The MAGNIFI Trial: Metastasis assessment with Gallium-68 PSMA and Nanoparticle Imaging Fusion International

Prospective evaluation of lymph node imaging for the nodal staging of prostate cancer with a high risk of lymph node metastases: A prospective cohort study to determine the concordance between two imaging modalities, "Combidex" Nanoparticle-Magnetic Resonance Lymphography (Nano MRL) and 68Ga-PSMA positron emission tomography (PET)

CLINICAL TRIAL PROTOCOL

Version number 2.4

Protocol date: 24th January 2019

SYNOPSIS

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Prospective evaluation of lymph node imaging for the nodal staging of prostate cancer with a high risk of lymph node metastases: A prospective cohort study to determine the concordance between two imaging modalities, "Combidex" Nanoparticle-Magnetic Resonance Lymphography (Nano MRL) and 68Ga-PSMA positron emission tomography (PET)

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LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
68Ga-PMSA PET	[68Ga] Gallium-labelled prostate-specific membrane antigen positron emission tomography
HREC	Human Research Ethics Committee
LND	Lymph Node Dissection
Nano MRI	Nanoparticle-Magnetic Resonance Imaging
Nano MRL	Nanoparticle-Magnetic Resonance Lymphography
SAE	Serious Adverse Event
APCRC-NSW	Australian Prostate Cancer Research Centre-NSW

Summary

TITLE	**The MAGNIFI Trial: Metastasis assessment with Gallium-68 PSMA and Nanoparticle Imaging Fusion International**
SHORT TITLE	Magnifi Trial
VERSION NO.	2.4 24th January 2019
SPONSOR	The Garvan Institute of Medical Research 384 Victoria St DARLINGHURST NSW 2010
INDICATION	Diagnosis and treatment of lymph node metastases in men with prostate cancer
OBJECTIVES	1. To compare "Combidex" Nanoparticle-Magnetic Resonance Lymphography (Nano MRL) and 68Ga-PSMA positron emission tomography (PET) to the gold standard and current practice; the histology of pelvic lymph node dissection, to locate the position of lymph nodes 2. Determine whether concordance of these two imaging technologies (68Ga-PSMA PET - functional imaging, and Nano MR - anatomical imaging) is worse, better or equal to lymph-node dissection
TRIAL DESIGN	An investigator initiated, prospective, non-randomized study
PLANNED NUMBER OF PARTICIPANTS	120 participants will be recruited over a two year period; 60 participants from St Vincent's Hospital Sydney and 60 participants from the Wesley Hospital Brisbane
TARGET POPULATION	Men diagnosed with prostate cancer with and without suspicion of lymph node involvement but have yet to undergo a radical prostatectomy.
INCLUSION CRITERIA	• Male, aged 18 years or over • Confirmed adenocarcinoma of prostate and at least clinical stage T3A and/or Gleason sum >= 4+3=7, or preoperative PSA ≥ 15 ng/ml and planned radical prostatectomy • Suspected lymph node involvement pre- radical prostatectomy based on Briganti nomogram >= 10%. • Suitable for radical prostatectomy and pelvic lymph node dissection, as per institutional guidelines and not yet treated pre-prostatectomy • Subject is able to understand and willing to sign the participant information statement and consent form • Subject is expected to remain available for 24 months of clinic visits
EXCLUSION CRITERIA	• Past history any other type of cancer (except skin cancer). • Previous treatment for prostate cancer (surgery, radiotherapy, chemotherapy, hormone androgen deprivation therapy) • Proven bony metastatic disease, visceral metastases or lymph node metastases above the level of the aortic bifurcation

	• Previous surgery in pelvis (e.g. bilateral hip replacement) that limit the extent of pelvic lymph node dissection • Patients who refuse radical prostatectomy or pelvic lymph node dissection • Patients who refuse to join the trial or are unable to consent • Patients not being considered for further therapy • Patient has absolute contra-indications to undergoing MRI scanning • Patients who cannot lie still for at least 60 to 75 minutes or comply with imaging • Subject has medical conditions that would limit study participation (per physician discretion) • Subject is enrolled in one or more concurrent studies that would confound the study results of this study as determined by the study investigators • Subject has a limited life expectancy that would not allow completion of the 24 month visits
STUDY PROCEDURES St Vincent's Hospital, Sydney	1. Men diagnosed with prostate cancer are referred to a participating urologist for a radical prostatectomy 2. The patients are consented to the study by the urologist following fulfilment of the selection criteria 3. The patient is referred to the Department of Nuclear Medicine, St Vincent's Hospital, Sydney 4. The 68Ga-PSMA PET Scan is performed at the Department of Nuclear Medicine, St Vincent's Hospital, Sydney 5. On the return visit, "Combidex" is administered to the patient and the patient is referred to Medscan Barangaroo for a MRI scan 6. Radiologist and Urologist annotate suspect lymph nodes using the Pelvic Lymph Node Diagnostic Template and assign index of suspicion to each area 7. Patient undergoes radical prostatectomy including the removal of lymph nodes 7-10 days following Combidex nano-MRL 8. The prostate and the lymph nodes are sent to histology for reporting 9. Analysis: a. Histology Vs Nano-MRL b. Histology Vs Ga68 PSMA PET c. Histology Vs Nano-MRL Vs Ga68 PSMA PET 10. Repeat Ga68 PSMA and Nano-MRL if not concordant with Histology within 6-8 weeks of surgery 11. Follow up Visits: The participant will have clinical follow up reviews as part of their care at 6 weeks, 2 months, 6 months, 12 months and 24 months 12. Participant will complete the Expanded Prostate Cancer Index Composite (EPIC) survey at baseline (prior to surgery), 6 weeks, 3 months, 6 months, 1 years and then yearly for a minimum of 5 years).
ENDPOINTS	1. Diagnostic: a. Concordance of 68Ga-PSMA PET and Nano MRL

	b. Histology of LND c. Concordance of (a) and (b) d. Results of reimaging after LND 2. Clinical – Follow up at 24 months
STATISTICAL ANALYSES	We will recruit 120 patients. Considering that each patient has 6 packets (a lump of fat containing lymph nodes) on average, we will be comparing 720 packets in total. This number will give 90% power to detect a 10% or less discordance between final histology analysis and the combined imaging modalities consensus.
STUDY DURATION	10 years (Anticipated January 2016 to December 2026)

CONTENTS

1.BACKGROUND

1.1. DISEASE BACKGROUND

Following curative intended therapy in prostate cancer patients, a high proportion of patients (approx. 25%) relapse with local and/or distant recurrence [1]. The metastasis of a lymph node (LN) in a patient with prostate cancer means that the disease has become systemic with the increased risk of disease progression. Therefore the ability to detect the presence of LN metastasis is important in terms of disease prognosis and treatment selection. In the past, patients with LN metastasis have had poor prognoses due to the scarcity of accurate staging techniques and toxic treatment regimens such as radiotherapy. For those patients with a medium to high risk of having LN metastasis, the current procedure is a bilateral pelvic lymph node dissection (LND). It is generally accepted that a LND provides important information for prognosis witch cannot be matched by other current procedures. Therefore, it is the standard procedure prior to curative treatment with either radical prostatectomy or radiation therapy. Besides being a staging procedure, pelvic LND may be curative, or at least beneficial, in a subset of patients with limited lymph node metastases[2, 3]. The number of nodes removed during LND has been significantly correlated with the time to progression[3, 4]. However, results from ongoing prospective studies are awaited. On the other hand, the LND is not optimal due to the frequent inability to remove all suspicious lymph nodes within the dissection area. 41% of metastatic LN disease is not found [5], due to these LN being outside the routine surgery field. As a result, many urologists will perform an extended lymphadenectomy (e-LND), which leads to extended operating times and the risk of complications [6]. Also, radiotherapy of LN metastases has limitations: more than 50% of metastatic LN are outside the routine (RTOG-CTV) radiation field [7]. As a result, the effect of standard salvage LN radiotherapy is limited [8]. Currently used imaging techniques such as CT and conventional MRI are not sensitive enough to detect prostate cancer metastases due to the small size of the nodes (< 8mm) [9]. Finally, 11C-Choline PET/CT fails to detect metastatic LN, when they are smaller than 6 mm since a minimum amount of tracer needs to be present in the LN to be detected [10].

It has been suggested that patients with metastatic LN ≤8 mm have a significantly better 5-year distant metastases-free (79% vs 16%) and overall survival (81% vs 36%), than patients with larger positive lymph nodes [11]. Thus detection and localization of most –small- LN and subsequent focused, patient tailored treatment of these small metastatic LN may reduce side effects and enable cure [12, 13].

An accurate non-invasive imaging modality in combination with existing treatment techniques, may lead to a therapeutic shift for patients who have in the past been restricted to palliative treatment. Recently developed imaging modalities to detect small lymph node metastases, which offer promise, include Nano Magnetic Resonance (Combidex) Lymphography (Nano MRL) and 68Gallium-Prostate Specific Membrane Antigen (PSMA) Positron Emission Tomography Imaging (68Ga-PSMA PET). However, the true value of 68Ga-PSMA PET and Nano MRL is still unknown, underscoring the need for well designed further studies with histopathology as the standard as reference.

Recently developed imaging modalities to detect small lymph node metastases

Nano MRL (Combidex)

Nano MRL is a non-invasive technique, which can be used to detect small prostate cancer lymph node metastases [14-17]. Currently, lymph node staging is performed with the use of invasive pelvic lymph node dissection (LND). Literature shows three potential advantages of the use of Nano MRL for lymph node staging in men with newly diagnosed prostate cancer: 1) a negative Nano MRL will preclude a LND; 2) a positive Nano MRL supports LND lymph node staging, and can “target” the dissection; and 3) a positive Nano MRL might improve the opportunity for curative treatment in patients with limited lymph node involvement [17].

Intravenous Nano-MR, using dextran coated small iron oxide particles (ferumoxtran-10, Combidex®, Radboudumc, The Netherlands), allows detection of metastatic LN in even very small (>2 mm) LN [14-16]. Thus Nano-MR results in a significant improvement of the detection of LN metastases compared to other existing techniques [14-16]. For example, compared to 11C-Choline PET/CT, Nano-MR detected more metastatic LN (738 vs 132) in more patients (23/29 vs 13/29) in smaller LN (mean diameter 4.9 vs 8.4 mm)[18]. Nano-MR also obviates the use of surgical removal of LN [5, 16], and thereby reduces unnecessary side effects and decreases health care costs. A large prospective multi-centre study demonstrated the cost-effectiveness [10, 19]. Furthermore, with Nano-MR LN metastases are more accurately detected than with current nomograms [20, 21]. Nano-MR images can guide selective radiation of small, thus far undetected metastatic LN [12], and is expected to improve patient outcomes again [13, 22]. No prospective data is available comparing Nano-MR with 68Ga-PSMA.

History:

Approximately 15 years ago Nano MRI using Combidex became available for human use. The data from primary pharmacokinetic studies, a Phase I study and the data in a Phase II study were consistent, despite the different designs and rates of administration of the contrast agent. These studies showed:

1. A single intravenous dose of Combidex up to 1.7 mg Fe/kg is safe and tolerated. MRI results demonstrated the agent's ability to affect imaging characteristics of the blood pool, well-perfused organs, and cervical LN.

2. The Combidex doses of 1.1, 1.7, 2.6 and 3.4 mg Fe/kg could be safely administered. Signal intensity data and specificity rates for detecting normal LN demonstrated that the best imaging results were achieved with doses of 2.6 and 3.4 mg Fe/kg when MRIs were obtained 24 or 36 hours after Combidex administration. Because the results for those two doses and two imaging times were similar, the lower dose (2.6 mg Fe/kg) was chosen as the dose to be used in Phase III LN studies, with an imaging time of 24 to 36 hours. Pharmacokinetic results were similar to those from other studies, suggesting that the elimination of Combidex is unaffected by the rate of administration.

3. The administration of Combidex at the doses proposed (1.1 and 2.6 mg Fe/kg) has no immediate or delayed effect on immune function. The pattern of immune cell activity in the Combidex groups was similar to that in the placebo group during 8 weeks of pre-dose evaluations and 6 months of post-dose evaluations.

4. The pharmacokinetics of Combidex were linear in the range of doses tested. The half-life is 25 to 30 hours. There were no differences between the sexes in any pharmacokinetic parameters. Signal intensity analyses showed that the maximum contrast effect of Combidex occurred immediately after dose administration for liver and spleen and 24 hours after administration for lymph nodes. Most of the changes in signal intensity disappeared from LN within 7 days after administration of the dose recommended for lymph node MRI (2.6 mg Fe/kg). Assays of serum ferritin showed that total body iron stores were elevated to maximum levels 72 hours after dose administration and then slowly returned to normal.

In the US, two attempts were made to register Combidex through the FDA for clinical lymph node imaging, two similar attempts were made by Guerbet in Europe (under sublicensing) by EMEA. All four attempts failed due to suboptimal trial design, suboptimal statistics, and suboptimal central reading of imaging studies.

Finally in December 2007 the last application was withdrawn. The CHMP (EMEA) stated that, despite potential benefits and an acceptable safety profile; the pivotal study failed to demonstrate a consistent and statistically significant benefit for Combidex in sensitivity and failed to confirm non-inferiority with regards to specificity. All outstanding issues on quality, non-clinical documentation,

and clinical safety were, however, resolved before dossier withdrawal. A summary of the evaluation of the EMEA CHMP registration process, concerning the value and safety of Sinerem/Combidex is attached.

The Oncology Drugs Advisory Committee published a briefing document on Combidex in 2005 is attached. They concluded that Combidex could be safely administered by slow infusion over a period of approximately 30 minutes following dilution in 100 ml of normal saline. This method of administration minimizes adverse events and allows management of adverse events that may occur by stopping the infusion. The rate of serious events is less than a third of the rates experienced with iodinated contrast agents currently used with CT.

68Ga-PSMA PET Imaging:

Prostate specific membrane antigen (PSMA) is a cell-surface protein, which is significantly overexpressed in prostate cancer cells when compared to other PSMA-expressing tissues [23, 24]. Additionally, an up-regulation of PSMA was shown in tumour cells of patients with hormone-refractory prostate cancer [25, 26] as well as a significant increase in PSA recurrence [27]. Overall, PSMA provides a promising target for prostate cancer-specific imaging. Recently methods have been developed to label PSMA ligands with 68Ga to enable their use for PET imaging [28, 29]. A study by Afshar-Oromieh et al evaluating PET/CT using a 68Ga-labelled PSMA ligand suggests that this novel tracer can detect prostate cancer relapses and metastases with high contrast by binding to the extracellular domain of PSMA, followed by internalization [30, 31].

In recent studies the use of 68Ga-PSMA is compared with the current standard of choline PET-CT using 18-fluoromethylcholine in the diagnosis of disease recurrence[32, 33]. Overall, 68Ga-PSMA was more sensitive than PET-CT using 18-fluoromethylcholine for the detection of prostate cancer recurrence in patients with low PSA values. In the study by Morigi et al, in men with PSA <0.5ng/ml the detection rate of 68Ga-PSMA and 18-fluoromethylcholine was 50% and 12.5% respectively, for PSA 0.5-2.0 ng/ml 69% and 31% respectively (p-values all <0.05). A drawback to this studies is that only a small number of patients had histological correlation performed with imaging findings, however in this small group there were no false negative or false positive findings.

1.2. Rationale for Performing the Study

The current lack of imaging techniques to detect lymph node metastases and the realization of the variability of the lymphatic drainage of the prostate has led to: 1) inadequate treatment of positive nodes outside the usual fields, 2) many thousands of negative node dissections and 3) the recurrence of PSA after treatment due to unrecognized or untreated nodal metastases. Promising emerging imaging technologies including 68Ga-PSMA PET and Nano-MR Lymphography are now available but are yet to be validated in the clinical environment. An accurate non-invasive imaging modality in combination with improved treatment techniques, may improve the treatment outcomes in terms of survival (more specific and extended LND) and morbidity (exclude a high percentage of patients from an unnecessary LND) in prostate cancer patients with high risk of lymph node metastases.

2. STUDY OBJECTIVES

Hypothesis:

THE ADVANTAGES OF ACCURATE NODAL IMAGING FOR PATIENTS WITH INTERMEDIATE AND HIGH-RISK PROSTATE CANCER:

(i) If combined anatomical and functional nodal assessment is negative, then patients do not need a node dissection.

(ii) If combined anatomical and functional nodal assessment is positive, then appropriate treatment to the nodes (in conjunction with treatment to the primary cancer) can be planned. This may involve:

(a) Anatomically targeted node dissection (in place of e-LND)

(b) Anatomically targeted radiotherapy dose-painting

(c) The use of systemic chemotherapy (multiple small nodes in many locations) followed by the use of hormonal treatment (protocols analogous to those used in breast cancer oncology).

(iii) This multi-modal approach will decrease the failure rate of current treatment protocols where nodal status is unknown and standard nodal fields are irradiated or dissected based on probability.

2.1. PRIMARY OBJECTIVE

To compare "Combidex" Nanoparticle-Magnetic Resonance Lymphography (Nano MRL) and 68Ga-PSMA positron emission tomography (PET) to the gold standard and current practice; the histology of pelvic lymph node dissection, to locate the position of lymph nodes

2.2. SECONDARY OBJECTIVES

Determine whether concordance of these two imaging technologies (68Ga-PSMA PET - functional imaging, and Nano MR - anatomical imaging) is worse, better or equal to lymph-node dissection.

3. STUDY DESIGN

3.1. DESIGN

This study will be a prospective clinical trial, conducted by St Vincent's Hospital, Sydney, St Vincent's Prostate Cancer Centre, the Wesley Hospital, Brisbane, the Garvan Institute of Medical Research and the Radboud University Nijmegen, the Netherlands. Participant recruitment will occur at St Vincent's Hospital Sydney and the Wesley Hospital Brisbane. One hundred and twenty participants will be required, with 60 participants recruited from each recruitment site.

A trial management steering committee will be convened every six months to monitor the progress of the study. The committee will consist of members from each of the participating institutions.

3.2. STUDY GROUPS

There will only be one study group and it will consist of intermediate and high-risk cancer patients with a >10% probability on LN where LND would currently be performed as part of the treatment protocol (guided by the updated Briganti nomogram) [34]

3.3. NUMBER OF PARTICIPANTS

One hundred and twenty participants will be recruited over a two-year period; 60 participants will be recruited from St Vincent's Hospital, Sydney and 60 participants will be recruited from the Wesley Hospital, Brisbane.

3.4. NUMBER OF CENTRES

St Vincent's Hospital, Sydney (Participant recruitment)
The Wesley Hospital, Brisbane (Participant recruitment)
St Vincent's Prostate Cancer Centre (Participant recruitment)
The Garvan Institute of Medical Research/The Kinghorn Cancer Centre (Study management)
I-Med Radiology, Randwick

3.5. DURATION

This study is anticipated to run for 10 years. The first two years will be dedicated for participant recruitment while the subsequent years will be dedicated for participant follow-up and the completion of the Expanded Prostate Cancer Index Composite (EPIC Survey).

4. PARTICIPANT SECTION

4.1. INCLUSION CRITERIA

Patients must meet the following inclusion criteria to be eligible to participate in the study:

- Male, aged 18 years or over
- Confirmed adenocarcinoma of prostate and at least clinical stage T3A and/or Gleason sum >= 4+3=7, or preoperative PSA ≥ 15 ng/ml and planned radical prostatectomy
- Suspected lymph node involvement pre- radical prostatectomy based on Briganti nomogram >= 10%.
- Suitable for radical prostatectomy and pelvic lymph node dissection, as per institutional guidelines and not yet treated pre-prostatectomy
- Subject is able to understand and willing to sign the participant information statement and consent form
- Subject is expected to remain available for 24 months of clinic visits

If patients do not meet the inclusion criteria, (e.g. PSA < 15) they can still receive the same treatment and go through the LND but they will not take part in the study.

4.2. EXCLUSION CRITERIA

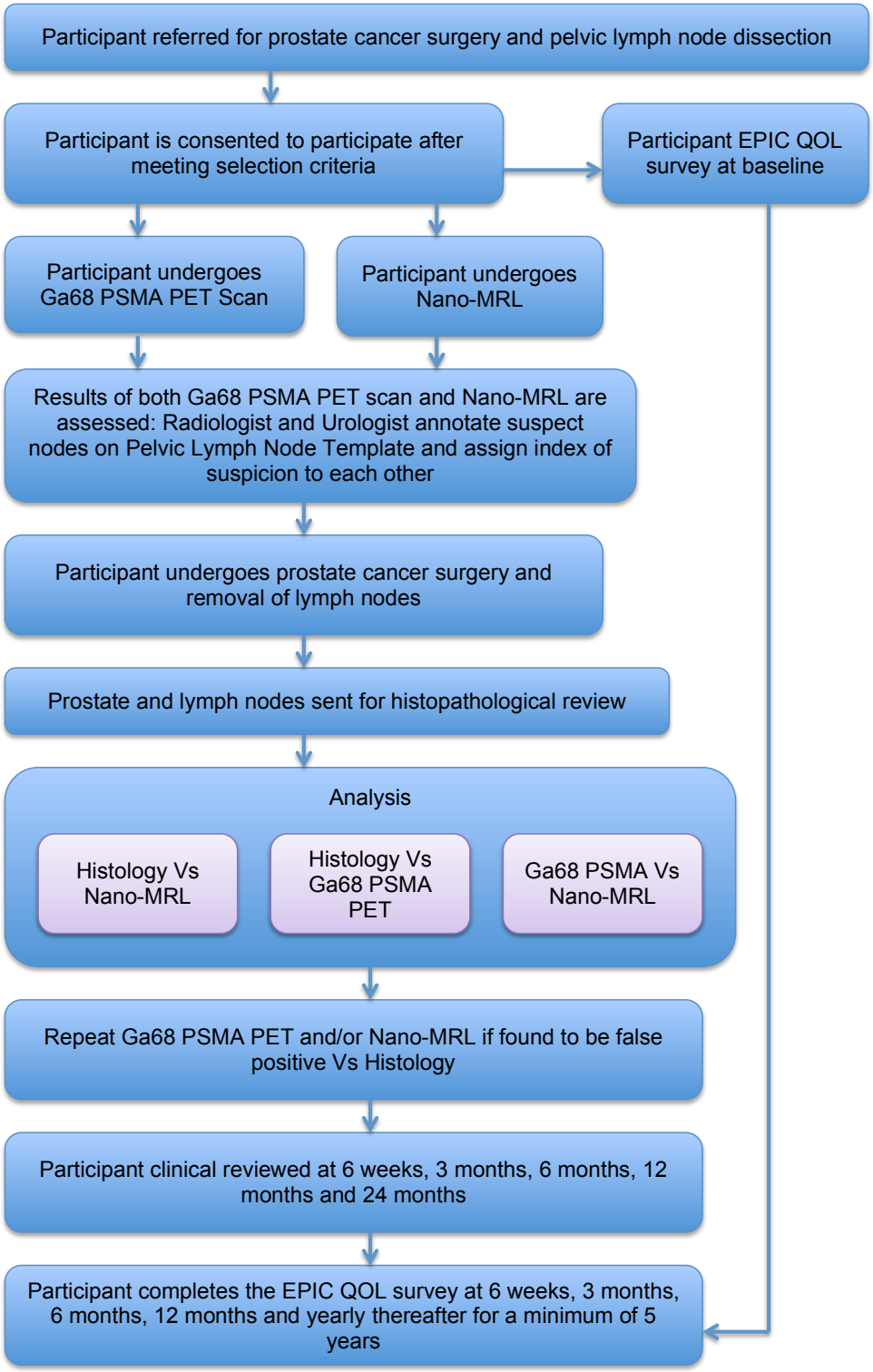
Patients who meet any of the following exclusion criteria are not eligible to participate in the study.

- Previous treatment for prostate cancer (surgery, radiotherapy, chemotherapy, hormone androgen deprivation therapy)
- Secondary malignancy expect skin cancer
- Proven metastatic disease
- Patients who refuse radical prostatectomy or pelvic lymph node dissection
- Patients who refuse to join the trial or are unable to consent
- Patients not being considered for further therapy
- Patient with previous pelvic surgery (e.g. bilateral hip replacement) that will limit the eLND
- Contra-indication to MRI scanning, IV iron infusion, allergy to dextran or other injectable contrast media used in this trial
- Patients who cannot lie still for at least 60 - 75 minutes or comply with imaging
- Unequivocal evidence of disease outside the pelvis on conventional imaging
- Subject has medical conditions that would limit study participation (per physician discretion)
- Subject is enrolled in one or more concurrent studies that would confound the study results of this study as determined by the study investigators
- Subject has a limited life expectancy that would not allow completion of 24 month visits

- Subject meets the exclusion criteria required by local law

5. STUDY OUTLINE

5.1. STUDY FLOW CHART



5.2. INVESTIGATION PLAN

1. Screening Procedures

Participants will be screened when they attend their first urology consultation for a radical prostatectomy following the diagnosis of prostate cancer. The participant will be intermediate and high-risk cancer patients with a >=10% probability on LN where LND would currently be performed as part of the treatment protocol (guided by the updated Briganti nomogram) [34]. All patients will have a clinical work-up in line with the current international guidelines for the treatment of high-risk prostate cancer including a pelvic MRI and routine bone scan. They will be assessed against the inclusion and exclusion criteria. Should they be deemed eligible for the trial, they will be provided with details of the trial and will be asked to participate by providing written consent.

2. Imaging

Participants who have consented to participate will then be referred to the St Vincent's Nuclear Medicine Department will have the following imaging services prior to surgery:

- 68Ga-PSMA PET scan
- Diagnostic CT (part of the 68Ga-PSMA PET scan)

In the event that a participant had a clinically indicated 68Ga-PSMA PET scan within 3 weeks at St Vincent's Hospital, the participant will not be required to have another scan. If the 68Ga-PSMA PET scan was performed elsewhere, the participant will be required to have one performed at St Vincent's Hospital for consistent reporting. The 68Ga-PSMA PET scan will be double assessed by two experienced readers at St Vincent's Hospital, Sydney and the Wesley Hospital.

At the return visit and prior to the surgery, Combidex, the imaging agent, will be administered to the patient at St Vincent's Hospital, Sydney. Combidex will be administed by a trained member of staff. Combidex will be administered by slow infusion over approximately 30 minutes following dilution in 100mls of normal saline. This method of administration minimises adverse events and allows the management of adverse should they occur by the halting the infusion. The protocol for Combidex Nano MRL infusion is found appendix C.

Following the infusion, the participants will be observed for one hour before being allowed to return home. The risk management of the infusion are described in item 5.3. In the next 2 to 3 days, the participants will be referred to have a MRI at Medscan Bangaroo. All Nano MRL scans will be double assessed by two experienced readers (one at I-Med Radiology and the other at The Wesley Hospital) and then by an experienced reader of Radboud University Nijmegen, the Netherlands.

The assessment of Nano MRL and 68Ga-PSMA PET scans represents a crucial endpoint in this study. Consequently, before the start of the trial we will define imaging standards and provide an intensive training of image interpretation. In order to ensure a homogeneous high quality of image assessment according to the requirements of MAGNIFI Trial, extensive effort will be made for training, including a 10 days training at the Radboud University Nijmegen the Netherlands. To assure the quality of this training, each investigator judging the images in the MAGNIFI Trial will have to pass a certification.

3. Radical prostatectomy with pelvic lymph node dissection

Patients will undergo radical prostatectomy and extended pelvic lymph node dissection, as clinically indicated within 7-10 days following Combidex nano-MRL imaging, with all dissected lymph node packets being dissected and labelled. Suspicious lymph nodes detected on nano-MRL or PSMA will be specifically targeted for resection during lymph node dissection.

After all imaging is complete, Patients will undergo radical prostatectomy and extended pelvic lymph node dissection, as clinically indicated, with all dissected lymph node packets being dissected and labelled. Approximately 6 packets of lymph nodes are expected per patients, each hemipelvis providing node packets from the external iliac vein, obturator fossa and internal iliac vessels as described by Bader et al. Specifically, all fibro-fatty tissue along the external iliac vein along the pelvic sidewall, caudal to the femoral canal and proximally to the bifurcation of the common iliac artery will be dissected and removed to be labelled as 'external iliac vein nodal packet'. All fibro-fatty tissue within the obturator fossa along the obturator muscle, skeletonising the obturator nerve and vessels will be labelled 'obturator fossa'. Finally the internal iliac artery and internal iliac vein will be skeletonised, all tissue removed from this dissection will be labelled 'internal iliac vessels'. Suspicious lymph nodes detected on nano-MRL or PSMA will be additionally targeted for resection during lymph node dissection, particularly presacral and mesorectal nodes. Specifically identified nodes in the mesorectal plane may be localised with percutaneous hookwire prior to dissection. At the discretion of the operating surgeons, and in consultation, suspicious nodes outside this template may also be resected if doing so does not place the patient at significant additional risk. Each nodal packet removed will also be qualified as either 'complete' or 'incomplete' for imaging vs histology concordance analysis. The reason for 'incomplete' dissection will be recorded.

An accredited robotic urological surgeon will perform the pelvic lymph node dissection. All participating urologists will undergo external video analysis and independent validation prior to commencement of the MAGNIFI trial.

4. Histopathology

After dissection, the specimens will be sent to pathology for histopathological examination. The lymph nodes will be reviews at 2mm dissections. The result of histological examination of the lymph nodes (gold standard) will be compared with the result of 68Ga-PSMA PET scan and Nano MRL. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for Nano MRL and Ga68-PSMA PET scan in pelvic lymph nodes with corresponding CT size measurement in comparison with histopathology will be assessed for detection of lymph node metastases.

Analysis will include assessing sensitivity, specificity, diagnostic accuracy, positive and negative predictive values for different levels of Nano MRL and PSMA PET avidity in pelvic lymph nodes with corresponding CT size measurement in comparison with histopathology.

5. Re-imaging

In participants where the 68Ga-PSMA PET and/or Nano MRL detected metastases in the lymph nodes but these were not seen in the histopathology (i.e., a false positive result), the participant will undergo a repeat PSA test, a 68Ga PSMA PET scan and a Nano MRL 6 weeks after the radical prostatectomy to confirm the accuracy of the original results and to ensure that no other sites of metastases missed. As noted in section 5.3, correspondence from Professor Jelle Barentsz (Appendix D) and from clinical evidence to date, there have been no safety issues as a consequence of having a repeat 68Ga PSMA PET scan and/or a Nano MRL. All precautionary safety measures will be performed.

6. Follow up visits

As part of the participant's clinical care, follow up consultations with the treating urologist are planned for 6 weeks, 2 months, 6 months, 12 months and 24 months post surgery.

7. Quality of Life (QOL) survey

To determine the outcome of treatment, the participant will be asked to complete the self-reporting Expanded Prostate Cancer Index Composite (EPIC) survey. The EPIC survey has been extensively used to report on the physical, emotional and psychological outcomes of the prostate cancer patients. The participant will ask to complete the survey at baseline (prior to surgery), at 6 weeks, 3 months, 6 months, 1 year and then yearly for a minimum of 5 years.

5.3. STUDY PROCEDURE RISKS

Risks of 68Ga-PSMA PET

The PET tracer, 68Ga-PSMA, is a PSMA ligand radiolabelled with 68Ga to enable its use for PET imaging. Several preclinical and clinical studies have shown the safety of 68Ga-PSMA. The critical dose-organs are the kidneys (0.16 mSv/MBq). Based on the FDA, a single-organ dose of 0.05 Sv is allowed. This corresponds to an activity of 289.9 – 414 MBq (7 – 11 mCi) of 68Ga-PSMA for a 70-100 kg male patient with a prostate cancer. Accordingly, the effective dose expected to the whole body is 0.01 Sv, which is below the 0.03 Sv upper limit recommended by the FDA (DeGrado et al., JNM 43,1:92-96, 2002). No adverse effects due to intravenous administration of 68Ga-PSMA for imaging have been reported in the published literature. Overall, 68Ga-PSMA PET SCAN may be used in clinical research with no risk to patients with prostate cancer.

Risks of ferumoxtran-10, Combidex® Nano MRL:

A single death during infusion of Combidex has been reported in the United States. This was associated with rapid infusion of the agent without a rate-limiting IV micro-filter in a patient with pre-existing cardiac morbidity. There is a known risk of hypersensitivity, anaphylaxis and cardiac compromise associated with the IV infusion of iron or dextran products. Manufacturer recommendations stipulate that Combidex must be administered by a slow IV-infusion through a micro-filter over at least 30 minutes. To date over 200 patients have undergone Combidex scanning at Radboud UMC, with only 2 patients experiencing any issues – one patient experienced dizziness/light-headedness which was relieved by stopping the infusion for several minutes. The other patient developed a mild cellulitis at the injection site. Currently a larger study in Russia is underway recruiting over 400 patients. Many of these have already undergone Combidex scanning, adding to the safety data using the prescribed infusion protocol. During this trial patient safety will be ensured during infusion through the following steps:

Medical investigators, the radiologists and a radiology technician will travel to Nijmegen to personally learn the safe injection technique of Combidex from Prof Barentsz, as well as the reading of the Nano MRL. They will also convey this information to other members who have responsibility for reading the Nano MRL as well as its administration at St Vincent's Hospital.

This will be done at the The Kinghorn Cancer Centre (a facility of the St Vincent's Hospital) with a full anaphylaxis and resuscitation kit at the bedside, as well as an anaesthetist who is present in the hospital being on standby for emergencies. The intensive care staff will also be advised of the trial and will be notified in advance each day that patients are having an infusion, with a team member on standby by phone in the case of emergency. These extra-ordinary precautions will hopefully ensure that any adverse event during infusion is rapidly dealt with and controlled with minimal risk to patients. Should adverse reactions be noted at anytime throughout the procedure, the infusion will be stopped immediately and the St Vincent's Hospital IV Contrast Allergy Protocol will be referred to.

Upon the completion of Combidex infusion, each patient will be required to remain at St. Vincent's Hospital for at least one hour.

5.4. Recruitment and Screening

Participants have been referred to an urologist for a radical prostatectomy and lymph node dissection following a diagnosis of prostate cancer. The participant will be intermediate and high-risk cancer patients with a >=10% probability on LN where LND would currently be performed as part of the treatment protocol (guided by the updated Briganti nomogram) [34].

The participant will provide the following information as part of the referral and for assessment to participate:

- 99mTc bone scan and MRI scan of abdomen and pelvis
- Documentation of demographic variables
- Pre-prostatectomy PSA, clinical stage, grade
- Use of hormones or other therapies prior to prostatectomy

The urologist will then assess the participant for enrolment into the trial based on the inclusion and exclusion criteria. Should the participant meets the inclusion criteria and none of the exclusion criteria, the participant will be referred to the St Vincent's Nuclear Medicine Department for recruitment into the trial.

5.5. Informed Consent Process

The St Vincent's Prostate Cancer Centre will provide details of the trial and will provide the participant with the Participant Information Statement and Consent Form. If the participant wishes to participate, written consent will be requested from the participant by a member of the research team

5.6. Enrolment Procedure

The potential participant will be identified by the urologist for prostate cancer surgery. The urologist will assess the potential participant using the inclusion and exclusion selection criteria. If the participant is eligible, consent will be sought. Following participant consent, a unique study will be provided to the participant in place of any identifiable information. An initial assessment form (Form A) will be completed to collect demographic and clinical information.

6. SAFETY

6.1. Adverse Event Reporting

An adverse event to either 68Ga-PSMA PET Scan and/or Nano MRL will be considered as any unfavourable and unintended sign, symptom, or disease temporally associated with their use, whether or not they are directly related to the 68Ga-PSMA PET Scan and/or Nano MRL. Should an adverse event occur, it will be reported to the trial investigators, as well as documented in the participant's medical records.

6.2. Serious Adverse Event Reporting

A serious adverse event (SAE) is defined as:
For medicines, also referred to as serious adverse drug reaction, any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event or reaction.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

In the result of a serious adverse event, it will be reported to the St Vincent's HREC, documented in the participant's medical record and presented to the Data Safety and Monitoring Board.

6.3. Data Safety and Monitoring Board

A data safety and monitoring board will be created to review any safety concerns arising from the trial. It will consist of investigators from St Vincent's Hospital Sydney, the St Vincent's Prostate Cancer Centre, the Wesley Hospital, Brisbane and Radboud University Nijmegan, the Netherlands and a two nominated independent observers.

6.4. Early Termination

The trial may end early if the welfare of participants is at risk. Participants will be informed in this situation.

7.STATISTICAL CONSIDERATIONS

a) Trial Size:

We will now recruit 120 patients (60 from St Vincent's Hospital, Sydney and 60 from the Wesley Hospital, Brisbane) from the originally planned 80 patients. Based on the previous calculation, that each of the 80 patients will have 6 packets (a lump of fat containing lymph nodes) on average, we will be comparing 480 packets in total. This number will give 90% power to detect a 10% or less discordance between final histology analysis and the combined imaging modalities consensus. Sample size was calculated based on agreement of combination of both images together with histology. We used 15% as the probability of positive lymph node from histology results, based on literature the probability of positive lymph node result from histology is between 11% and 17% [35].

For 95% sensitivity and 90% specificity of combination of the two images, we need to test 178 packets. To achieve this number of packets we need to recruit a maximum of 32 patients. To account for correlation between packets from each patient, we have considered high effect size of equal to 2.5 which results in the requirement of 80 patients. The new recruitment target will exceed this requirement.

Statistical calculations for the MAGNIFI trial sample size are set out below:

The data for N patients, with n packets per patient, will be tabulated as follows:

Combined Test	Histology		
	Positive	Negative	Total
Positive	A	B	A+B

Negative	C	D	C+D
Total	A+C	B+D	N×n

To take account of clustering, a variance inflation factor VIF is calculated as follows:

$$VIF = 1 + (n-1)\rho$$

where n is the number of packets per patient (6) and ρ is the intra-class correlation, a measure of clustering within patients (assumed to be a maximum of 0.3). This yields a VIF of 2.5.

The formula for the sample size for a two sided McNemar test, taking into account the VIF, is then (based on reversing equation (5) of Gönen, 2004):

$$N = \frac{(z_{1-\alpha/2}\phi + z_{1-\beta}\sqrt{\phi^2 - 0.25\delta^2(\phi+3)})^2}{n\phi\delta^2/(1+(n\phi-1)\rho)}$$

where:

z is a percentile from the standard normal distribution

α is the level of significance (two-sided test, α = 0.05)

1-β is the power (assumed to be 0.90)

φ is the total proportion of discordant pairs: (B+C)/ (N×n) in above table

δ is the difference in the proportions of the two types of discordant pairs: (B-C)/ (N×n)

n = number of observations per patient (6)

For the calculations, it was additionally assumed that the proportion of positive packets was 0.15, φ = 0.10, and δ = 0.04. This assumes the following proportions:

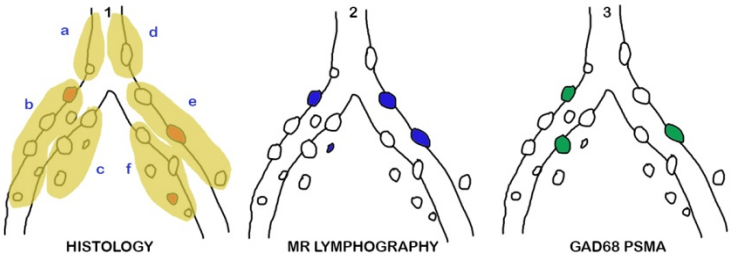
Combined Test	Histology		
	Positive	Negative	Total
Positive	0.12	0.07	0.19
Negative	0.03	0.78	0.81
Total	0.15	0.85	N×n = 480

Gonen M. Sample size and power for McNemar's test with clustered data. *Statistics in Medicine* 2004, 23: 2283-2294

b) Statistical Analysis:

We will compare 'packet concordance rate' between histology and MR Lymphography using a MRA arterial map (that can be acquired at the MRL) to locate the position of the lymph node, the 68Ga PSMA PET SCAN plus a combined evaluation, and histology. As indicated in the diagram below, lymph nodes are removed by one lump of fat (region-packet) at a time (refer to region-packets 'a' to 'f' in figure below). The two tests (MR lymphography and 68Ga PSMA PET) will indicate (with error)

whether each node is positive or not, and thus whether each region-packet is positive (at least one node positive) or not (no nodes positive). The combined evaluation is a consensus of the two tests: region-packets are positive if one or both tests indicate positive and negative only if both tests indicate the region-packet is negative. Using histology, we can assess the accuracy of the two tests (plus combined evaluation) in terms of false positives.



	Histology	MR Lymphography	Ga68 PSMA	Imaging Consensus
a	Negative	Negative	Negative	Negative
b	Positive	Positive	Positive	Positive
c	Negative	Positive	Positive	Positive
d	Negative	Negative	Negative	Negative
e	Positive	Positive	Positive	Positive
f	Positive	Negative	Negative	Negative

We will calculate the CONCORDANCE rate for positive nodes in each packet with their corresponding region on imaging, both against each individual imaging modality and against a summed score from both imaging techniques. Sensitivity, specificity, negative predictive values (NPVs), and positive predictive values (PPVs) will be reported [31, 32]. The maximum likelihood estimates (MLEs) of PPV and NPV will be calculated from the MLEs of the sensitivity, specificity, and prevalence rate. Hierarchical modelling will be used to test for concordance between matched results from each packet.

Secondary outcome of interest is quality of life and the complications. As part of initial longitudinal analyses quality of life (as measured using EORTC-QLQ-C30) will be evaluated using one-way ANOVA. To examine differences in quality of life scores between the two groups (standard eLND versus super-eLND), baseline characteristics will be compared between groups to assess whether the groups are balanced using Chi-square tests and Fisher's exact tests. The additional analysis involves comparing the change in quality of life scores (worsened, stable or improved quality of life) from baseline to 2 and 6 months between the groups using Chi-square tests and Fisher's exact tests. Similar method will be used evaluating the differences in the complication score.

c) Interim Analysis:

An analysis of the data will be performed after every 10 patients have completed imaging and pelvic lymph node dissection. This will allow the trial statistician and data monitoring committee to identify any problems or discrepancies with data collection and recording, in addition to identifying any possible technical issues that might jeopardise

8. CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY DOCUMENTS

All documents and electronic files will be kept in a secure area with access given to authorised personnel only. Data used for reporting purposes will be de-identified and only group data will be

used in any publications arising from this trial. Documents and electronic files will be kept indefinitely following the completion of the trial.

9. FUNDING

The Garvan Institute of Medical Research has received a grant from the Paul Ramsay Foundation for the conduct of the study on the St Vincent's Hospital Research Campus (St Vincent's Hospital Sydney, the St Vincent's Prostate Cancer Centre and the Garvan Institute of Medical Research).

The Wesley Research Institute will fund the conduct of the trial and the recruitment of participants at the Wesley Hospital, Brisbane.

10. OTHER STUDY DOCUMENTS

Appendix A: Magnifi Trial: Eligibility Check List Version 1.1 1st Oct 2015

Appendix B: St Vincent's Hospital HREC Serious Adverse Event Reporting Form June 2015

Appendix C: Protocol Infusion "Combidex" Nano MRL Version 1.0 29th Sept 2015

Appendix D: Repeat Combidex (ferumaxtran-10) correspondence from Prof Jelle Barentsz, 15th March 2018.

ST VINCENT'S HOSPITAL SYDNEY
A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

Office use only	Initial:_____
PT ID:_____	Date:_____

ELIGIBILITY CHECK LIST
MAGNIFI TRIAL

This form is to assess the eligibility of the participant for the Magnifi Trial

Patient Details (or Label)		
Surname:	Given Name:	MRN:
DOB:	Address:	
Telephone:		

INCLUSION CRITERIA		**EXCLUSION CRITERIA**	
Male, aged 18 years or over	☐Yes ☐No	Past history any other type of cancer (except skin cancer).	☐Yes ☐No
Confirmed adenocarcinoma of prostate and at least clinical stage T3A and/or Gleason sum >= 4+3=7, or preoperative PSA ≥ 15 ng/ml and planned radical prostatectomy	☐Yes ☐No	Previous treatment for prostate cancer (surgery, radiotherapy, chemotherapy, hormone androgen deprivation therapy)	☐Yes ☐No
Suspected lymph node involvement pre- radical prostatectomy based on Briganti nomogram >= 10%.	☐Yes ☐No	Proven bony metastatic disease, visceral metastases or lymph node metastases above the level of the aortic bifurcation	☐Yes ☐No
Suitable for radical prostatectomy and pelvic lymph node dissection, as per institutional guidelines and not yet treated pre-prostatectomy	☐Yes ☐No	Previous surgery in pelvis (e.g. bilateral hip replacement) that limit the extent of pelvic lymph node dissection	☐Yes ☐No
Subject is able to understand and willing to sign the participant information statement and consent form	☐Yes ☐No	Patients who refuse radical prostatectomy or pelvic lymph node dissection	☐Yes ☐No
Subject is expected to remain available for 24 months of clinic visits	☐Yes ☐No	Patients who refuse to join the trial or are unable to consent	☐Yes ☐No
		Patients not being considered for further therapy	☐Yes ☐No
		Patient has absolute contra-indications to undergoing MRI scanning	☐Yes ☐No
		Patients who cannot lie still for at least 60 - 75 minutes or comply with imaging	☐Yes ☐No

Office use only	Initial:_____
PT ID:_____	Date:_____

INCLUSION CRITERIA		**EXCLUSION CRITERIA**	
		Subject has medical conditions that would limit study participation (per physician discretion)	☐Yes ☐No
		Subject is enrolled in one or more concurrent studies that would confound the study results of this study as determined by the study investigators	☐Yes ☐No
		Subject has a limited life expectancy that would not allow completion of the 24 month visits	☐Yes ☐No

I have assessed _____ for participation in the Magnifi Trial.

Tick one box only

☐ He has met ALL the inclusion criteria (responses must all be "Yes") and none of the exclusion criteria (responses must all be "No"). He is eligible to participate in the Magnifi Trial.

☐ He has NOT met ALL the inclusion criteria (responses must all be "Yes"). He is ineligible to participate in the Magnifi Trial

Signature of Assessor: _____

Name of Assessor: _____

Date of Assessment: _____

St Vincent's Hospital Sydney Human Research Ethics Committee (HREC)

SERIOUS ADVERSE EVENT (SAE) and/or
SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) REPORT

Instructions

1. Complete this form electronically before printing (hand written forms will not be accepted)
2. Please enter only one event per form
3. SAEs and SUSARs must be reported to the HREC:
   a) For investigator initiated studies, within **24 hours** of the researchers becoming aware of the event
   b) For all other studies, within **72 hours** of the researchers becoming aware of the event.

Adverse event reporting for clinical trials involving therapeutic products, must meet the requirements of the National Health and Medical Research Council, Australian Health Ethics Committee (AHEC) Position Statement "*Monitoring and reporting of safety for clinical trials involving therapeutic products*" (May 2009), which can be found at:
www.nhmrc.gov.au/guidelines-publications/e112

Initial electronic submission will meet reporting timelines however this must be followed by the submission of a full report in hard copy.

4. For multi-centre studies, the Principal Investigator is responsible for reporting SAEs and SUSARs at their site directly to the Lead HREC. A copy of this report, once acknowledged by the Lead HREC, should be provided to the site Research Governance Officer and the Coordinating Investigator.
5. All other safety reports, such as line listings, should be submitted directly to the Lead HREC by the Coordinating Investigator
6. Please submit both **a hard copy** and an **electronic copy** of the completed report:

Electronic copy to be sent to: SVHS.Research@svha.org.au The hard copy **must** have an original signature from the site Principal Investigator.	**Original to be sent to:** Research Office Level 6, de Lacy Building St Vincent's Hospital 390 Victoria St Darlinghurst NSW 2010
A copy of the signed form should be retained by the Investigator	

Research Project Details	
SVH File Number (xx/xxx)	
HREC Reference Number (eg. HREC/xx/SVH/xxx)	
Full Study Title	
Coordinating Principal Investigator (for single centre studies, this is synonymous with Principal Investigator)	
Principal Investigator at site where participant is enrolled (If multi-site study)	
SAE/SUSAR* Event Details *Note SUSARS submitted on this form must have occurred at a site under SVH HREC approval	
Participant study identification number/code	
SITE NAME where participant was consented	
Date event occurred	

Date event resolved	**OR** **Event ongoing** ☐
Type of report **<u>The submission of supporting documentation is required for all INITIAL events:</u>** **<u>ie:</u>** ***<u>For Investigator initiated studies,</u>*** *submit a copy of source documentation ie. relevant (de-identified) section from relevant medical records* ***<u>For Commercially sponsored or collaborative group studies,</u>*** *submit a copy of the sponsor's completed adverse event report form*	**Initial** ☐ **Follow-up** ☐ **Final** ☐ If this is an initial event, please ensure you submitted the appropriate supporting documentation. Is this information provided with this report: **Yes** ☐ **No** ☐ If no, please note that hardcopy SAE/SUSAR forms received without supporting documentation will be returned. If this is a follow-up and/or final report, please provide the date of initial report: Initial report date
Description of Event **(Please provide a brief clinical description)**	
Investigator's opinion of relationship of the adverse event to the study drug, device, intervention, procedure.	Unrelated ☐ (clearly not related) Possibly ☐ (may be related) Probably ☐ (most likely related) Definitely ☐ (clearly related)
Has this event been reported to the sponsor?	Yes ☐ No ☐ N/A ☐ If NO, please provide detail why not:
Does the Investigator believe that this event may affect the ongoing ethical conduct of the study or the safety of the participants or their willingness to continue participation?	Yes ☐ No ☐ Please comment:
Does the event necessitate amendments to: **The Study Protocol** **The Participant Information Sheet and Consent Form** **Other**	 Yes ☐ No ☐ Yes ☐ No ☐ N/A ☐ Yes ☐ No ☐ If YES, please confirm when these amendments will be submitted for HREC review:
Is the study continuing at all sites?	Yes ☐ No ☐ If NO, please list the active sites:

INVESTIGATOR DECLARATION

Signature of Principal Investigator_____
Date:

Contact details for enquiries and electronic acknowledgement of this report:
Name:
Phone:
Email:

Cc: Coordinating Principal Investigator (if applicable)
Cc: Local Research Governance Officer

St Vincent's Hospital Research Office use only

Date Reviewed by HREC Executive:

Action:

Name:

Signature:

Designation:

St Vincent's Hospital Research Office use only

Date Reviewed by SVH Research Governance Officer: _____ **or N/A** ☐

Action:

Name:

Signature:

Designation:

Appendix C: Protocol Infusion "Combidex" Nano MRL Version 1.0 29th Sept 2015

Protocol Infusion "Combidex" Nano MRL Version 1.0 29th Sept 2015

To perform a MRI NANO scan, infusion of NANO contrast fluid (Combidex) is required (Iron-Dextran nanoparticles 20mg/ml). The contrast fluid should be administered 24 to 36 hours before the MRI scan, by intravenous infusion that will take at least 30 minutes for administration. In this protocol we describe how the NANO contrast fluid should be prepared and administered.

Equipment Required:

Material	**Quantity**
Drawing up equipment (10ml syringe, 18g needles x 2)	1x
Sodium Chloride 0.9%	2x 100ml
Cannulation equipment	1x
Intravenous Giving Set	1x
Intravenous Infusion Pomp	1x
Iron-Dextran nanoparticles 200mg Iron = 10ml (20mg/ml) (NANO contrast fluid "Combidex")	Based on total body weight
Filter 0.22 µm	1x
Alcohol Swabs	1x

Dose table. The dose of Iron-Dextran Nanoparticles 20mg/ml is based on body weight = 0.13 ml per kg.

Kg	**Dose**	**Kg**	**Dose**	**Kg**	**Dose**	**Kg**	**Dose**
40	5,2	**63**	8,2	**86**	11,2	**109**	14,2
41	5,3	**64**	8,3	**87**	11,3	**110**	14,3
42	5,5	**65**	8,5	**88**	11,4	**111**	14,4
43	5,6	**66**	8,6	**89**	11,6	**112**	14,6
44	5,7	**67**	8,7	**90**	11,7	**113**	14,7
45	5,9	**68**	8,8	**91**	11,8	**114**	14,8
46	6,0	**69**	9,0	**92**	12,0	**115**	15,0
47	6,1	**70**	9,1	**93**	12,1	**116**	15,1
48	6,2	**71**	9,2	**94**	12,2	**117**	15,2
49	6,4	**72**	9,4	**95**	12,4	**118**	15,3
50	6,5	**73**	9,5	**96**	12,5	**119**	15,5
51	6,6	**74**	9,6	**97**	12,6	**120**	15,6
52	6,8	**75**	9,8	**98**	12,7	**121**	15,7
53	6,9	**76**	9,9	**99**	12,9	**122**	15,9
54	7,0	**77**	10,0	**100**	13,0	**123**	16,0
55	7,2	**78**	10,1	**101**	13,1	**124**	16,1
56	7,3	**79**	10,3	**102**	13,3	**125**	16,3
57	7,4	**80**	10,4	**103**	13,4	**126**	16,4
58	7,5	**81**	10,5	**104**	13,5	**127**	16,5
59	7,7	**82**	10,7	**105**	13,7	**128**	16,6
60	7,8	**83**	10,8	**106**	13,8	**129**	16,8
61	7,9	**84**	10,9	**107**	13,9	**130**	16,9
62	8,1	**85**	11,1	**108**	14,0	**131**	17,0

Preparation:

1. Ensure there is a current valid prescription.
2. Make an infusion system and 100ml 0.9% Sodium Chloride.
3. Prepare the correct dose of Iron-Dextran Nanoparticles "(NANO contrast fluid "Combidex") based on the dose table in this protocol and dissolve in 100ml 0.9% Sodium Chloride.
4. Review the dose and fluid calculations with a second practitioner.
5. Make sure the name and date of birth is specified on the NANO contrast fluid (Combidex).

Administration:

1. Put in the 18G intravenous cannula
2. Connect the 100ml 0.9% Sodium Chloride and start slow infusion
3. Call Dr Bao Ho (radiologist) to administer the NANO contrast fluid (Combidex)
4. The radiologist will change the 100ml 0.9% Sodium Chloride for the NANO contrast fluid (Combidex) and will specify date and time start infusion
5. The NANO contrast fluid (Combidex) will be administered in at least 30 minutes
6. At the time the NANO contrast fluid (Combidex) is completed, infusion will be changed to 0.9% Sodium Chloride will a slow rate.
7. Remove the intravenous cannula
8. The patient must remain at the health centre for at least 60 minutes after the end of infusion

Side effects:

Like every medical product, the NANO contrast fluid could have side effects. Side effects include headache, dizziness, light-headedness, nausea, an itchy skin. Normally, these side effects will resolve after a short period.

Allergic reaction:

Anaphylaxis is a severe, potentially fatal allergic reaction. It is characteristically unexpected and rapid in onset. If a patient has an anaphylaxis, the anaphylaxis protocol of St Vincent's Hospital should be followed: appendix IV Contrast Allergy Protocol.

Should adverse reactions be noted at any time throughout the infusion:

1. **Stop the infusion immediately**
2. **Contact Dr Bao Ho (radiologist)**
3. **Refer to anaphylaxis protocol of St Vincent's Hospital IV Contrast Allergy Protocol.**

IV CONTRAST ALLERGY PROTOCOL

5. Treatment of contrast reactions

Mild

Nausea / Vomiting
Supportive measures (antiemetics if prolonged vomiting)

Urticaria (mild)
Supportive measures

Urticaria (protracted)
Antihistamine (oral or intramuscular depending on severity)

Moderate

Marked Urticaria

- Antihistamines
- Consider use of Adrenaline 1:1000
  - In adults 0.1-0.25ml (0.1-0.25mg) intramuscularly – repeat as necessary
  - In children 0.01 mg/kg intramuscularly up to 0.3mg maximum dose

Bronchospasm

1. Oxygen by mask (6-10 l/min)
2. β-2-agonist (e.g. Salbutomol or Terbutaline) metered dose inhaler (2-3 deep inhalations).
   In more severe cases, give Salbutamol or Terbutaline by nebuliser.
3. Consider Adrenaline
   Normal blood pressure
   In adults: 1:1,000, 0.1-0.25 ml (0.1-0.25 mg) intramuscularly
   [use smaller dose in patients with coronary artery disease or elderly patients]
   In paediatric patients: 0.01 mg/kg up to 0.3 mg max intramuscularly
   Decreased blood pressure
   In adults: 1:1,000, 0.5 ml (0.5 mg) intramuscularly
   In paediatric patients: 0.01 mg/kg intramuscularly

Hypotension

- Isolated hypotension
  1. Elevate patient's legs
  2. Oxygen by mask (6-10 l/min)
  3. Intravenous fluid: rapidly, normal saline or lactated Ringer's solution
  4. If unresponsive: adrenaline: 1:1,000 , 0.5 ml (0.5 mg) intramuscularly, repeat as needed

- Vaso-vagal reaction (hypotension and bradycardia)
  1. Elevate patient's legs
  2. Oxygen by mask (6-10 l/min)
  3. Atropine
     - In adults 0.6-1.0 mg intravenously, repeat if necessary after 3-5 min, to 3 mg total (0.04 mg/kg).

- In paediatric patients give 0.02 mg/kg intravenously (max. 0.6 mg per dose) repeat if necessary to 2 mg total.

4. Intravenous fluids: rapid infusion of normal saline or Hartmann's solution 20 ml/kg, repeat as necessary.

Severe

Generalized anaphylactoid reaction

1. Stop contrast injection
2. Call for resuscitation team
3. Suction and maintain airway as needed
4. Oxygen by mask (6 - 10 l/min)
5. Intramuscular adrenaline, intramuscularly into the lateral thigh

In adults (and in children >25 kgs), Adrenaline 1:1,000

< 50 kg	give 0.25 - 0.5 mL
> 50 kg	give 0.5 mL

In children, Adrenaline 1:1,000

1 year	10 kg	give 0.1 mL
3 years	15 kg	give 0.15 mL
5 years	20 kg	give 0.2 mL
8 years	25 kg	give 0.25 mL

- If necessary, repeat intramuscular dose every 5 minutes.
- Large doses of adrenaline may be needed, up to a maximum of 5 mL (5 mg).
- If the patient remains shocked after two intramuscular doses, consider an adrenaline infusion to restore blood pressure. (See notes 3,4).

6. Intravenous fluids (e.g. normal saline or Hartmann's solution 20mL/kg). Continue as necessary
7. Ventilate patient if severe respiratory and circulatory collapse
8. Additional measures:

Bronchodilators	For bronchospasm, give salbutamol or terbutaline by nebuliser, or aerosol with spacer device.
Corticosteroids	Hydrocortisone 2-6mg/kg or Dexamethasone 0.1-0.4 mg/kg intravenously
Nebulised adrenaline	May be tried for laryngeal oedema (5ml of 1:1,000)

9. Supportive measures

Observe vital signs frequently, and, if possible, monitor ECG and pulse oximetry.

Arrange for transfer to hospital if reaction occurs in an outpatient facility.

Keep under observation for at least 4-6 hours after complete resolution of signs and symptoms, as biphasic reactions may occur.

Notes:

1. Adrenaline is life-saving and must be used promptly. Withholding adrenaline due to misplaced concerns of possible adverse effects can result in deterioration and death of the patient.

2. Adrenaline 1:1000 contains 1000 microgram in 1 mL (1 mg/mL). The volumes of adrenaline recommended for adults and children approximate to 5 to 10 microgram/kg. Children's weights are approximate for age.

3. If critical care facilities are not immediately available, give the following adrenaline infusion:

   - Mix 1 mg adrenaline (1 ampoule) in 1000 mL of normal saline
   - Start infusion at 5 mL/kg/hour (approx. 0.1 microgram/kg/minute)
   - Titrate rate up or down according to response.

4. Some cases are resistant to adrenaline, especially if the patient is taking beta blocking drugs. If adequate doses of adrenaline are not improving the situation, give glucagon 1 to 2 mg intravenously over 5 minutes.

5. Drug-assisted intubation for impending airway obstruction is a very high-risk procedure and should only be attempted by an expert.

6. Corticosteroids may modify the overall duration of a reaction and may prevent relapse. However, onset of action will be delayed. Never use these to the exclusion of adrenaline.

Appendix D: Repeat Combidex (ferumoxtran-10) correspondence from Prof Jelle Barentsz, 15th March 2018

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To whom it may concern,

Date	Our reference	Page
March 15, 2018		1 of 1
Your reference	Contact	

L.S.,

With this letter I want to make the statement,
that I have given many multiple injections with ferumoxtran-10 to the same patients.
Thus far this has caused no problems whatsoever.
Thus, if needed, the patients can have without additional risk a second or even more injections.

Kind regards,

Jelle Barentsz,

Professor of Radiology,
Chairman Prostate MR-Reference/Expertise Center

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