NCRI
National
Cancer
Research
Institute

NCRI Prostate Group

Annual Report 2018-19

Partners in cancer research

NCRI Prostate Group
Annual Report 2018-19

1. Top 3 achievements in the reporting year

Achievement 1 STAMPEDE has reported on the local radiotherapy arm which is likely to impact on the treatment of men with low volume metastatic prostate cancer
Achievement 2 The largest screening trial internationally, CaP, reported that a one-off PSA test did not improve the cancer specific or overall survival, compared to men within normal practice. This reinforces the controversy over screening for prostate cancer and highlights ongoing need for study of new risk based assessment of community based testing for prostate cancer
Achievement 3 A new screening study, PREDICT, is now funded by Prostate Cancer UK, and due to start later this year

2. Structure of the Group

The Prostate CSG works through two subgroups, the Localised Disease Subgroup (chaired by Rakesh Heer (Consultant Urologist) and the Advanced Subgroup (chaired by Rob Jones, Glasgow). A new chair for the Advanced Subgroup has been now been appointed through a competitive open application process and we are delighted that Professor Gert Attard, London will take on this role. We underwent our Quinquennial Review in 2018 and will be taking note of the advice given. Our formal CSG strategy day occurred on 26th March 2019 and a document is currently in draft for wider CSG input before being finalised (anticipated for final draft end June 2019). The subgroups remain tremendously active and are continuing to encourage an open submission process with a nurturing yet robust process for new proposals to take to funders.

3. Prostate Group & Subgroup strategies

Prostate Group

Minimise the harms from the investigation and treatment of localised prostate cancer

A. Our reporting year was much spent on a number of key studies being set up that are due to start in 2019 but will mature over a few years:

1. Personalised screening

- PREDICT [PCUK; £4.5M] (CI: Ahmed/Gabe): Pilot provisionally funded to test recruitment strategies (pending contractual sign-off). Evaluation of a novel risk calculator incorporating clinical and fluidic biomarkers in screening for prostate cancer (N=20,000).
- IP1-PROSTAGRAM (Wellcome; £0.5M) (CI: Ahmed): Pilot and feasibility of PSA, fast MRI and ultrasound screening for prostate cancer in the community with biopsy in secondary care. N=410
- Re-IMAGINE WS2 (MRC/CRUK) (CI: Moore). Pilot and feasibility of PSA, fast MRI screening for prostate cancer in the community followed by multi-parametric MRI +/- biopsy in secondary care. N=410

2. Stratified diagnosis (re-IMAGINE [MRC/CRUK]) (CI: Emberton/Ahmed/van Hemelreihjk/Moore/Attard): £5.5M. Deeply phenotyping a cohort of N=1000-1500 men who present with an elevated PSA who then subsequently undergo a MRI and biopsy.
3. Minimally invasive therapies to reduce treatment-related harms which were worked up and supported by CSG from inception to funding.

- PART [NIHR-HTA] (CI: Hamdy). Full grant awarded pending further internal pilot. RCT of focal photodynamic therapy versus radical therapy
- CHRONOS [PCUK] (CI: Ahmed). Pilot funded. Preference based randomisation similar to PACE.

  CHRONOS-A: RCT of focal HIFU/cryotherapy versus radical therapy.

  CHRONOS-B: Multi-arm multistage design testing neoadjuvant strategies prior to focal therapy
- Neurosafe-PROOF (NIHR-RfPb and Jon Moulton Foundation] (CI: Shaw): Fresh frozen section directed nerve-preservation radical prostatectomy. CSG supported from inception to funding. Highly successful pilot accruing ahead of time. The full RCT has now been funded.

B. New studies

1. Diagnostic

- IP6-PACIFIC (Leads: Ahmed/Gabe): Evaluating the role of fast MRI compared to multi-parametric MRI and the role of image-fusion targeted biopsy compared to cognitive targeted biopsies in detecting clinically significant prostate cancer. Work up stage.

2. Treatment of localised prostate

- TIGERS (Lead: Dasgupta). MRI 3-D model directed radical prostatectomy compared to standard of care RP in the treatment of men with localised prostate cancer. Discussed and supported by CSG and now at funding application stage (to NIHR EME following discussions with NIHR).

Maximise the quality of life and overall survival of patients with advanced prostate cancer

The STAMPEDE RCT has recently shown that men with low volume metastatic prostate cancer benefit from local radiotherapy. There has been some debate around the sub-group effect but it seems there is wide buy-in from the oncology community.

Other studies are being conducted or starting in this disease space:

- STAMPEDE: the new arm(s) to STAMPEDE were discussed extensively at CSG in 2018 at main group and at advanced subgroup. CRUK funding application pending at time of writing.
- CORE RCT (CRUK) (CI:Hall/Khoo) of stereotactic radiotherapy for extracranial metastases in prostate cancer, breast and non-small cell lung cancer. CSG discussed the extension to phase III at advanced subgroup. Application outcome to CRUK pending at time of writing.
- IP2-ATLANTA RCT (Wellcome £1M) (CI: Ahmed). Standard systemic therapy versus radical therapy (surgery/radiotherapy) versus ablation (cryotherapy/HIFU) for metastatic prostate cancer (fully funded Phase II with embedded pilot; Wellcome Trust). Due to start recruitment May 2019. N=960
- CTC-STOP (PCUK/Movember Centre of Excellence) To determine whether use of CTCs can direct discontinuation of chemotherapy in patients with metastatic castrate-resistance disease

Promote a clinical research culture within urology which encourages young urologists to develop an interest in clinical trials

We continue to promote this as a key component of delivering research in surgical trials which is a neglected area. Our success through PART, Neurosafe and CHRONOS as well as new studies and proposals in the pipeline (STAMPEDE new arm, TIGERS) attests to this. At the last CSG meeting it was discussed that this strategic aim should also include young oncologists, and this will be changed to reflect that discussion.

Promote international collaborations on prostate cancer trials

Discussions are continuing with CRUK Clinical Research team and the Liaison office at CRUK with EORTC about CHRONOS. A plan for when, if the pilot is successful, CHRONOS should be submitted to CRUK has been provisionally drawn up jointly with EORTC. Commercial discussions on this trial with device companies and pharma are at an early stage.

Further focused collaboration, where there is a mutual need, through our new member Professor Silke Gillessen is anticipated.

Foster links with the British Uro-oncology Group (BUG) and the British Association of Urological Surgeons (BAUS) Section of Oncology

We continue to work with these groups in a focused manner where required through individual trial proposals and ideas or when delivery is an issue. It was decided at the last CSG meeting that inviting representation of these groups to CSG meetings was not required.

Work with the Bladder & Renal and TYA & GCT (the Testis CSG has merged with the TYA CSG) CSGs to encourage clinical research in the uro-oncology community

This has been and will continue to be through the National Urological Groups Trials Meeting. A recent teleconference meeting of the relevant chairs and the secretariat has drawn up a plan for the next meeting.

Foster a harmonised approach to tissue biomarker collection for future translational studies accompanying clinical trials

There continues to be little work for the CSG in this area as biobanking is something delivered specifically in a hypothesis led manner through individual trials. At our last CSG meetings, there was a recognition that we lacked expertise in translational scientists (non-clinical and clinical) and researchers in imaging. This is something the CSG will focus on going forward through targeted recruitment.

Strengthen links with Prostate Cancer UK

We now work closely with PCUK with representation at all meetings and cross-membership with their research strategy group (Ahmed/Gillessen). Recent examples of successful funding such as PREDICT and STRATOSPHERE have attested to this. The NCRI Prostate Group Chair has recently met with their new Head of Research, David Montgomery, to keep dialogue going.

The NCRI Prostate Group Chair has also recently met with the Chair of the Prostate Cancer Research Centre (PCRC) charity who are conducting open calls now. Discussions continue as to how this charity might wish to interact with the CSG.

Advanced Disease Subgroup (Outgoing Chair, Professor Robert Jones)

- *This current section remains outstanding and will be provided as an amendment prior to the review*

Build on the success of STAMPEDE, introducing new treatment comparisons into the trial
Identify intermediate endpoints to hasten clinical development of new agents
Collaborate with the Supportive and Palliative Care CSG
Focus on translational science with an overarching focus to progress the theme of personalized medicine in advanced prostate cancer
Engage with the Experimental Cancer Medicine Centres (ECMC) network

Localised Disease Subgroup (Chair, Mr Rakesh Heer)

Evaluate strategies to reduce the over-diagnosis and over treatment burden in localised prostate cancer

Projects with a focus on novel biomarker-based detection and will be developed, including imaging and molecular (blood and tissue) markers. Over treatment will be considered with studies looking at disease risk stratification.

Recently established studies: (i) PCUK PREDICT trial (Gabe Rhian/Hash Ahmed, Imperial) – Stockholm3 index validation – aiming to reduce over-diagnosis. Pilot study. (ii) MRC PROSPER study (Gary Cook, KCL) combined imaging with positron emission tomography (PET) and magnetic resonance imaging (MRI) in a hybrid PET/MRI scanner using choline and prostate specific membrane antigen (PSMA) PET tracers to try to improve detection and grading of prostate cancer. (iii) TUF/Welcome Trust PROSTAGRAM study (Hash Ahmed, Imperial). The aim is to find an imaging technique, like mammograms for breast cancer. MRI and ultrasound will be tested to diagnosis of clinically significant prostate cancer. (iv) Swedish Cancer Society funded Prostate Cancer Active Surveillance Trigger Trial (SPCG-17; PCASTT) (Mieke Van Hemelrijck, KCL) is an RCT testing the safety of an active surveillance protocols comparing current practice with standardised triggers for initiation of curative treatment. Currently, across the UK, decisions to re-biopsy and initiate curative treatment are not guided by any set criteria and tend to be at the clinician's discretion. (v) CRUK funded new prostate screening studies PROFILE and BARCODE 1 (Ros Eeles, ICR) to identify those men at the highest genetic risk of prostate cancer to offer them prostate screening.

New studies in development/submitted: (i) PACIFIC (Hash Ahmed/Rhian Gabe, Imperial) An RCT evaluating the role of fast MRI and image-fusion for detection of clinically significant prostate cancer. Planned submission to NIHR. (ii) Supporting men with options to manage localised prostate cancer study (presented by Athene Lane of behave of The CHOICE STUDY TEAM Bristol) – health service research to understand treatment decisions and reducing

treatment regret. (iii) Implementing and evaluating a recovery package to improve the lives of men living with and beyond prostate cancer (Anne Henry, Leeds). This project is looking to implementation research framework to investigate and evaluate the implementation of Late Radiotherapy Bowel Toxicity Service and Prostate Cancer Recovery Package into Leeds Teaching Hospitals NHS Trust.

Evaluate strategies to improve current treatment

Studies reducing morbidity/toxicity from treatments will supported. These can include surgical (whole gland or focal), radiotherapy and/or adjuvant treatments.

Recently established studies: (i) CRUK PROMOTE (Prostate Molecular Targeting to Enhance Surgery) using "fluorescent markers" to reduce positive surgical margins in prostatectomy (Freddie Hamdy, Oxford). (ii) Wellcome Trust funded ATLANTA (Hash Ahmed, Imperial) is a phase II randomised controlled trial that will explore sequential multi-modal treatment using systemic therapy, local physical cytoreduction and metastasis directed therapy in men with newly diagnosed metastatic prostate cancer against a comparator of standard of care alone. (iii) PART study - an RCT of partial ablation looking at using VTP versus radical treatments for unilateral intermediate risk prostate cancer is now fully funded by NIHR (Freddie Hamdy, Oxford). (iv) PCUK Focal therapy study (CHRONOS) (Hash Ahmed and Taimur Shah, Imperial)- to assess failure free survival of focal therapy alone compared to focal therapy with neoadjuvant and adjuvant strategies in treating clinically significant prostate cancer.

Progress on established/completed studies: (i) CRUK PIVOTAL trial (David Dearnaley, ICR) is now published - Toxicity and patient reported outcomes of a phase II randomised trial of prostate and pelvic lymph node versus prostate alone radiotherapy in advanced localised prostate cancer (PIVOTAL). Int J Radiat Oncol Biol Phys. 2018. Demonstrated safety of pelvic lymph node irradiation. Led to standardisation of radiotherapy technique and to (ii) phase III CRUK PIVOTALboost study (Isabel Syndikus, Clatterbridge Cancer Centre). (iii) Acute toxicity from PACE-B study (Nicholas van As, Royal Marsden) was presented at ASCO GU in February 2019. This is an international phase III randomied controlled trial comparing stereotactic body radiotherapy (SBRT) to conventionally fractionated or moderately hypofractionated external beam radiotherapy (CFMHRT) for prostate cancer. (iv) NeuroSAFE PROOF study – An NIHR RfPB feasibility RCT to evaluate the use of frozen section technology to improve oncological and functional outcomes in robotic radical prostatectomy is now completed and HTA application considered (Greg Shaw, UCL). (v) SMART study - Using mpMRI after radiotherapy to predict long term failure. Pilot study extended to capture 5 more patients over 12 m to determine whether immediate post-radiotherapy mpMRI might predict long term outcomes. Follow on study being considered (Anita Mitra, UCL).

Encouraging trials with value added secondary themes of biobanking and health service research

Looking at utilising clinical trials (observational or interventional) in development to consider, if appropriate, translational biobanking and Health economics and Health Service Research (HRQoL, stakeholder opinion/experience/needs/re-mapping clinical pathways).

New studies in development/submitted: (i) PCUK PREDICT trial (Hash Ahmed/Rhian Gabe, Imperial) – depending on funder review of pilot phase and progression to full study that is planned to include biobanking for biomarker studies (supporting potential follow on funding). (ii) PROVENT- A randomised, double blind, placebo-controlled feasibility study to examine the clinical effectiveness of aspirin and/or Vitamin D3 to prevent disease progression in men on Active Surveillance for prostate cancer (Greg Shaw and Jack Cuzick (UCL)) remains active in seeking funding.
To encourage, nurture and enable young/new investigators to the field Build on recent new additions to further strengthen CSG group to bring balance of new and young investigators and also those with established expertise in translational, big data analyses and innovative trial designs. There has been turnover in the group to bring in broader expertise from trialists and statisticians. Further scoping of individuals fitting the expanded brief will be undertaken in this year. A new young investigator (Hannah Tharmalingham) has joined the localised subgroup and is mentored by a senior member (Suneil Jain).

4. Task groups/Working parties

The Prostate Cancer Group had no task groups or working parties during the reporting year.

5. Funding applications in last year

Table 2 Funding submissions in the reporting year

Cancer Research UK Clinical Research Committee (CRUK CRC)					
Study	**Application type**	**CI**	**Outcome**	**Level of CSG input**	**Funding amount**
May 2018					
Not applicable					
November 2018					
Not applicable					
Other committees					
Study	**Committee & application type**	**CI**	**Outcome**	**Level of CSG input**	**Funding amount**
MRI compared to biopsy in active surveillance of localised prostate cancer	J P Moulton Charitable Foundation	Emberton	Successful	Developed with input	~£0.25M
Partial ablation versus Radical Therapy	NIHR-HTA	Hamdy	Successful	Developed with input and feedback prior to and after pilot and prior to main RCT submission	~£3.5M
Neurosafe RCT	J P Moulton Charitable Foundation	Shaw	Successful	Developed with input and feedback prior to and after pilot and prior to main RCT submission	~£0.25M
Aspirin and Vitamin D in men with low risk cancer on active surveillance	NIHR HTA	Shaw/Cuzick	Unsuccessful	Developed with input	N/A

6. Consumer involvement

Sue Duncombe and Derek Price have been members of the CSG since summer 2016. Sue joined the Advanced Disease Subgroup 18 months later and Derek joined the Localised Disease Subgroup at the same time. They have contributed to discussions in their respective groups either directly or by email if they have not been available to attend the meeting. After the launch of the NCRI Living with and Beyond Cancer, their objective was to ensure this was included in the strategy for the CSG. Following their presentation at the Prostate CSG strategy day in March 2019, this became one of the CSG key strategic priorities for the next 3 years.

Their involvement with CRUK (Sue) and PCUK (Derek) enables them to bring a wider perspective and knowledge to the Prostate CSG which also benefits their activities with the charities. Derek and Sue communicate regularly to exchange information, ideas and opinions about current research and issues in prostate cancer and feedback from meetings.

Derek Price:

Is active in communicating with patients and the community about prostate cancer. He participates in PCUK Volunteers Midland Hub meetings and attends meetings of a local Prostate Support Group. He has given a presentation on a clinical trial to the latter group. Has undertaken activities to raise awareness of prostate cancer by giving presentations, on behalf of PCUK, to a range of organisations and businesses and running an information stand at a car manufacturing factory.

Has lay reviewed literature for PCUK to help make it more comprehensible to patients.

Is a member of three TMG's - CORE, PROSTAGRAM and ATLANTA. He has attended Trials Ethics Committee Meetings for PROSTAGRAM and ATLANTA trials to express support for the trials. In addition, he has participated in TMG meetings, and has provided feedback on the Patient Information Sheets and has commented on various other trial documents to help improve their accessibility to patients.

As a member of the PCUK RAC PPI group, he has reviewed and commented on clinical research applications and attended discussions on these with the PPI group. The group's consensus views are then represented at the RAC meeting.

Has attended a Prostate Cancer Patient Day at Queen Elizabeth Hospital Birmingham to hear presentations from prostate cancer specialists.

In order to gain a broader overview of PPI, he has participated in a PPI workshop at Warwick University Clinical Trials Unit and the online course "Public reviewing with the National Institute for Health Research (NIHR)."

Has been involved in two current research applications concerning advanced disease; this has involved commenting on one proposal, from the patient's perspective (and its likely acceptability to patients) and acting as a co-applicant and PPI lead for the other (phase III trial) grant application. Has also reviewed various additional trial documents including, the lay summary, for the latter application.

Sue Duncombe:

As part of Sue’s development she:

- Attended the NCRI conference
- Attended Consumer Forum meetings
- Completed a Future Learn course in Radiation Oncology

Her attendance at the launch of the PCUK work 'Life After Prostate Cancer' meant that she could compare some of the top-line results of this work with the results of NCRI LWBC to emphasise to the CSG that the results of LWBC were particularly relevant to the 400k men who had been diagnosed with prostate cancer.

Sue's contribution at a Dragons' Den session in November on a trial proposal in Prostate Cancer, meant that the researcher recognised the need to consider the acceptability of bone biopsies and to look for ways in which patients in the study could gain some value from this procedure.

As an NIHR Patient Research Ambassador Sue has presented to researchers on the importance of effective consumer involvement.

She has provided advice and patient support materials to the Mayor of Wallingford in order that he could include Prostate Cancer awareness in a local health event. She gave constructive feedback to her MP on a draft article he had written for the local paper on the government's plans to improve early diagnosis of cancer and the value of screening for prostate cancer. This feedback meant that the final article did not advocate that all men should go to their GP for a PSA test. It also contained a link to the PCUK website in order to provide further information to the readers.

7. Priorities and challenges for the forthcoming year

Priority 1 To design and work-up up funding proposal within the year for new functional imaging modalities such as PSMA PET and whole-body MRI for testing of utility in management of newly diagnosed prostate cancer
Priority 2 To design and work-up new diagnostic studies and risk stratified approaches that further improve detection of high-risk disease but minimise the over-diagnosis of low risk disease
Priority 3 To continue and build on the support of surgical trials possibly embedded within novel trial designs
Challenge 1 Supporting trials in the Advanced disease space that might compete with STAMPEDE (as per previous annual reports and Quinquennial Review (QQR))
Challenge 2 To ensure that previous successes in radiotherapy studies is maintained through CSG membership and encouragement of study discussion at CSG at an early phase
Challenge 3 Challenges faced by members with clinical and academic duties especially in light of cancer waiting time targets and rising numbers of referrals to prostate services (15-20% year on year increases)

8. Collaborative partnership studies with industry

1. The STAMPEDE (CI: James) group continues to work with various pharmaceutical companies to deliver new arms within a phase III setting.

2. The PART study (CI: Hamdy) has a collaboration with Steba Biotech to provide the focal vascular targeted therapy device and drug for free within the main RCT now funded by NIHR-HTA (£3.5M).

3. The re-IMAGINE study (CI: Emberton) funded by MRC and CRUK (£4.5M) has collaborations with approximately 15 commercial companies involved in diagnostic biomarkers and imaging, equivalent to in-kind contributions of at least £4-5M in total.

4. The IP4-CHRONOS and IP2-ATLANTA RCTs (CI: Ahmed) have close collaboration with device companies in cryotherapy and HIFU and currently in discussions with EORTC-GU group about a Europe-wide study for CHRONOS with additional pharmaceutical commercial collaboration.

5. The IP5-PREDICT screening study (CI: Ahmed, Gabe) to be funded by Prostate Cancer UK will involve collaboration with Thermofisher for provision of the multiplex biomarker panel (final discussions still pending).

9. Appendices

Appendix 1 - Membership of Prostate Group and Subgroups

Appendix 2 – Prostate Group and Subgroup strategies
- A – Prostate Group Strategy
- B – Advanced Disease Subgroup Strategy
- C – Localised Disease Subgroup Strategy

Appendix 3 - Portfolio Maps

Appendix 4 – Top 5 publications in reporting year

Appendix 5 – Recruitment to the NIHR portfolio in the reporting year

Appendix 6 – QQR feedback

Professor Hashim Ahmed (Prostate Group Chair)

Appendix 1

Membership of the Prostate Cancer Group

Name	Specialism	Location
Dr Suniel Jain	Clinical Oncologist	Belfast
Dr Aravindhan Sundaramurthy	Clinical Oncologist	Glasgow
Dr Hannah Tharmalingam*	Clinical Oncologist	London
Dr Alison Tree	Clinical Oncologist	London
Dr Nicholas van As	Clinical Oncologist	London
Dr Mohini Varughese	Clinical Oncologist	Somerset
Ms Sue Duncombe	Consumer	Childrey, Oxfordshire
Mr Derek Price	Consumer	Solihull
Professor Silke Gillessen	Medical Oncologist	Manchester
Professor Robert Jones	Medical Oncologist	Glasgow
Dr Simon Pacey	Medical Oncologist	Cambridge
Professor Daniel Berney	Pathologist	London
Dr Athene Lane	Reader in Trials Research	Bristol
Dr Tristan Barrett	Radiologist	Cambridge
Dr Richard Wagland	Senior Research Fellow	Southampton
Dr Fay Cafferty	Statistician	London
Professor Hashim Ahmed (Chair)	Surgeon	London
Mr Rakesh Heer	Surgeon	Newcastle
Mr Tom Leslie	Surgeon	Oxford
Mr Greg Shaw	Surgeon	London
Professor Rob Bristow	Urologist	Manchester
Mr Taimur Shah*	Urologist	London
Mr Alex Hoyle*	Urology Registrar	Manchester

* denotes trainee member

Membership of the Subgroups

Advanced Disease Subgroup		
Name	**Specialism**	**Location**
Dr Satinder Jagdev	Clinical Oncologist	Leeds
Dr Zafar Malik	Clinical Oncologist	Liverpool
Dr Alison Tree	Clinical Oncologist	London
Dr Mohini Varughese	Clinical Oncologist	Somerset
Dr Philip Turner*	Clinical Research Fellow	Belfast
Ms Sue Duncombe	Consumer	Childrey
Professor David Waugh	Director, CCRCB	Belfast
Dr Gerhardt Attard (Incoming Chair)	Medical Oncologist	London
Dr Simon Chowdhury	Medical Oncologist	London
Professor Silke Gillessen	Medical Oncologist	Manchester
Professor Robert Jones (Outgoing Chair)	Medical Oncologist	Glasgow
Dr Jonathan Shamash	Medical Oncologist	London
Dr Nuria Porta	Statistician	London
Dr Matthew Sydes	Statistician	London
Mr Prasanna Sooriakumaran	Surgeon	Oxford

Localised Disease Subgroup		
Name	**Specialism**	**Location**
Dr Ann Henry	Clinical Oncologist	Leeds
Dr Anita Mitra	Clinical Oncologist	London
Professor John Staffurth	Clinical Oncologist	Cardiff
Mr Christof Kastner	Consultant Urologist	Cambridge
Mr Derek Price	Consumer	Solihull
Dr Mehran Afshar**	Medical Oncologist	London
Professor Daniel Berney	Pathologist	London
Dr Shonit Punwani	Radiologist	London
Dr Athene Lane	Senior Research Fellow	Bristol
Dr Rhian Gabe	Statistician	York
Professor Hashim Ahmed	Surgeon	London
Mr Paul Cathcart	Surgeon	London
Professor Frank Chinegwundoh	Surgeon	London
Mr Rakesh Heer (Chair)	Surgeon	Newcastle

* denotes trainee member
**denotes non-core member

Appendix 2

Prostate Group & Subgroup Strategies

A – Prostate Group Strategy

Overall goals

1. To minimise the harms from the investigation and treatment of localised prostate cancer.
2. To maximise the quality of life and overall survival of patients with advanced prostate cancer.

Aims

- To promote a clinical research culture within urology which encourages young urologists to develop an interest in clinical trials.
- To promote international collaborations on prostate cancer trials.
- To foster links with the British Uro-oncology Group (BUG) and the British Association of Urological Surgeons (BAUS) Section of Oncology.
- To work with the Bladder & Renal and TYA & GCT (the Testis CSG has merged with the TYA CSG) CSGs to encourage clinical research in the uro-oncology community.
- To foster a harmonised approach to tissue biomarker collection for future translational studies accompanying clinical trials.
- To support consumer involvement in clinical research and establishing links with the Prostate Cancer Support Federation.
- To strengthen links with Prostate Cancer UK.

B – Advanced Disease Subgroup Strategy

Aims

- To focus on translational science with an overarching focus to progress the theme of personalised medicine in advanced prostate cancer.
- To engage with the ECMC network.
- To build on the success of STAMPEDE, introducing new treatment comparisons into the trial.
- To identify intermediate endpoints to hasten clinical development of new agents.
- To collaborate with the Supportive and Palliative Care CSG.
- To identify and address knowledge gaps where the UK has a unique opportunity to bring change.

C – Localised Disease Subgroup Strategy

1. Evaluate strategies to reduce the over-diagnosis and over treatment burden in localised prostate cancer

Project 1: Screening MRI in the community
The Subgroup discussed, developed and worked up (with the Chair as CI) to successfully gain funding from the Wellcome Trust (£2.1M; 2017-22) to develop and deliver a screening study using multi-parametric MRI (T2W and diffusion only) in the community with a primary focus on high risk men, e.g. African and African-Caribbean men, family history. The study will start in Q4 2017 and aims to recruit between 1,000-2,000 men.
Project 2: Validation of Stockholm-3 panel
The Subgroup has worked with the SPED Advisory Group and Primary Care CSG to develop a protocol and application for funding to conduct a validation study in the UK of the Stockholm-3 biomarker panel. The Chair, Rhian Gabe (York) and Fiona Walters (Cambridge) (both from NCRI Primary CSG, Walters and Ahmed from the NCRI SPED) will be co-leads of this project. At the time of writing, Prostate Cancer UK have shortlisted and interviewed our team as the preferred bidder and we are in further discussions about the next stages of changes prior to a final decision on funding. We expect this study to recruit 20,000 men in the community.
Project 3: re-IMAGINE proposal
We have worked with Professor Mark Emberton (UCL) to help the consortium he successfully led for an MRC Stratified Medicine bid. It aims to recalibrate the current risk tools we have in localised prostate cancer which are based on Transrectal biopsy to one that is based on upfront multi-parametric MRI and targeted biopsies.

2. Evaluate strategies to improve current treatments

Project 1: Neurosafe technique to reduce surgical margins
We are working with a new PI, Greg Shaw (UCL), to develop a protocol to comparatively evaluate a new surgical technique which might improve nerve-sparing surgery during radical prostatectomy called Neurosafe. This is being worked up for a feasibility/pilot study.

Project 2: Strategies to minimize cardiovascular toxicity of hormones during radiotherapy
We are working with Ann Henry (Leeds) who is also working on funding for a comparative randomized study to evaluate strategies to minimized cardiovascular toxicity of hormones during radiotherapy.

Project 3: Using mpMRI after radiotherapy to predict long term failure
We are working with Anita Mitra (UCL) who has now obtained pilot funding to determine whether immediate post-radiotherapy mpMRI might predict long term outcomes.

Project 4: CHRONOS - Focal therapy Multi-arm Multi-Stage RCT
The role of ablative therapies is increasing and might be a strategy to reduce the harms of therapy in a select group of men who require treatment and would normally have surgery or radiotherapy. The Chair, Melissa Williams and Matt Sydes (MRC CTU), alongside the EORTC-GU group and one of the CSG trainee representatives (Taimur Shah), worked on an MAMS RCT design to evaluate neoadjuvant and adjuvant strategies with focal ablative therapy. This has been combined with a PACE style preference based RCT design with a direct comparison of radical therapy with focal therapy as well as the focal MAMS RCT. This has been funded in pilot by Prostate Cancer UK.

Project 5: PART study

An RCT of partial ablation looking at using VTP versus radical treatments for unilateral intermediate risk prostate cancer. The full application is going through its second iteration with the NIHR HTA panel now (Freddie Hamdy, Oxford).

Project 6: The 5-3-1 study
Innovative MR-guided adaptive radiotherapy regimes will be studied, including the potential for a one off treatment (Alison Tree (ICR) and Choudhury Ananya (NHS Christie))

3. To evaluate methodological strategies to improve accrual and success of comparative surgical research.

This aim primarily concerns surgical research. We have seen countless RCTs of surgery in prostate cancer, but also in bladder and renal cancer, where RCTs evaluating strategies compared to surgery were proposed as the intervention arm. Novel trial designs and methods are needed. The Chair is working with members of the CSG such as Matt Sydes to evaluate novel trial designs such as the MAMS design (see above), as well as other designs such as the cohort-multiple RCT described by Jon Nicholls and Clare Relton from Sheffield.

4. Encouraging trials with value added secondary themes of biobanking and health service research

Project 1: PREVENT trial
Stockholm3 index validation study full submission to second round PCUK review – will include biobanking for biomarker studies (supporting potential follow on funding).

Project 2: PROVENT
A randomised, double blind, placebo-controlled feasibility study to examine the clinical effectiveness of aspirin and/or Vitamin D3 to prevent disease progression in men on Active Surveillance for prostate cancer (Greg Shaw and Jack Cuzick (UCL)).

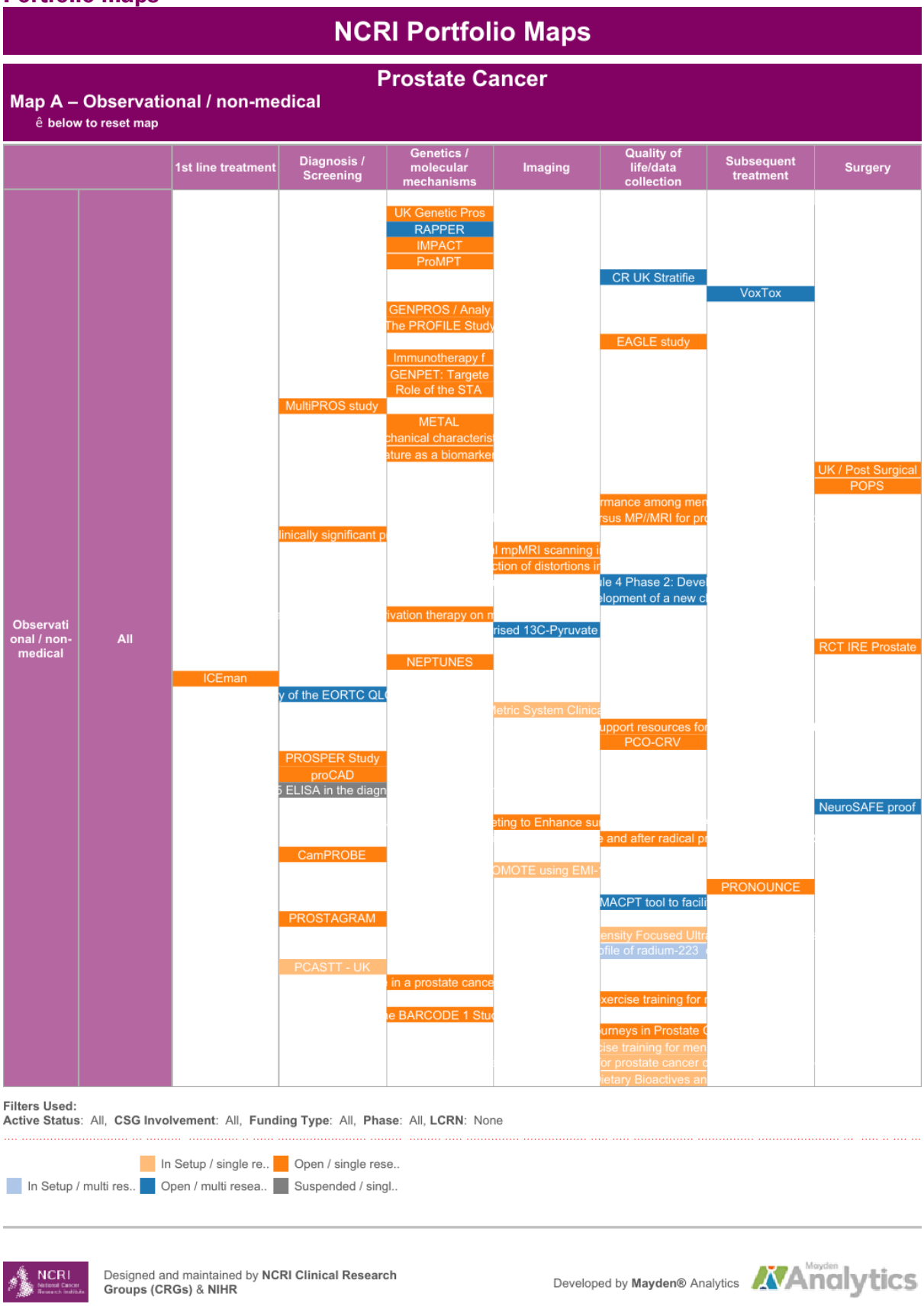
Project 3: CTC study
The exploration of novel non-invasive liquid biopsy approaches for prostate cancer diagnosis - aims to develop an efficient circulating biomarker model for non-invasive triage/diagnosis of clinically significant PCa. We will combine the CTC and CtRNA analyses in a same cohort of pre-biopsy patients with mpMRI data to improve the accuracy of non-invasive triage for biopsy. CtDNA (methylation) and CTC RNA expression will also be explored in the same samples for their triage/diagnostic value (Lu Yong-Jie and Hayley Whitaker, Queen Mary and UCL).

5. To encourage, nurture and enable young/new investigators to the field.

We have started to help and encourage a number of new PIs in the field including Rhian Gabe, Anita Mitra, Ann Henry, Greg Shaw, Taimur Shah, Paul Cathcart and Declan Cahill in a robust but supportive manner. We hope those not part of the CSG will apply to become Localised Disease Subgroup members and, in time, some of the Subgroup members will apply to become main CSG members. This will be in tandem with working up their own ideas, protocols and grant submissions.

Appendix 3

Portfolio maps



NCRI Portfolio Maps

Prostate Cancer

Map B – Metastatic

ê below to reset map

		1st line treatment	Diagnosis	Genetics / molecular mechanisms	Imaging	Quality of life/data collection	Subsequent treatment	Surgery
Refractory metastatic	All	PATCH PEACE III ic Castration Resist ith mCRPC and DN TRITON2 TRITON3 AZD5069 in combin SK525762 in CRP ROCLAIM-CX-200 25281 with Enzaluta sess SRA737 in Co CYPIDES ib vs Abiraterone Ac MAGNITUDE			cular stratification pr	CR UK Stratifie CAPRA ERVAL - MCRPC v IRONMAN	PATCH ZD3965 in adv canc masit. V docet. RE/AKT Add/Aspirin Talazoparib in Men MedImCRPC PERSEUS1 C2321001 TRAP nts with Advanced rium-227 study in pa A-617 in the treatme LU-PSMA - A206T- Keynote 921 apy in HRRm or HR IP2 - ATLANTA	
Refractory psa only	All	PROpel I3Y-MC-JPCM KEYNOTE-641					The ACE Study BXCL701 in Prostrat VARIANT IP2 - ATLANTA	
Sensitive metastatic	All	STAMPEDE y study of VAL201 ROCLAIM-CX-200 aluate CCS1477 in a A CHOICe-PC PARADIGM mours with HER2 or	PARADIGM	INNOVATE CTC/STOP PARADIGM	PARADIGM	IRONMAN PARADIGM	BARCODE 2 TRAP	

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All, **LCRN**: None

In Setup / single re.. Open / single rese..
In Setup / multi res.. Open / multi resea.. Suspended / singl..

Designed and maintained by **NCRI Clinical Research Groups (CRGs)** & **NIHR**

Developed by **Mayden®** Analytics

NCRI Portfolio Maps

Prostate Cancer

Map C – Localised

ê below to reset map

		1st line treatment	Diagnosis	Genetics / molecular mechanisms	Quality of life/data collection	Subsequent treatment	Surgery
Localised	All	DELINEATE The PACE Study PIVOTALBoost	PREDICT: Prostate Patient Study PERSONAL Study	TAPS01		Add/Aspirin	
Locally advanced	All	PATCH combination of pembrolizumab with study of VAL201 in PIVOTALBoost PROCLAIM-CX-2009 PROTEUS		with Isatuximab in trial of ipatasertib in combination with dose-escalation study of		PATCH AdUP Add/Aspirin ADVANCE B9991032 PET/CT imaging in primary and recurring TRANSLATE	

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All, **LCRN**: None

In Setup / single re.. Open / single rese..
In Setup / multi res.. Open / multi resea..

Appendix 4

Top 5 publications in the reporting year

Trial name & publication reference	Impact of the trial	CSG involvement in the trial
1. STAMPEDE. Parker CC, et al, Sydes MR; Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE)investigators. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet. 2018;392(10162):2353-2366.	Many clinicians in the UK have now adopted local radiotherapy for low volume metastatic prostate cancer as standard care.	CSG and Advanced Subgroup feeds into the TMG discussions around impact of results and generation of new arms to the trial.
2. CAP. Martin RM, et al; CAP Trial Group. Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. JAMA. 2018;319(9):883-895.	Reinforcement that screening in its current form cannot be offered.	Trial set-up prior to NCRI CSG structure although study was adopted onto portfolio.
3. PART. Hamdy FC, et al. Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. Health Technol Assess. 2018;22(52):1-96.	Proof of concept that randomisation in surgery could still occur successfully with robust QRI input. Subsequent NIHR-HTA main study funded.	Significant pre-trial and pre-funding discussions and input from CSG to team.
4. SmartTarget. Hamid S, et al, Ahmed HU. The SmartTarget Biopsy Trial: A Prospective, Within-person Randomised, Blinded Trial Comparing	Study demonstrating that image-fusion targeted biopsies might be superior to cognitive targeting. Numerous physicians are now incorporating this into their diagnostic pathway.	Significant pre-trial and pre-funding discussions and input from CSG to team.

	the Accuracy of Visual-registration and Magnetic Resonance Imaging/Ultrasound Image-fusion Targeted Biopsies for Prostate Cancer Risk Stratification. Eur Urol. 2019;75(5):733-740.		

Appendix 5

Recruitment to the NIHR portfolio in the reporting year

In the Prostate Group portfolio, 24 trials closed to recruitment and 48 opened.

Summary of patient recruitment by Interventional/Non-interventional

Year	All participants		Cancer patients only		% of cancer patients relative to incidence	
	Non-interventional	Interventional	Non-interventional	Interventional	Non-interventional	Interventional
2014/2015	4164	2836	4021	2786	9.9	6.9
2015/2016	3469	4025	3328	3892	8.23	9.62
2016/2017	6072	3317	4690	3260	11.59	8.06
2017/2018	3017	5028	1467	5028	3.63	12.43
2018/2019	3543	5251	2353	4946	4.99	10.49

Appendix 6

Feedback from the Quinquennial Review Panel

The Panel thanked the Prostate Cancer CSG for the documentation provided and the openness with which they had engaged in discussions.

The Panel identified a number of strengths of the Group and issues that the CSG need to consider:

Strengths

- The Panel commended the work of the CSG in developing a broad portfolio.
- The Group was commended on its outstanding international profile and work being done particularly in reference to STAMPEDE, ProtecT and PROMIS. It was acknowledged that the CSG has a track records of delivering world practice changing trials, with an impact that is inspiration to other CSG's.
- Panel members commended the Localised Subgroup in bringing new ideas and new researchers into the Group.

Issues for the CSG to consider

- It was highlighted that local therapy is primarily a UK-led line of research and is currently challenged internationally. The Panel recommended that Group members give further consideration to how they plan to preserve the theme of treatment reduction going forward with research to determine who will and who will not benefit from treatment.
- It was highlighted that the majority of the Groups portfolio of trials was concentrated in early and advanced disease, and that further effort is required to identify populations where there is currently gaps in research (i.e. management of locally-advanced disease and those who progress from STAMPEDE).
- Whilst the Panel supported continued perpetuation of STAMPEDE, it also recommended that the Group consider parallel research efforts to validate the changes in practice established from the platform, as not all findings are being accepted as standard of care globally.
- The Panel felt that the portfolio is currently dominated by a few senior internationally renowned individuals. The Group was encouraged to integrate new investigators and encourage new trial ideas across the spectrum of disease, from both within and outside of the CSG.
- The Panel encouraged the Group to actively build upon relationships with funding partners and identify areas where funding partners can help to support and develop their studies.
- The Panel recommended that the Groups should strengthen its basic scientist membership to encourage development of translational research. The Group was encouraged to hold a workshop bringing together clinicians, translational research experts and basic researchers (similar to the colorectal 'Mind the Gap' workshop).
- Further to previous recommendation from the NCRI, the Panel continued to stress the need for the CSG to actively engage with the Psychosocial Oncology & Survivorship (POS) and Supportive & Palliative Care CSGs to progress work in this area. The Panel also encouraged the Group to refer to the recent priorities published by the LWBC initiative.

Issues for the NCRI/NIHR CRN to consider

- The NIHR and NCRI Executive Team will arrange an annual meeting between all the SSLs and the CSG to promote better collaboration.

In concluding the Review, Professor Seymour thanked everybody for participating and the NCRI CSG Team for preparing the paperwork and organising the Review. The business of the meeting took four hours. ***The Group will be reviewed in five years' time.***