breast and palliative.

Main project contact:

Name	Susan Adamson
Job title	Advanced Practitioner G.U
Service *(see section U)*	Radiotherapy - WGH
Division *(see section T)*	LUHS
Phone number	01315372627/ 07817115763
E-mail address	susan.adamson@luht.scot.nhs.uk

Supervisor / Line Manager

Name	Lesley Jean Rugg
Job title	Superintendent Radiographer

E-mail address	Lesley-Jean.Rugg@luht.scot.nhs.uk

Methodology *(see section F)*

This research question is based on an audit retrospective data analysis of prostate patients. A non-experimental (observational), retrospective cohort study method will be employed for this study. Patient data will be retrospectively analysed from previously collected data readily available within the imaging verification system.

Due to time constraints of the study data will be collected using a convenience sample. All eligible patients meeting the inclusion criteria over the timescale of 18 months from the start date of the study will be included. Inclusion criteria are as follows:

- Low risk prostate cancer T1-2, PSA<10ng/ml Gleason score of 3+3=6
- Intermediate risk prostate cancer with 1 or more of T1-T2, PSA10-20ng/ml, Gleason score ≤7 (3 +4 only)
- WHO performance status 0-2
- Prostate volume ≤90cc (no androgen deprivation therapy will be given in the study or for downsizing the prostate)
- IPSS Score ≤20
- Q-max>10cc/sec
- Urinary residual <250mls total
- No prior TURP
- Medically fit for radical radiotherapy
- No contradiction to receiving radiotherapy such as inflammatory bowel disease
- No previous pelvic radiotherapy
- Able to give informed consent
- Aged between 18-80 years of age

A timescale for recruitment should provide an opportunity to reduce selection bias. Eligible patients can be identified using the CT appointment system, containing patient diagnosis information. The statistical significance, desired power and effect size would also need to be determined (Creswell, 2013).

The data collected will be retrospectively analysed to investigate the intrafraction motion recorded by the Raypilot system and the Aria record and verify system already in use in the department.. Using a common planning margin calculation, the infrafraction motion will be used to calculate sufficient planning margins and these will be assessed in relation to current departmental protocols.
If the margins can be reduced, then the treatment plan will be recreated in the Eclipse planning system using smaller margins and escalated dose. The resultant organ at risk dose and tissue complication predictors can be used to therefore, predict the effects and severity of side effects.

For each patient a treatment plan is produced, taking into account dose constraints to surrounding organs at risk and providing optimum coverage of the target volume (in this case the prostate being the target and the rectum/bladder being the organs at risk). Due to the position of the prostate, rectal volume, gas or bladder volume can increase the risk of organ motion of the prostate throughout the treatment duration. To account for this we then apply geometric margins around the target volume to ensure adequate coverage of the target at all times. The primary researcher will use the Raypilot data to assess intrafraction motion and calculate whether the margins that we currently use clinically are acceptable or could they be reduced.

Once the treatment course has been completed the primary researcher aims to recreate a second treatment plan (which will not be used clinically) to assess the impact of the smaller margins and increased hypofractionated dose to the organs at risk. This data will provide the basis for the study.

As the patient data is routinely accessible by the primary researcher in their role and the fact that there is no direct patient involvement or change in patient treatment, the patient will not need additional consent.

The data will be analysed independently by the primary researcher only, to reduce inter-observer error. In accordance with the host centres departmental protocol, the primary researcher is competent and entitled in this task and has adequate and appropriate experience. The primary researcher will also be responsible for data storage and compliance with Caldicott guidelines. The primary researcher will have access to the CHI number of the patients involved so that planning data can retrospectively be analysed. At this point the primary researcher will then anonymise any resulting and future data in relation to patient identifiable information by using numerical substitutes.

Estimated start date: *(day /month /year):* 01/01/2019	**Estimated completion date:** *(day /month /year):* 31/06/2020
Confirmation that the governance topics in this workbook have been addressed (✓)**:**	**Brief explanation if the governance topic is considered to be not applicable**
✓ Other people involved (Section H)	
✓ Literature search (Section J)	
✓ Resources (Section K)	
✓ Ethical considerations (Section L)	
✓ Equality and Diversity (Section M)	

✓ Consent (Section N)
✓ Data protection (Section O)
✓ Caldicott principles (Section P)

Please complete the form and send it to your QIT Chair or Clinical Effectiveness Facilitator (see Section I of the workbook or intranet page for details). **Thank you.**

Section B

Is your Quality Improvement project audit, service evaluation or research?

The main aim of carrying out a project in healthcare is to gather information that can be used to improve the quality of patient care.

Research, audit and service evaluation are all means of generating useful quality improvement information. Much of the methodology used in research is also common to audit and service evaluation and there can be a 'grey area' where it is difficult to decide where the project fits.

Definitions

Audit finds out if the right thing is being done at the right time to the right patient. It involves checking what is happening against a standard of what should be happening (and this often includes setting the standard in the first place).

Service evaluation provides information about how well a service / treatment is functioning. It may compare information with standards, e.g. national standards or benchmarks but generally it gives new information to assess if the service is fulfilling its role. If the service has changed, there may be comparison with information about previous service provision. If the service is new, service evaluation aims to see if predictions are being achieved.

Audit, Service Evaluation and Quality Improvement projects should follow the advice in this booklet.

Research tries something new to see what happens and has a control or other treatment group for comparison. It may necessitate randomisation or allocation into groups and often involves a procedure or data collection additional to routine care

Research governance information and the process to follow can be found on the NHS Lothian intranet http://www.accord.ed.ac.uk/

Some general information about AUDIT in Quality Improvement

Audit provides information about a service or treatment – it looks to see how well evidence has been implemented into practice, whether standards have been developed for the service/ treatment, to what level standards are being complied with, finds out what patients/ staff feel about a service or treatment, or whether the changes made to improve performance against the standards have been effective.

It can include extracting information from casenotes (retrospective) or gathering information from patient contacts as they happen (prospective), often using a checklist - or asking patients their opinion.

Audit has a well-established set of steps to follow:

1) define the criteria and/or standards
standards should always be 100% with appropriate pre-determined exceptions

2) measure practice against these standards
the information collected must be suitable to show if the standard is met or not

3) compare practice with standards
did it meet the standard or not – if not there is an issue to address

4) implement change in order to improve practice to meet standards
decide what would need to happen in order to improve compliance and try it out

5) re-audit to check that practice meets standards
repeat the study and observe improvement

The process should be repeated until the standard is met, perhaps requiring a change each time or maybe just reminding people about the recommended standards. It is really an audit *spiral* because the end point should have moved on from the starting point.

In the past, audits have often been large data collection projects, taking a lot of time and only producing results long after the data is collected - but you don't need to look at lots of patients if there are problems with the first one. It is far more beneficial to the patient if information relating to improving a service can be put into practice as soon as possible.

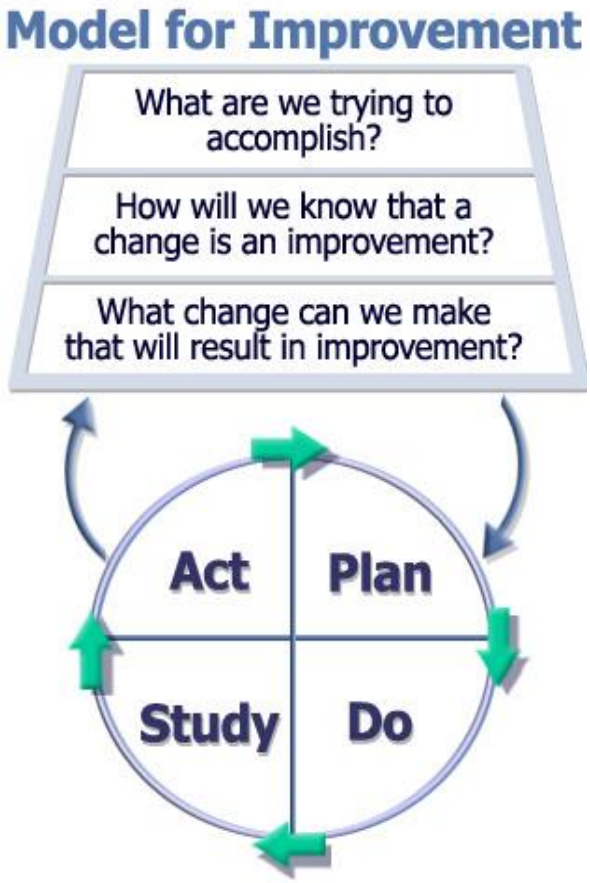
The Scottish Patient Safety Programme is a unique national initiative aimed to drive improvements across the whole of NHSScotland. To find out more please click on the link below: http://www.scottishpatientsafetyprogramme.scot.nhs.uk/programme and for information on SPSP in NHS Lothian please click on the link below: http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/SPSP/Pages/default.aspx

Plan-Do-Study-Act

Testing on a small scale can indicate quickly if a change will be beneficial and for this SPSP recommends the PDSA cycle (shorthand for Plan-Do-Study-Act). This is

similar to the audit spiral and is the terminology used by the Institute for Healthcare Improvement (IHI) for putting evidence based medicine into practice.

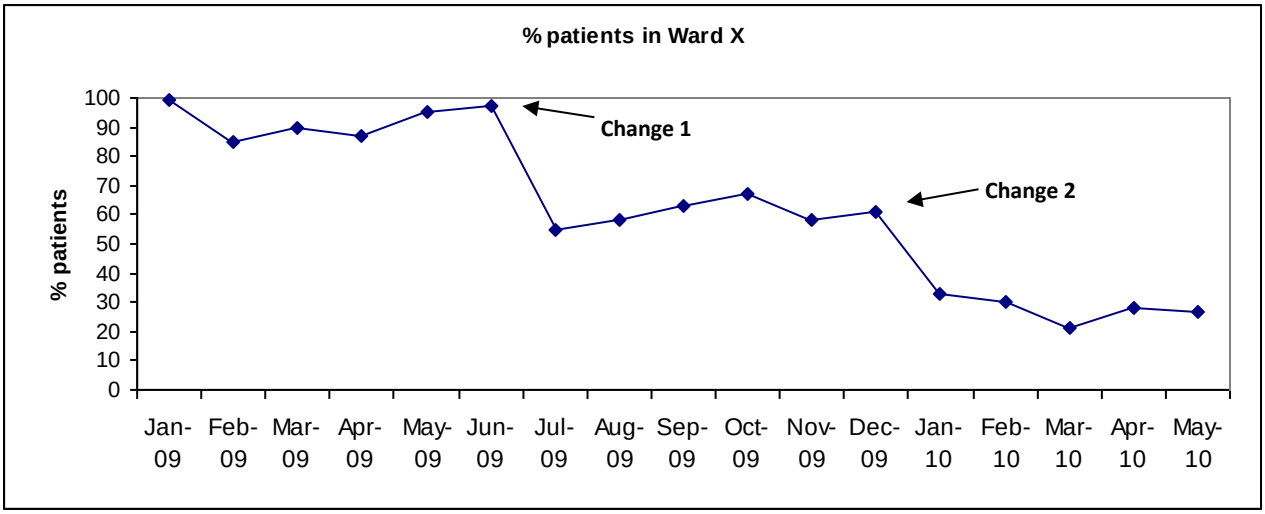
Small tests of change are a form of audit where a good idea is tried out once, then if the result is positive, it is tried on three, then five and so on. It works particularly well for system and processes and where a large number of patients go through the same procedure.



In a patient care situation, if there is an evidence base to suggest a change in practice, then that should be tried on one patient first rather than going ahead and implementing a large scale change. Remember that change is not always improvement.

[Please note that this is not licence to try out new treatments that do not already have a strong evidence base - that remains a research issue and the correct research governance procedures for this must be followed].

Depending on the objective, it can be useful to repeat the process often and record your compliance with standards over time by plotting the data on a **runchart**. This is particularly valuable in showing where changes to the process have been made and demonstrating the resulting improvement.


% patients in Ward X
% patients
100
90
80
70
60
50
40
30
20
10
0
Change 1
Change 2
Jan-09
Feb-09
Mar-09
Apr-09
May-09
Jun-09
Jul-09
Aug-09
Sep-09
Oct-09
Nov-09
Dec-09
Jan-10
Feb-10
Mar-10
Apr-10
May-10

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Section C

Reason for selecting the project TOPIC

There are a number of reasons why a project is selected and it is useful to consider this to justify the time and effort of carrying out the project and maintaining focus. It will also be useful in deciding the project title and objective(s).
For example:

• to set a baseline	• to evaluate a new service
• to evaluate user/ carer satisfaction	• to evaluate a change in practice
• in the development of a policy / protocol	• as a result of a complaint
• because it is a high risk procedure	• QIT priority project
• because the service feels the need to investigate practice (suspicion of a problem)	
• to improve patient outcomes and reduce risk as part of the Scottish Patient Safety Programme (SPSP) process	
• to measure compliance with Guideline, Best Practice Statement, Quality Indicator etc	
• as part of a quality improvement process such as LEAN, Better Together, Patient Experience etc.	
• other reason ……	

Reason(s) for selecting topic:

Implementation of prostate SABR and the use of Raypilot. Future development of ultra-hypofractionated treatment regime.

Section D

The project TITLE

The title of the project is very important. It should not be too long but it is useful to ensure that it contains key words to describe the **population** you are looking at, the **condition** that selects them and the **intervention** that takes place. It should be sufficient to highlight your project in a search of project titles in a database.

An example of a descriptive project title could be: *An investigation into the factors influencing choice of pain medication by Edinburgh GPs treating patients with arthritis.*
Here the population is the GPs, the condition is arthritis and the intervention is the prescribing decision.

Examples of <u>insufficient</u> titles would be *Painkiller prescribing in Edinburgh* or *Arthritis audit*

Section E

OBJECTIVES

Why are you doing the project? What do you hope to achieve?

Objectives should be	**S**pecific	*What are you going to do? Why is it important?*
SMART	**M**easurable	*How will you see progress?*
Achievable	*Can it be achieved and attained?*	
Realistic	*Do what is possible.*	
Timed	*Need a timescale to mark progress.*	

Every project should therefore have at least:

one clear objective

a way of measuring success

Statement of aims: *What do you hope to find out?*

How will you know that you have achieved your aim?

How do you know that a change is an improvement?

The objective should outline an **activity**, e.g.

to determine the number of ….	*to ensure that a standard is being met*
to assess the extent to which ……	*to indicate the level of compliance with …..*
to increase the compliance with ….	*to reduce the incidence of …….*

Project objective(s): To assess the impact of Raypilot on treatment margins and use this information to research the effects of ultra-hypofractionated prostate radiotherapy. This would reduce the incident of associated toxicity and reduce the fractionation schedule from 20 consecutive treatments to 5.

Section F

Data collection strategy (methodology)

It is good practice to plan your project in detail and this includes thinking about how you are going to get your data and what you will do with it.

- What sort of data, how often, where from, who will collect and collate it etc
- Will the data you collect adequately answer your audit/ evaluation question?
- Only collect the information you really need to measure if the objective is being met
- Will you look at a population, a sample or start with just one?
  If it is a sample, how large and how was the number determined?
  (it doesn't have to be thousands of casenotes or years of data collection – a small test of change can be valuable)
- Is a standardised, validated measurement tool available to use?
- Qualitative or quantitative?
- Paper recording sheets or direct entry into computer?

Who will enter and analyse the data? Primary Researcher
What information will be collected? Planning data (from Aria), intrafraction motion data (form Raypilot system), current margin protocols, new plan data, toxicity scoring data
What population will the data relate to? Prostate patients with Raypilot device having prostate SABR.
What is the sample size? Convenience sample – approx 24 patients based on 2 per month
How was the sample size determined? Convenience sample
Is the data quantitative / qualitative? Quantitative
Is the information already in the notes or in a system? Yes in both Raypilot and Aria
Who will collect the information? Primary researcher only
Will it be on paper data collection sheets or via the computer? Computer secured with password protected log in
If there is data entry to be carried out, who will do this? Primary researcher

How will the data be stored (and for how long)? 2 years – until completion of study in accordance with Caldicott and NHS Lothian policy

Section G

Preparation for a project

It is important that you discuss the project with your line manager and consider the following issues as part of your planning phase BEFORE you proceed any further.

* Who is going to be involved in the project
* Resource implications
* Ethical considerations
* Caldicott principles
* Patient consent
* Data collection strategy
* Data Protection
* What will be done once you have the results

(e.g. how data will be analysed and recommendations implemented, what you will do if the project uncovers a serious problem or safety issue etc)

Section H

People involved in the project

In designing an audit or evaluation you should consider who might be affected by the project, (stakeholders) especially if the findings will indicate the need for improvement.

You will not be carrying out your project in isolation – there will be a number of people you should be discussing the idea with before you start, e.g.

- Line manager
- Clinical colleagues
- Admin staff
- Clinical supervisor
- University academics
- Service users / carers

As much as possible you should involve service users and carers in the design of the project and perhaps voluntary services, advocacy etc will also be involved.

People involved in your project: Primary researcher, head of radiotherapy planning (Michael Trainer), lead consultant GU team (Dr Duncan McLaren), Bill Nailon (lead Clinical Scientist) QMU PHD supervisor (Lindesay Irvine, Jackie Jones).

Section I

Quality Improvement Teams (QI Teams)

Your service will be aligned with a **Quality Improvement Team** (see list below). It is important that they are aware of all the audit and service evaluation projects going on in the service area and this information also feeds into a Lothian-wide list of quality initiatives.

The QI Teams and their programmes are key to delivering and monitoring all aspects of quality throughout NHS Lothian services and this is reaffirmed in the Quality Strategy for the NHS, Local Authorities and 3rd Sector Organisations *http://www.gov.scot/Topics/Health/Policy/Quality-Strategy* and the NHS Lothian Quality Improvement Strategy 2011-14 http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/ClinicalGovernanceinNHSLothian/keypapers/Documents/NHS%20LOTHIAN%20QUALITY%20IMPROVEMENT%20STRATEGY%202011-2014.pdf

For the organisation as a whole, for QI Team members and individual clinical teams, the programmes provide a valuable summary of all QI activity, facilitating sharing of information and practice, as well as having the potential for collaboration on similar or cross-cutting themes and the Board receives an annual QIT report.

As QI Teams mirror operational management structures, and are chaired by at least one member of the Clinical/ HCPS/ Single System management team, quality issues become integral to the routine business and decision-making processes of that clinical area. As such, they can become part of both performance management and providing a route for bringing quality issues to the fore.

Acute & Gen Med - RIE	Critical Care RIE	Laboratory Medicine	Radiology
Adult Acute and Rehab - REAS	DCN	Learning Disabilities	Rehabilitation - ED HSCP
BPOFMS and Ophthalmology	Dermatology	LUCS	Renal
Breast Screening	AHP / Physio - Ed HSCP	Maternity	Respiratory RIE
CAMHS	Edinburgh Dental Institute	MEDAS (including Cardiology, CTS) - RIE	Respiratory WGH
Cancer, Breast and Palliative Care	Edinburgh HSCP	Medical Photography	Rheumatology
Cardiology (all sites)	RIE - Emergency Medicine	Midlothian HSCP	RIDU
Chalmers Sexual and Reproductive Health	Endoscopy	MOE (all sites)	Substance Misuse
Children's Services	SJH - General & Acute Med. ED. MOE	MSK Orthopaedic	T&A RIE
Chronic Pain	General Surgery / Vascular / Liver	Neonatal	T&A SJH
Colorectal / Urology	Gynaecology	Older People's Mental Health Services	T&A WGH
Complex Care - Ed HSCP	Health Protection Team	Pharmacy	Transplant Unit
Critical Care Pan Lothian	HMP Edinburgh	Public Dental Service	West Lothian CHCP

QIT contacts are listed in QIT Directory on the Intranet http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/ClinicalGovernanceinNHSLothian/Alerts/Documents/QI%20Teams%20contacts%20Oct%202014.pdf

Approval for corporate projects covering a wide range of services, or projects from people external to NHS Lothian should be sought initially from the Associate Director for Quality Improvement and Safety.
For this and other enquiries please contact QIST (robert.pritchard@nhslothian.scot.nhs.uk).

The appropriate QIT for this project is:

Section J

LITERATURE SEARCH – has anyone else done anything similar?

It is important that you find out as much as you can about your project topic because the findings of other groups may influence how you carry out your project - it might save
re-inventing the wheel.

It may be that there is no available written information about your audit or evaluation – people are more willing to publish research results than audit or service evaluation, but these can also be a useful resource.

Information about literature searching is widely available on the internet and also on the NHS Lothian intranet.

http://hronline.lothian.scot.nhs.uk/About/OurServices/EducationandEmployeeDevelopment/libraries/Pages/Libraries.aspx

Section K

Resource implications

All projects take up resources, whether it is your time thinking up the project or analysing the results or the cost of printing and posting a set of questionnaires. Other people might also be involved.

- Staff time
- Postage / printing
- Storage facilities
- Support or supervision
- Additional clinical investigations / tests
- Space / accommodation
- IT systems / IT licences
- Travel / attendance at conferences

Resource implications for the project: Time for primary researcher, clinical supervision, IT systems and computer storage/access

Section L

Ethical considerations

While research projects have to go through the Research Ethics Committee where they will be given confirmation that their project complies with ethical principles or advice for altering their project, there is not a formal ethical approval system for audit and service evaluation. However, the basic ethical principles that apply to research also apply to any project. Everyone, therefore, has the responsibility to ensure that their audit or service evaluation project is conducted in a respectful manner.

Ethical considerations link closely with Equality & Diversity (Section M), Consent (Section N) and Data Protection issues (Section O).

The three fundamental ethical principles are:

Respect for persons
Each individual is unique and free, has the right to decide, has value and dignity and has the right to informed consent.
Beneficence
This means doing good for the people involved, avoiding risks as much as possible and at least not doing any harm.
Justice
This relates to fair and equal recruitment into the study and includes special protection for vulnerable people. This can include people who might find it difficult to understand consent information and drug users (or others who engage in illegal activities)

Therefore, consider the following:

- Is there any potential for harm / distress / infringement of rights (of participants, relatives, researchers etc)
- Confidentiality of communications e.g. letters, telephone calls
- Vulnerable groups – there should be special procedures for consent e.g. children under 16, people detained under the Mental Health (Care and Treatment) (Scotland) Act 2003, people with Learning Disabilities, Adults with Incapacity (Scotland) Act 2000 etc

Ethical issues you have considered in the project: Patient need for consent, data storage, researcher involvement, patient information needs, all communications will be from NHS accounts with no patient identifiable data, anonymisation of patient details.

Section M

Equality and Diversity

Everyone should ensure that their project design does not inadvertently disadvantage any groups of people or be biased towards any particular groups (unless they are the focus of the project).

Issues to consider include: age
cultural diversity
disability
gender
learning disability
mental health
minors
religion and spirituality
sexual orientation
social or economic factors

All new policies, plans, strategies and new service development should undergo a integrated impact assessment to ensure that changes do not inadvertently cause adverse impacts on any groups of people.

Further information can be found on the Intranet – http://hronline.lothian.scot.nhs.uk/About/EqualityAndDiversity/Pages/EqualityandDiversity.aspx

Completed impact assessments should be sent to:

impactassessments@nhslothian.scot.nhs.uk

Section N

Consent to participating in the project

When patients are admitted to healthcare services they consent to routine clinical data being recorded but they must give their permission if extra information is to be collected. This often involves a consent form where the all the necessary information is given to participants and they sign a document. They should know what happens if they do not want to be included or if they later change their mind.

There is implicit consent in the return of completed questionnaires, but patients must be told what the information is to be used for and if it is to be anonymous or treated in confidence.

Consider: Explicit or implicit consent?

Extra consent procedures?

Implications of participation and non-participation re: clinical care

Provision of information for participants

Process of giving consent e.g. consideration period, ability to withdraw consent without influence on treatment

Recording consent

Will any participants in your study need to give explicit consent? No
What will they be consenting to? NA
How will you give them the necessary information: (e.g. leaflet)
How will consent be recorded: (e.g. consent letter)
What happens if someone changes their mind once the study has started? (e.g. their data will or will not be included in the final analysis, they will be assured that withdrawing from the study will not affect their care)
What happens with potential participants who do not give consent: (e.g. they will be assured that withdrawing from the study will not affect their care)

Section O

Data Protection

All information accessed in the course of the project must be handled in a confidential and secure manner to appropriate legal, ethical and quality standards, in accordance with the Information Governance framework.

Collect the minimum amount of information you require and consider how data will be recorded, transported, analysed and stored.

Everyone accessing patient information must have signed the Data Protection Act and abide by the regulations. An Honorary contract may be required. Guidance is available on the Information Governance website regarding the use of e-mail, memory sticks, CDs etc.

You should seek guidance if your project will include any transfer of information between University and NHS computers.

Principle 1 – FAIR
Information will be processed fairly and lawfully and, in particular, shall not be processed unless specific conditions are met.

Principle 2 – SPECIFIC
Information will be obtained only for one or more specified and lawful purposes, and shall not be further processed in any manner incompatible with that purpose or these purposes.

Principle 3 – ADEQUATE
Information will be adequate, relevant and not excessive in relation to the purpose or purposes for which they are processed.

Principle 4 – ACCURATE
Information will be accurate and, where necessary, kept up-to-date.

Principle 5 – RETENTION
Information will be kept for no longer than is necessary for that purpose or those purposes.

Principle 6 – RIGHTS
Information will be processed in accordance with the rights of data subjects under the Act.

Principle 7 – SECURITY
Information will be protected by appropriate technical and organisational measures to prevent unauthorised or unlawful processing of personal data and protect against accidental loss or destruction of, or damage to, personal data.

Principle 8 – TRANSFER
Information will not be transferred to a country or territory outside the European Economic Area unless that country or territory ensures an adequate level of protection for the personal rights and freedoms of data subjects in relation to the processing of personal data

Information Governance guidance can be found on the Intranet:

http://intranet.lothian.scot.nhs.uk/NHSLothian/Corporate/A-Z/ehealth/operationsandinfrastructure/InformationGovernance/Pages/default.aspx

Elaine Downie, Data Protection Officer
Tel: 465 (3)5684 Mob.No: 07715803253
Elaine.Downie@nhslothian.scot.nhs.uk

Tracey McKinley, Information Governance Manager
Tel: 465 (3)5444 Mob. No: 07990 563 417
Tracey.McKinley@nhslothian.scot.nhs.uk

Section P

Caldicott permission

Are you going to record the CHI number, patient name, age, gender, date of birth, address, postcode or any other identifiable information ?

Use only essential information and as little as possible.

Why do you need to use patient identifiable information at all?
Patient identifiable information should only be available for justified purposes. Everyone involved in audit, evaluation or research should be aware of their responsibilities for having access to this information and ensure that they comply with the legal requirements of handling patient information.

Information to be used only within a department (for example for audit purposes) may not need Caldicott approval but it should not be transferred outwith that department without approval. If you are unsure whether Caldicott approval is needed, then please ask.

Principle 1 - **Justify the purpose(s)**
Every proposed use or transfer of patient-identifiable information within or from an organisation should be clearly defined and scrutinised, with continuing uses regularly reviewed, by an appropriate guardian.

Principle 2 - **Don't use patient-identifiable information unless it is absolutely necessary**
Patient-identifiable information items should not be included unless it is essential for the specified purpose(s) of that flow. The need for patients to be identified should be considered at each stage of satisfying the purpose(s).

Principle 3 - **Use the minimum necessary patient-identifiable information**
Where use of patient-identifiable information is considered to be essential, the inclusion of each individual item of information should be considered and justified so that the minimum amount of identifiable information is transferred or accessible as is necessary for a given function to be carried out.

Principle 4 - Access to patient-identifiable information should be on a strict need-to-know basis
Only those individuals who need access to patient-identifiable information should have access to it, and they should only have access to the information items that they need to see. This may mean introducing access controls or splitting information flows where one information flow is used for several purposes.

Principle 5 - **Everyone with access to patient-identifiable information should be aware of their responsibilities**
Action should be taken to ensure that those handling patient-identifiable information - both

clinical and non-clinical staff - are made fully aware of their responsibilities and obligations to respect patient confidentiality.

Principle 6 - **Understand and comply with the law**
Every use of patient-identifiable information must be lawful. Someone in each organisation handling patient information should be responsible for ensuring that the organisation complies with legal requirements.

Further information and the Caldicott form can be found on the Intranet:
http://intranet.lothian.scot.nhs.uk/NHSLothian/Corporate/A-Z/Caldicott/Pages/default.aspx
Application form for Caldicott approval
http://intranet.lothian.scot.nhs.uk/NHSLothian/Corporate/A-Z/Caldicott/Caldicott/Caldicott%20Form%20NHS%20Lothian%20-%20October%202011.doc

Caldicott Guardian for NHS Lothian
Dr A McCallum, Director of Public Health and Health Policy, NHS Lothian, Waverley Gate, EH1 3EG
Tel: 0131 465 5452 E-mail: Caldicott.Guardian@nhslothian.scot.nhs.uk

Section Q

COMPLETING THE PROJECT

It is important that the results from your project are shared with other services so that methodology and findings can be adapted or built upon and also that you get credit for your efforts.

You may not wish to publish your findings formally, but your line management and the Quality Improvement Teams need an idea of what has happened – whether you regard the project as a success or not. Participants might also get feedback. Lengthy documents are not necessarily the most efficient form of reporting and summary reports are often sufficient with the offer to provide fuller information on request.

The last page of this workbook gives a form that should be completed at the end of a project and sent to the Clinical Governance Support Team for discussion at Quality Improvement Team meetings and also for recording in the Audit/ Evaluation database.

Section R

IMPLEMENTING THE FINDINGS

The findings from your project should, where possible and appropriate, be implemented into practice to the benefit of patients. Part of the reporting process is to consider how they may be used and plan ways of doing this.

Section S

CLOSING THE LOOP

It is also important once findings have been implemented that you check at a later date that all is going well and modify practice if necessary at that stage. A re-audit at a suitable time after implementation will ensure that improvements become embedded into practice.

Section T

NHS Lothian LIST		
Edinburgh HSCP	West Lothian CHCP	Midlothian HSCP
LUHS	REAS	Pan-Lothian
National / International	East Lothian HSCP	HMP Edinburgh

Section U

SERVICE LIST			
Accident & Emergency	Diabetic Retinal Screening	Medical Physics	Rehabilitation
Admin Staff	Dietetics	Medical Records	Renal
Anaesthetics	Ear, Nose & Throat	Mental Health	Rheumatology WGH
Bed Management	Edinburgh Breast Unit – WGH	Mental Health Care of the Elderly	Social Work
Biochemistry	Endocrinology WGH & RIE	Microbiology	Speech and Language Therapy
Blood Bank	Endoscopy	Minor Injuries Unit	Surgery
Cardio/Thoracic/ Respiratory	Family Planning	Musculoskeletal	Theatres RHSC
Catering	Gastrointestinal	Neonatal	Theatres RIE
Clinical Pharmacy	General Medicine	Obstetrics	Theatres St John's
Clinical Psychology	General Practice	Occupational Health	Theatres WGH
Colorectal and General Surgery	Genetics	Occupational Therapy	Therapies
Community Dental Service	Genito-urinary Medicine	Pathology	Thoracic Surgery
Community Nursing	Gynaecology	Patient movement	Toxicology
Community Pharmacy	Haematology	Phlebotomy	Transfusion
Continence Care	Head & Neck	Physiotherapy	Urology WGH
Cytogenetics	High Dependency Unit	Podiatry	Vascular RIE
Department of Clinical Neurosciences	Health & Homelessness	Psychiatry	Other
Delayed Discharge	Hospital at Night Team	Public Health	
Dementia Care	Hospital Sterilisation & Decontamination Unit	Radiology	
Diabetes WGH & RIE	Infection Control	Radiotherapy - WGH	

PROJECT COMPLETION FORM

A form is required for each completed project

Project Title: (include *population, condition* and *intervention* – see section D)

Main project contact:

Name .....

E-mail address .....

Quality Improvement Team: .....

Objective(s): What were you hoping to achieve in the project?

Do you feel that you achieved this?

Please give a brief summary of your findings:

What were the action points arising from the results?

-
-
-

How will the information from the project be put into practical use?

What plans are there to measure the effect that the results from the project have had on the service? (e.g. plans for re-audit)

Did you encounter any problems during the course of the project?

Have you, or do you intend to, publish your results? If so, where?

THANK YOU. Please detach the completed form and send it to the Chair of the QIT which approved the project (see list in Section I)

10.6 APPENDIX 6 – QIT APPROVAL LETTER

NHS
Lothian

Radiotherapy Management Group (RTMG)
Edinburgh Cancer Centre, Edinburgh
EH4 2XU

Ms Susan Adamson
Advanced Radiotherapy Practitioner (GU)
Edinburgh Cancer Centre

15th April 2019

Re: Implications on planning margins using Raypilot for hypofractionated radiotherapy in prostate cancer

Dear Susan,

Thank you for giving us the opportunity to review your project, which received positive feedback from the Radiotherapy Research Group and the Radiotherapy Management Group. We are therefore pleased to grant approval for the project under the terms set out in the Edinburgh Cancer Centre, Research projects data management policy, which is attached.

Under the terms of this approval all information collected will be for the purpose of service development and clinical audit and all information extracted from the patient archive must be anonymised. If anonymised data is to be stored outside of the NHS network it must be stored on an encrypted device. We require you to read and sign the attached document at your earliest convenience and to return it to the Radiotherapy Research Group.

The very best of luck with your project and please get in touch if you require further approval or if the conditions of your project change.

Yours Sincerely,

On behalf of RTMG

Dr C Bedi, Clinical Oncologist, Radiation Oncology IRMER Lead
Mrs. L Carruthers, Head of Oncology Physics
Mrs. L-J Rugg, Head of Therapeutic Radiography

10.7 APPENDIX 7 – DEPARTMENTAL WORK INSTRUCTIONS

Instructions for the use of Ray pilot and motion management.

Relating Documents

Work Instructions For Prostate SABR EP2/ECC/2264

Work Instructions For Importing Patients To Raypilot EP2/ECC/2262

Treatment Delivery EP2\ECC\2205

External Beam Protocol EP2\ECC\0050

IRMER Entitled Staff List EP2/ECC/2000

IMRER Exposure Package EP2/ECC/2900

Roles and Responsibilities

Three competent radiographers will be involved in PRINToUT treatments.

Radiographer A will be responsible for the monitoring of the Raypilot system. They will be responsible for monitoring the motion management system and for instructing radiographer B and C on whether the tolerance has been breached and the beam has to be interrupted.

Radiographer B and C will be responsible for carrying out the treatment in accordance with departmental protocol EP2/ECC/2205 – Treatment Delivery.

Use of Raypilot

1. Open the quality control file on the Raypilot Micropos system.

2. Attach raypilot couch top receiver using the index bars. Index at H2 and F5, indicated by white markers.

3. Connect the power cable to source in the treatment room. Turn on in room monitor (3 sockets clearly marked).

4. Prior to each use carry out the Raypilot QA before the patient is in the room.

5. Attach the QA base plate onto the receiver couch top at position 3 & 4 – ensure that the base plate is firmly installed into the receiver.

6. Connect the Raypilot transmitter cable to the matching network cable.

7. Use the lasers to line up the base plate into the correct position. Then set the values stated on the raypilot system i.e 15.1 vert, 153.9 long.

8. Press the right arrow button on the receiver plate to start the quality assurance programme.

9. The two options will then be available;

   a) 'the system passed the quality control'. Click **FINISH** and is now ready for clinical use.
   b) 'the quality control failed. If it failed repeat the quality assurance process again.

   If the system fails this needs to be escalated to the lead radiographer and lead physicist.

10. Patient must have been imported from Aria following work instruction EP2/ECC/2262 to the Raypilot system at this point and the patient isocentre/transmitter displacement and tolerance levels will already be programmed for treatment. (Refer to EP2/ECC/2262)

PATIENTS FIRST TREATMENT

Before The Patient Enters The Treatment Room

11. Open the patient from the queue and in the Raypilot Micropos system. Verify that the patient ID's match.

12. Attach the Raypilot Table Displacement Meter onto the side of the receiver couch top at the indicated magnetic sites.

13. Align the positioning lasers with the marked isocentre on the Raypilot Table Displacement Meter (indicated with a black crosswire) **without** the patient on the couch top.

14. Record the vert and lng values on the patient specific displacement form.

15. Remove the Raypilot Table Displacement Meter from the receiver couch top.

With The Patient In The Treatment Room

16. Position the patient so that the treatment isocentre is within the defined radiation zone, indicated by the white square.

17. Attach the trans-peritoneal transmitter cable to the matched network cable.

18. Verify the patients details on the in room monitor – if correct proceed. Follow the directions onscreen using the right arrow on the receiver couch top to confirm or the left arrow to cancel.

19. Reattach the Raypilot Table Displacement Meter and repeat steps 12-14. Once completed a radiographer will exit the room and edit the patient details in the Raypilot Micropos system.

20. On the Raypilot computer system, locate the table displacement section.

a) Click on SET, this will then display the table co-ordinates.
b) Enter the co-ordinates without the patient, click SET.
c) Enter the co-ordinates with the patient, click SET. This will then calculate the table displacement values automatically.

21. Now select FIELD TEMPLATE, click LOAD and select the preset tolerance protocol from the dropdown menu, click OK.

22. In the patient matching section click on **Match Transmitter ID**. The transmitter ID will now be matched to the patient imported data. Check that the details match and click **SAVE**.

SUBSEQUENT TREATMENTS

23. Open the patient from the queue in the Raypilot Micropos system. Verify the patient ID's match.

24. Repeat steps 15-17.

25. The in room monitor will now display the patient displacement indicators.

If the indicators are out with the 'blue' fields the transmitter is outside the measured volume, therefore the patient has to be repositioned in the defined radiation zone on the couch top and the position registered.

a) Recheck isocentre position using patient tattoos.

b) Press the right arrow button on the receiver couch top as instructed on the in room monitor; this will store the patients initial treatment position and track motion. If the patient moves out with the defined treatment position then click 'new treatment position' and this will record the new starting co-ordinates for treatment.

26. The system is now ready for treatment.

27. Pre-treatment imaging to be acquired in accordance with PRINToUT trial regulations (see work instruction EP2\ECC\2264) Apply all required shifts to isocentre following the fiducial matching. This does not affect any displacement values as the Raypilot coordinate system is only dependent on the transmitter to receiver couch top coordinates.

28. Organ Tracking – the transmitter movement will be trakced on the graphical illustration;

a) Blue – the target volume is in tolerance

b) Yellow – the target volume is out of tolerance.

29. If any parameters turns yellow the beam will be stopped by the radiographers on the Truebeam console immediately (see roles and responsibility section).

30. Monitor the motion pattern for a maximum period of 90 seconds.

a) If all parameters return to blue arrows indicating the target has moved back into tolerance then treatment can be resumed.

b) If the parameters remain yellow then a new treatment position must be registered. This is done by selecting the NEW TREATMENT POSITION button which will give new coordinates.

31. After completion of treatment press the 'end session' button. Then 'save'.

32. Once the treatment course has been completed the data can be exported back into Aria by using the Raypilot export application.

Author SA 27/09/2018

10.8 APPENDIX 8 - TRAINING PLAN.

Training Plan : RAYPILOT TRAINING PLAN

Scope

This Training Plan covers the use of the Raypilot transmitter system.

Reference documentation: **EP2/ECC/2000**

EP2/ECC/2235

EP2/ECC/2236

Prior Learning assessment

Eligibility criteria:

All staff employed as an IRMER Operator and with Radiotherapy Pre-

Treatment or Treatment entitlement

Pre-requisites:

1. Understanding of the Radiotherapy process in Edinburgh Cancer Centre.
2. Successful completion of Image Verification Part 2 Training Plan.
3. Understanding of the rationale Raypilot implantation in prostate radiotherapy.
4. All corresponding documentation above has been read.

Previous learning & individual learning requirements (modified TP as appropriate)

Name of Trainer: ……..…….. Sign …… Date ……..

Name of Trainee: ……..…… Sign …… Date ……..……..

	Section 1	Section 2	Section 3
Date completed			
Trainee			
Trainer			
Entitled by			
Date added to Entitled Staff List			

Comments			

Section 1				
Step	**Task Description**	**Assess after**	**Pass Criteria**	**Trainer/date**
1.1	Read relelvant imaging protocols and work instructions stated above scope.	Induction	Discuss with Level 3 Entitled trainer Number and title of protocol is recorded on generic record of evidence. Trainee to sign each as evidence of reading.	

1.2	Observation and induction to the Raypilot equipment and software employing the use of departmental phantom.	Attending Raypilot equipment demonstration , tutorial on the Raypilot system, minimum of 2 phantom set-ups in training mode.	Discuss with Level 2 or 3 entitled operator.	
1.3	Undertake the clinical process, utilising the Raypilot system. To include raypilot QA, image verification (seed match), Raypilot use.	Minimum of 3 records of rationale and decision making for this site. Minimum of 3 records of rationale and decision making for first day patients.	Record rationale and decision making on the generic record of evidence forms. Detailed Q&A with an Entitled level 3 trainer, including discussing action levels, problem solving and decision making.	
	e.g. Demonstrate knowledge and understanding of your responsibilities under IRMER for this task		Q+A with level 3 trainer to demonstrate an understanding of the pathway, use of the Raypilot system.	

Completion of this training section indicates a proven competent independent operator, suitable for a change in IR(ME)R entitlement from level 0 to level 1 for this task.

- *Able to undertake this task.*
- *Able to check IRMER Entitled Level 2 or 3 Operators for this task*
- *Able to act as a Task Assessor*

Section 2				
Step	**Task Description**	**Assess after**	**Pass Criteria**	**Trainer/date**
2.0	Sufficient experience and competence with a full range of proven decision making skills in this task	Minimum of 3 online taking the lead role.	Q+A with level 3 trainer to demonstrate an understanding of the pathway, use of the Raypilot system	
2.1	Involved in training radiographer grade staff members in this technique	After completion step 2.0	Evidence of training staff and discussion with level 3 entitled operator. Complete generic record of evidence form for first 3 teaching sessions or any other relevant experience.	
Completion of this training section indicates a proven competent independent operator, suitable for a change in IR(ME)R entitlement from level 1 to level 2 for this task. • *Able to undertake this task.* • *Able to check IRMER Entitled Level 1, 2 or 3 Operators for this task* • *Able to act as a Task Assessor.*				

Section 3				
Step	**Task Description**	**Assess after**	**Pass Criteria**	**Trainer/date**
3.0	Experienced skilled independent operator with proven leadership and decision making skills in all tasks detailed in this training plan	Ongoing assessment by Trainer		
3.1	Has completed Train the Trainer or equivalent course			

Completion of this training section indicates a proven competent independent operator, suitable for a change in IR(ME)R entitlement from level 2 to level 3 for this task.

- *Able to undertake this task.*
- *Able to check IRMER Entitled Level 1, 2 or 3 Operators for this task*
- *Able to act as a Task Assessor.*
- *Able to act as Trainer for this Training Plan*

10.9 APPENDIX 9 – LENT SOMA QUESTIONNAIRE

EDINBURGH CANCER CENTRE
URO-ONCOLOGY PATIENT TOXICITY QUESTIONNAIRE

ID No: _____

Date Completed: _____

What stage in treatment: CT PLANNING
3 month follow up appointment
9 month follow up appointment
15 month follow up appointment
21 month follow up appointment
27 month follow up appointment

PLEASE ANSWER QUESTIONS AS TO HOW YOU'VE BEEN FEELING OVER THE LAST 2 WEEKS ONLY, BY CIRCLING THE APPROPRIATE ANSWER

The section refers to your bowels

Please state if you have had any operations relating to your bowels and when this took place

_____

Do you get any pain when you open your bowels?

0 = No
1 = Rarely
2 = Sometimes
3 = Often
4 = Always

If Yes, how severe is this pain?

1 = Minimal
2 = Tolerable
3 = Intense
4 = Excruciating

When you feel a desire to open your bowels do you need to go straight away?

0 = No
1 = Monthly
2 = Weekly
3 = Daily
4 = Constantly
How often have you felt the desire to open your bowels urgently and were unable to?

0 = Never

1 = Monthly
2 = Weekly
3 = Daily
4 = Constantly
Have you had any diarrhoea recently?

0 = No
1 = Yes

If Yes, how many times do you have diarrhoea each day?

_____
___

Do you have any difficulty in controlling your bowels (e.g. any accidents)?

0 = No
1 = Yes

If Yes, how often?

1 = Monthly
2 = Weekly
3 = Daily
4 = Constantly

Have you had any bleeding recently when you've opened your bowels?

0 = No
1 = Yes

If Yes, how often have you noticed this?

_____

Have you recently suffered with constipation?

0 = No
1 = Yes

If Yes, how often do you open your bowels?

0 = More than 4 times per week
1 = 3-4 per week
2 = 2 per week
3 = only 1 per week
4 = Less than this

Have you passed any black motions recently?
0 = No
1 = Yes

If Yes, how often have you noticed this?

1 = Monthly
2 = Weekly
3 = Daily
4 = Constantly

Please could you state your weight

_____

Have you passed any sticky / slimy motions recently?

0 = No
1 = Rarely
2 = Sometimes
3 = Often
4 = Always

Are you taking any tablets for diarrhoea?

0 = No
1 = Yes

If Yes, please give name

_____
_____

How often do you take this in any one week?
1 = Less than 2 tablets per week
2 = 2 or more tablets per week

Please give the names of any other medication you are taking for your bowels
and how often you take this

_____
_____

The next section refers to your bladder

Please state if you have had any operations relating to your bladder and when this took place

_____
_____

Are you getting any pain on passing urine?

0 = None
1 = Rarely
2 = Sometimes
3 = Often
4 = Always

If Yes, how severe is this pain?

1 = Minimal
2 = Tolerable
3 = Intense
4 = Excruciating

When you feel a desire to pass urine do you need to go straight away?

0 = No
1 = Monthly
2 = Weekly
3 = Daily
4 = Constantly

Have you had any blood in your urine recently?

0 = No
1 = Rarely
2 = Sometimes
3 = Often with clot
4 = Always

How frequently do you pass urine?

0 = Less than every 4 hours
1 = Once every 3-4 h
2 = Once every 2-3 h
3 = Once every 1-2 h
4 = Every hour

Do you have to get up during the night to pass urine?

0 = No
1 = Yes

If Yes, please state how many times?

0 = 0 - 1
1 = 2 - 3
2 = 4 - 6
3 = 7 or more

Do you suffer with incontinence of urine?

0 = None
1 = Less than every week
2 = Less than every day
3 = Several times a day

4 = All the time

Is your flow of urine weaker now than before Radiotherapy treatment?

0 = No
1 = Yes
8 = I have not had radiotherapy treatment yet

If Yes, how often have you noticed this?

1 = Monthly
2 = Weekly
3 = Daily
4 = Needed catheter

Are you taking any medication for you bladder?
0 = No
1 = Yes

If Yes, please state the name of your medication & how often you take this

_____
_____

Are you getting any tiredness and headaches together?

0 = No
1 = Yes

Are you passing less urine now than you usually do?

0 = No
1 = Yes

Are your ankles swollen?

0 = No
1 = Yes

The next section is about your sexual function and sexual satisfaction and although the following questions are very personal, your answers will be treated in strict confidence and will remain anonymous.

Do you have difficulty having erections?

0 = No
1 = Rarely
2 = Sometimes
3 = Often
4 = Always
9 = Do not wish to answer

To what extent have you been interested in sex recently?

0 = Always
1 = Often

2 = Sometimes
3 = Rarely
4 = Never
9 = Do not wish to answer

Has your interest in sex altered since your treatment?

0 = No
1 = Yes
8 = I have not had radiotherapy treatment yet
9 = Do not wish to answer

At present how does your frequency of intercourse compare to what is usual for you?

0 = Same as usual
1 = Less than usual
2 = Much less than usual
8 = Not sexually active
9 = Don't want to answer

Do you find this a problem?
0 = No
1 = Yes
9 = Don't want to answer

Do you get satisfaction?
0 = Always
1 = Often
2 = Sometimes
3 = Very rarely
4 = Never
8= Not sexually active
9 = Don't want to answer

Has your sex life changed since your treatment?

0 = No
1 = Yes
8 = I have not had radiotherapy treatment yet
9 = Don't want to answer

Many Thanks for completing this questionnaire we will use this to monitor the side effects you have experienced throughout your treatment and recovery.

10.10 APPENDIX 10 - RADIATION THERAPY AND ONCOLOGY GROUP TOXICITY SCORE.

RTOG	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Lower GI including pelvis	No change	Increased frequency or change in quality of bowel habits not requiring medication. Rectal discomfort not requiring analgesics	Diarrhoea requiring parasympatholytic drugs. Mucus discharge not requiring sanitary pads. Rectal or abdominal pain requiring analgesics.	Diarrhoea requiring parenteral support. Severe mucous or blood discharge necessitating sanitary pads. Abdominal distention (radiographically demonstrated distended bowel loops.	Acute or subacute obstruction, fistula or perforation. GI bleeding requiring transfusion. Abdominal pain or tenesmus requiring tube decompression or bowel diversion.
Genitourinary	No change	Frequency of urination or nocturia twice pretreamtent habit. Dysuria, urgency not requiring medicaiton	Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anaesthetic.	Frequency with urgency and nocturia hourly or more frequently. Dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic. Gross haematuria with/without clot passage.	Haematuria requiring transfusion. Acute bladder obstruction not secondary to clot passage, ulceration or necrosis.

10.11 APPENDIX 11 – EPIC CP QUESTIONNAIRE

Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP)

A Clinical Tool to Measure Urinary, Bowel, Sexual and Vitality/Hormonal Health **Date:** ___/___/___

Patients: Please answer the following questions by checking the appropriate checkbox. All questions are about your health and symptoms in the **LAST FOUR WEEKS**. Select one answer for each question.

1. Overall, how much of a problem has your urinary function been for you?
☐ No problem ☐ Very small problem ☐ Small problem ☐ Moderate problem ☐ Big problem

2. Which of the following best describes your urinary control?
0☐ Total control 1☐ Occasional dribbling 2☐ Frequent dribbling 4☐ No urinary control ____

3. How many pads or adult diapers per day have you been using for urinary leakage?
0☐ None 1☐ One pad per day 2☐ Two pads per day 4☐ Three or more pads per day ____

4. How big a problem, if any, has urinary dripping or leakage been for you?
0☐ No problem 1☐ Very small problem 2☐ Small problem 3☐ Moderate problem 4☐ Big problem ____

CLINICIANS: ADD the answers from questions **2-4** *to calculate the* ***Urinary Incontinence Symptom Score (out of 12):*** ☐

5. How big a problem, if any, has each of the following been for you?	**No problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	
a. Pain or burning with urination	0☐	1☐	2☐	3☐	4☐	____
b. Weak urine stream/incomplete bladder emptying	0☐	1☐	2☐	3☐	4☐	____
c. Need to urinate frequently	0☐	1☐	2☐	3☐	4☐	____

CLINICIANS: ADD the answers from questions **5a-5c** *to calculate the* ***Urinary Irritation/Obstruction Symptom Score (out of 12):*** ☐

6. How big a problem, if any, has each of the following been for you?	**No problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	
a. Rectal pain or urgency of bowel movements	0☐	1☐	2☐	3☐	4☐	____
b. Increased frequency of your bowel movements	0☐	1☐	2☐	3☐	4☐	____
c. Overall problems with your bowel habits	0☐	1☐	2☐	3☐	4☐	____

CLINICIANS: ADD the answers from questions **6a-6c** *to calculate the* ***Bowel Symptom Score (out of 12):*** ☐

7. How would you rate your ability to reach orgasm (climax)?
0☐ Very good 1☐ Good 2☐ Fair 3☐ Poor 4☐ Very poor to none ____

8. How would you describe the usual quality of your erections?
0☐ Firm enough for intercourse 1☐ Firm enough for masturbation and foreplay only 2☐ Not firm enough for any sexual activity 4☐ None at all ____

9. Overall, how much of a problem has your sexual function or lack of sexual function been for you?
0☐ No problem 1☐ Very small problem 2☐ Small problem 3☐ Moderate problem 4☐ Big problem ____

CLINICIANS: ADD the answers from questions **7-9** *to calculate the* ***Sexual Symptom Score (out of 12):*** ☐

10. How big a problem, if any, has each of the following been for you?	**No problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	
a. Hot flashes or breast tenderness/enlargement	0☐	1☐	2☐	3☐	4☐	____
b. Feeling depressed	0☐	1☐	2☐	3☐	4☐	____
c. Lack of energy	0☐	1☐	2☐	3☐	4☐	____

CLINICIANS: ADD the answers from questions **10a-10c** *to calculate the* ***Vitality/Hormonal Symptom Score (out of 12):*** ☐

CLINICIANS: Add the five domain summary scores to calculate the ***Overall Prostate Cancer QOL Score (out of 60):*** ☐

A downloadable version of EPIC-CP can be found at http://www.bidmc.org/epic

10.12 APPENDIX 12 - LEVEL 12 DESCRIPTORS

10.13 APPENDIX 13 - RTMG GROUP PRESENTATION.

WELCOME TO THE WORLD OF RAYPILOT

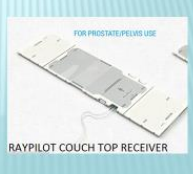
Susan Adamson
Advanced Practitioner GU

WHAT IS RAYPILOT??

- The Raypilot system is an electromagnetic tracking system for target localisation and motion tracking.
- The Raypilot system provides instantaneous and continuous monitoring of the position of the Raypilot device in relation to the isocentre.
- If the target moves out with a defined position tolerance, necessary actions can be taken i.e. Stopping the radiation or repositioning the patient.

WHAT MAKES UP THE RAYPILOT SYSTEM?



RAYPILOT COUCH TOP RECEIVER

HOW DOES IT WORK?

- The initial co-ordinates of the isocentre and transmitter are recorded in the Raypilot system and the system then uses the resultant displacements to track organ motion.
- The couch top receiver technology tracks the transmitter motion and alerts you to when it has moved out of a pre-determined tolerance level for action to be taken.

THE TRANSMITTER/HYPOCATH

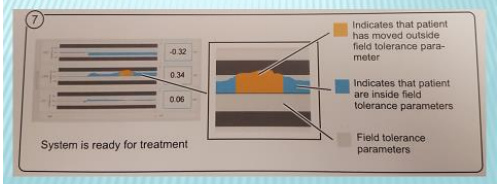
- Each Hypocath contains a patient specific data chip.
- The transmitter will be implanted in clean conditions using the Hypocath catheter.
- The fiducial markers are still used as our gold standard for localisation.
- The Hypocath remains in-situ for the treatment duration and is removed on the last fraction.

IMPORTANT POINT OF NOTE *

- Manual gating of the beam is required by the operator.
- System only configured for use on LA4.

TREATMENT

- During treatment the motion of the organ is shown graphically, if it remains blue the target is moving within tolerance, if it turns yellow the target has moved out of tolerance.



REQUIRED ACTIONS

- If any parameters turns yellow the beam will be stopped by the radiographers on the Truebeam console **immediately.**
- Monitor the motion pattern for a maximum period of 90 seconds.
- If all parameters return to blue arrows indicating the target has moved back into tolerance then treatment can be resumed.
- If the parameters remain yellow then a new treatment position must be registered i.e reposition to isocentre using fiducials.

IMPLEMENTATION

- ONLY centre in the UK to have technology.
- Work instructions – endorsed and positive feedback from Raypilot representatives.
- Exposure package agreement.
- Training plans and records of training.
- Reference documentation.
- OOQS documentation.
- Patient information leaflet approval.
- Pyramid training of other disciplines e.g treatment floor nurses, CAU, theatre, MR, GP information.

TRAINING

- Components of the Raypilot system.
- The treatment console and functions.
- Daily quality control procedure.
- First day process, subsequent treatment process.
- Treatment.
- Problem solving.
- End to end test.

CURRENT CORE TEAM

- Susan Adamson
- Joanne Mitchell
- Joanna Henderson
- Elaine Carse
- Niamh Fitzpatrick
- Joanne Matheson
- Amy Rhatigan
- Laura McKernan

*Staff training will be extended to staff rotating through LA4 in the first instance.

CURRENT CLINICAL APPLICATION

- Prostate SABR; 3625cGy in 5#.
- ? 3 arcs (current patients require 3)
- Clinical technique is still the same – patient positioning, marker match etc.
- Daily pre-treatment kv marker match, daily pre-treatment CBCT, kv marker match prior to each arc and if patient moves, then daily post-treatment CBCT to assess intrafraction filling.

IMAGING

- Standard kv marker match.
- Daily pre & post treatment CBCT.
- Kv imaging in-between each treatment arc.
- Repeat imaging if patient is repositioned.
- Exposure package updated to allow for multiple imaging.

MEDICATION REQUIREMENTS

- Prophylactic anti-biotics (ciproflaxin) for fiducials.
- Micro enema as per current protocol (MR, CT planning and all xrt fractions).
- Paracetamol and ibuprofen if required following Hypocath removal.
- Additional post xrt if required – tamsulosin, fybogel, simple analgesia (as per current departmental protocols).

CHALLENGES

- Multidisciplinary cohesion.
- Theatre time.
- Real time problem solving (all the issues are 'firsts' therefore understanding and training are crucial. The support staff are in Sweden so immediate answers are not readily available.
- Patient compliance.
- Confidence in insertion process.

MULTIDISCIPLINARY COHESION

- Theatre time – lack of theatre staff and slots.
- Radiologist availability.
- Day bed admission.
- MRI staff.
- ANP/advanced practitioner availability.
- Radiographers.
- GP information.

SOLUTIONS

- Advanced practitioner competence.
- Agreed patient pathway.
- Standardised information for all departments involved including patient information leaflets.
- Dissemination of information to all depts.
- Point of contact.
- Continual radiographer training.
- ? GP information pack for after care etc.

FINDINGS SO FAR....

- Well tolerated by patients.
- Information easily understood and followed.
- Comparable side effects to standard fractionation (most evident fraction 4).
- Removal of device unproblematic.
- No issues with infection following implantation or removal.
- No issues with wound sites.

PATIENTS

Patient	RTOG final #	RTOG 6/52	RTOG 3/12	PSA diagnosis	PSA 6/52	PSA 3/12
1	RTOG 1	RTOG 2	RTOG 1	9.1	6	6.1
2	RTOG 1	RTOG 2		12.9	2.8	
3	RTOG 2			3.2 (6.4) finasteride		
4	*Removed	From	Study *			
5	Implanted	Not started	Xrt Yet	7.1		
6	Booked	For	Implant	And	Xrt	

* Patient 4 – found to have metastatic disease on MRI scan on the morning of the implantation procedure therefore did not meet study inclusion criteria.

FUTURE PLANNING

- Aim for 1-2 patients per month.
- Long term data collection.
- Publications.
- Possibility that we will become a training centre for other departments.
- COVID recovery.

10.14 APPENDIX 14 - UKIO SUBMISSION.

Raypilot: The patient experience.

Author: Susan Adamson, Advanced Practitioner GU
Hospital: Edinburgh Cancer Centre, Western General Hospital, Edinburgh, EH4 2XU

Introduction

Prostate volumetric arc therapy dose escalation regimes i.e. SBRT (stereotactic body radiotherapy) require advanced methods of motion management to ensure effective and accurate beam delivery whilst limiting dose to the organs at risk e.g. rectum and bladder. The Micropos Raypilot device is an electromagnetic GPS tracking system used in prostate SBRT to record motion of the prostate gland throughout treatment – intrafraction motion (Figure 1 & 2). The device is surgically implanted using a transperineal approach and remains in situ for the duration of the radiotherapy treatment. In some cases this can be up to six weeks. As the only centre in the UK trialling this system it is imperative that patient experience data from surgical implantation to device extraction is collated and assessed.

Objectives

To assess the patient experience of Raypilot including surgical insertion, treatment, removal of the device and attitude towards the system.

Methods and Materials

- 11 patients have had the Raypilot motion management device implanted using surgical intervention (Figure 2).
- The patient received 3625cGy in 5# using Raypilot as a motion management system.
- The average length of time the device was in situ prior to removal was three to four weeks.
- The specialist radiographer conducted face to face discussions with the patient regarding their experience of the Raypilot device.
- The qualitative data was then recorded and collated for the purposes of the research study.

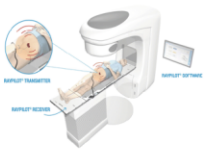
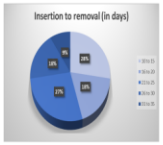
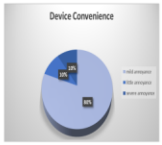


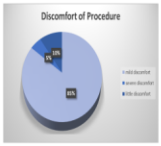
Figure 1

Figure 2

Results







- 90% of patients said they would have had the procedure again if required.
- 75% of patients had the Raypilot device in situ from insertion day until final radiotherapy fraction.
- 100% of patients found the device removal procedure only minimally uncomfortable.
- 100% of patients found that the device maintenance and care was unproblematic.
- 85% of patients suggest mild discomfort in the hours immediately after insertion but this quickly dissipates.
- 100% of patients concurred that the device was worthwhile if the could have a reduced treatment fractionation.
- Only one patient had evidence of device migration following implantation.

Conclusion

The Raypilot transmitter device is extremely well tolerated by patients, the evidence from this patient cohort implies that the device is easily looked after following implantation if given the correct literature. It appears to be minimally obtrusive and only causes minimum discomfort that subsides quickly. In conclusion, patients have shown a remarkably positive experience of the use of the Raypilot device.

10.15 APPENDIX 15 – SOCIETY OF RADIOGRAPHERS ANNUAL CONFERENCE PROFFERED PAPER

Non-Student Proffered Paper Abstracts Friday 24January 14:05e14:55

IMPLEMENTING RESEARCH IN TO CLINICAL PRACTICE; A REPORT OF THE IMPLEMENTATION OF THE PRINTOUT TRIAL AT THE EDINBURGH CANCER CENTRE

Joanne Mitchell, Susan Adamson, Joanna Henderson, Donna BurnsPollock.

Edinburgh Cancer Centre, Edinburgh, United Kingdom

Keywords: Stereotactic Body Radiotherapy Prostate; Printout; BreathAnalysis.

Introduction: The Printout (Using breath analysis to PRedIct NormalTissUe and Tumour response during prostate SBRT) [1] Trial is a prostate stereotactic body radiotherapy (SBRT) pilot study currently being undertaken at the Edinburgh Cancer Centre. The primary objective is to establish the possibility of measuring biomarkers in breath samples to monitor an individual's response to radiotherapy . It is hoped to gain enough data from the pilot to progress to a larger scale study. Responsibility for the running of the trial including patient screening, recruitment, treatment delivery, data collection and management has been delegated to radiographers.

Method and Materials: Printout patients attend for a multi parametric MRI scan, transperineal implantation of the raypilot prostate tracking device [2] and a planning CT scan as an outpatient during one day. A SBRT treatment plan is constructed using the rigidly fused MRI and CT scan. A dose of 36.25Gy is delivered in 5 fractions by a Varian Trubeam linear accelerator over 7 days, with breath samples acquired before and after each session. Kilovoltage imaging, CBCT and raypilot are used to monitor and verify treatment position. Patient reported outcome measures(PROMS) questionnaires are completed prior to treatment delivery, immediately on completion of treatment and at regular follow up appointments.

Results: 5 patients have participated in the trial. Early data suggests hypofractionated SBRT can be delivered safely to the prostate gland using the Raypilot Device as a motion management system. PROMS have re-ported toxicities which are well tolerated, with the regime itself a very welcome alternative to conventional fractionation. Data regarding het-erogeneity factors has yet to be reported.

Conclusion/ Discussion: The Printout Trial is the first time radiographers in the department have been involved in both the technical and administration part of trial set up and design. Recruitment, although slow initially, has improved and it is hoped that one patient per month will now be enrolled. The trial has demonstrated the vital role radiographers play in radiotherapy research and also problems which can arise from the regulations surrounding research governance.

10.16 APPENDIX 16 – AMERICAN SOCIETY FOR RADIATION ONCOLOGY POSTER SUBMISSION.

Analysis of the intra-fractional motion of the prostate during SBRT using an EM Transmitter

Michael Trainer[1], Linda Carruthers[1], Bill Nailon[1], Susan Adamson[1], Duncan McLaren[1], Mike Kirby[2]
[1]Edinburgh Cancer Centre (ECC) UK, [2]Liverpool University Directorate of Radiotherapy UK

NHS Lothian

Introduction

Intra-fraction motion of the prostate during hypo fractionated treatment regimens can potentially impact the delivered dose to the prostate. EM Transmitters such as RayPilot, can provide real-time positional information. The purpose of this study was to establish the efficacy of RayPilot for real-time positional verification in prostate SBRT and to assess overall target displacement during treatment.

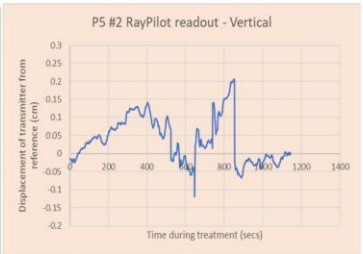
Methods & Materials

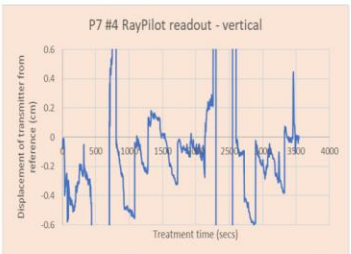
The RayPilot real-time tracking system[1] uses a transmitter inserted into the prostate trans-perennially which is detected by a table-top array containing an antennae. Positional data was exported to Excel for analysis.

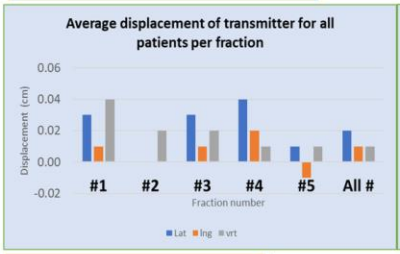
Study Detail:
- 7 PRINToUT trial patients
- 36.25Gy / 5#
- Imaging by kV Orthogonal pairs (Primary)
- Pre/post CBCT
- RayPilot system for real time tracking
- Imaging correction threshold 2mm
- 3 Arc VMAT

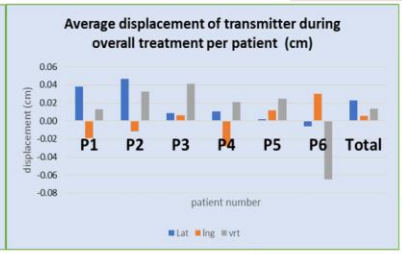
Results

The position of the transmitter after the 1st set up image was recorded and exported to Excel. This included positional information between arcs and during re-set up. Shown are 2 example readouts. P7 #4 required several additional images and re-positioning during this fraction.



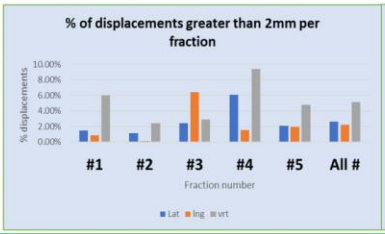


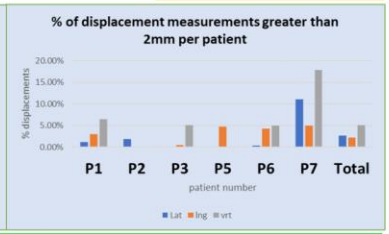




P4 was not treated with the RayPilot system after #2 so was excluded from the study. The average displacement of the transmitter was less than 1mm for all patients and all fractions.

Measurement points were taken every second. The overall % of points outside the imaging threshold for each patient and fraction are shown. These measurements included re-set up and time between arcs so do not necessarily correspond to the position during beam on.





Conclusion

RayPilot was a viable means for tracking the prostate during SBRT. The position of the target was within 2mm for 94.9% of the measurements. Synchronising the software to enable measurements only taken during radiation delivery to be used would strengthen the validity of the data. Further work should be carried out to asses if RayPilot could be the primary monitoring device during prostate SBRT.

References:
[1] Micropos Medical (2019) 'RayPilot', http://www.micropos.se/products/.

10.17 APPENDIX 17 – 360 FEEDBACK QUESTIONNAIRES.

Area of Practice	Feedback
What feedback would you give me on the way that I communicate with you?	I think you are very honest and open in your communications with me. You are able to point out areas where I could improve upon but this was done in a kind and supportive manner (when re-learning treatment!)
What feedback would you give me on the way I communicate with patients and their families?	I think you show compassion and kindness and an interest in patients well being.
What aspects of my work do you think people value?	Your knowledge and skills within prostate and general treatment capabilities. You enjoy your job and this shows through.
How do you think I respond to difficult or sensitive situations either with patients or staff?	You can be a little defensive if challenged and this may come across as negative but this is an area where I think you find difficult mainly because you judge yourself harshly and like most of us lack a bit of self confidence.
How do you see me in terms of my time management?	No issues
How person person-centred am I?	I think you are very person centred and have patient's best interests at heart
What would you say about the way in which I give and receive feedback?	Your feedback to me has always been supportive and helpful but I cannot comment on others. I think as above you can receive feedback a bit defensively in some circumstances.
How do you see me as a member of a team?	Good team player
What do I do that makes you want to work with me?	I think you are friendly, open, patient centred and willing to share your knowledge. Good teacher
What would you say about my ability to take on board and learn new things?	I think you embrace new things if you feel they have value and are willing to learn new things.
Adapted from 'Flying Start', NHS Education Scotland, the 'REACH' tool University of Ulster and Everybody Matters City University 2012	

Area of Practice	Feedback
What feedback would you give me on the way that I communicate with you?	Communication is very good, clear and precise.
What feedback would you give me on the way I communicate with patients and their families?	Cannot comment as not witnessed in our working relationship.
What aspects of my work do you think people value?	Honesty, Compassion, Commitment and Empathy
How do you think I respond to difficult or sensitive situations either with patients or staff?	With empathy, compassion and confidentiality if required.
How do you see me in terms of my time management?	Well managed
How person person-centred am I?	Very personable
What would you say about the way in which I give and receive feedback?	Open and honest
How do you see me as a member of a team?	Valued
What do I do that makes you want to work with me?	Team player. Great work ethic . Always trying to make life a little better to work with the day to day issues we may face.
What would you say about my ability to take on board and learn new things?	Willing and open to trying new approaches.
Adapted from 'Flying Start', NHS Education Scotland, the 'REACH' tool University of Ulster and Everybody Matters City University 2012	

Area of Practice	Feedback
What feedback would you give me on the way that I communicate with you?	Open, honest and professional
What feedback would you give me on the way I communicate with patients and their families?	Listens to what patients have to say, communicates and responds in a professional manner but also very sympathetic to their concerns if they have any
What aspects of my work do you think people value?	In depth knowledge in your area of expertise. Caring approach towards patients Willingness to help and support other colleagues
How do you think I respond to difficult or sensitive situations either with patients or staff?	Good listener Empathetic but proactive and tries to resolve issues
How do you see me in terms of my time management?	Excellent
How person person-centred am I?	Treat people as individuals and ensures that their preferences and needs are met whilst respecting their values
What would you say about the way in which I give and receive feedback?	Open and honest with a careful considered approach when giving feedback. Sometimes dismisses positive feedback from fellow colleagues towards herself
How do you see me as a member of a team?	Valuable member of the team. Supportive, reliable and always keen to help out the CNS team
What do I do that makes you want to work with me?	Easy going but responsive to demanding workloads.
What would you say about my ability to take on board and learn new things?	Very keen when taking on new projects and fully engages.
Adapted from 'Flying Start', NHS Education Scotland, the 'REACH' tool University of Ulster and Everybody Matters City University 2012	

Area of Practice	Feedback

What feedback would you give me on the way that I communicate with you?	I'd say you are very honest in the way you speak to me and you are very open for any questions, queries etc. You also don't hesitate to let your feelings known and you have a great way with words (I appreciate that as well)
What feedback would you give me on the way I communicate with patients and their families?	You are very professional when speaking to patients and their families on most occasions. However you can be very "real" with them too. By that I mean that you don't hesitate to have a heart to heart conversation with them if the situation is required. I've seen very few senior staff be able to have the heart to heart talks with patients as well as you have. Its one aspect that I learned from you and I hope to be able to use it as effectively in my career.
What aspects of my work do you think people value?	Being a good team leader and being open and honest. For me they are your two biggest qualities. You are also one of the best problem solvers in the department in my opinion; I suppose that's easy when you know damn near everyone who works in the GU team.
How do you think I respond to difficult or sensitive situations either with patients or staff?	You are always aware of other people's feelings whether that is staff or patients. I have a few examples of where I have spoke to you about difficult situation whether that is in work or going on in my life outside of work. You always seem to handle these situations with great integrity and sensitivity towards the situation. I personally know that I can come to you if I have a problem inside or outside of work and I really appreciate having a senior member of staff that has these qualities. I hope that later in my career I can model my own leadership and people skills on yours.
How do you see me in terms of my time management?	I'd say that you have pretty good time management skills and I cant think of a time that would counteract my statement.
How person person-centred am I?	I'd personally say that you are very person centred, as I spoke about earlier you are able to have heart to heart conversations with people if you think they need them. You also seem to care a lot about patient's mental health which is an aspect that can easily get ignored. You seem to be all about the holistic care of the patient
What would you say about the way in which I give and receive feedback?	You are always open and honest when giving feedback. It's another aspect that I appreciate cause I always like to improve myself as much as possible so getting feedback is always a good thing in my opinion. You can also be quite candid in the way you deliver the feedback sometimes and again with some members of staff this is needed.
How do you see me as a member of a team?	I see you as a strong leader that will fight for a cause if you need to but you can also be quite friendly and personally with members of the tea as

	well. I feel you have a good balance between being the leader and being a one of the group (If you get what I mean)
What do I do that makes you want to work with me?	You always have good vibes and banter which is always good to work with. But on top of that I always try and pick up new tricks or qualities as I work, I feel like I've learned a lot in terms with leadership and being able to deal with people from you. In general It's always good to work with you as you get the work done and at the same time it seems to be a nice chill time. (like you never seemed stressed)
What would you say about my ability to take on board and learn new things?	Radiotherapy seems to be an ever changing job so you have to be somewhat flexible. (unlike us with our lunchtimes lol) I'd say you are always willing to teach anyone who wants to learn. You always seem to embrace and try and learn new things as far as I've seen.
Adapted from 'Flying Start', NHS Education Scotland, the 'REACH' tool University of Ulster and Everybody Matters City University 2012	

Area of Practice	**Feedback**

What feedback would you give me on the way that I communicate with you?	Susan is very clear communicator, and always have potential solutions to problems that makes it easier to make decisions
What feedback would you give me on the way I communicate with patients and their families?	Very honest, helpful
What aspects of my work do you think people value?	She is a great team player
How do you think I respond to difficult or sensitive situations either with patients or staff?	She approaches patients in an empathetic manner, patient listener and engages patients in a conversation to approach difficult sitiations
How do you see me in terms of my time management?	Efficient
How person person-centred am I?	Her approach is always been patient centred
What would you say about the way in which I give and receive feedback?	Susan is open to analyse her decisions, approaches others decisions in a sensitive manner
How do you see me as a member of a team?	Great team player, inspires confidence in others and has a shared vision to improve cancer services
What do I do that makes you want to work with me?	She is a dependable person
What would you say about my ability to take on board and learn new things?	Susan has been a keen person to look at newer technologies, and work towards implementing this
Adapted from 'Flying Start', NHS Education Scotland, the 'REACH' tool University of Ulster and Everybody Matters City University 2012	