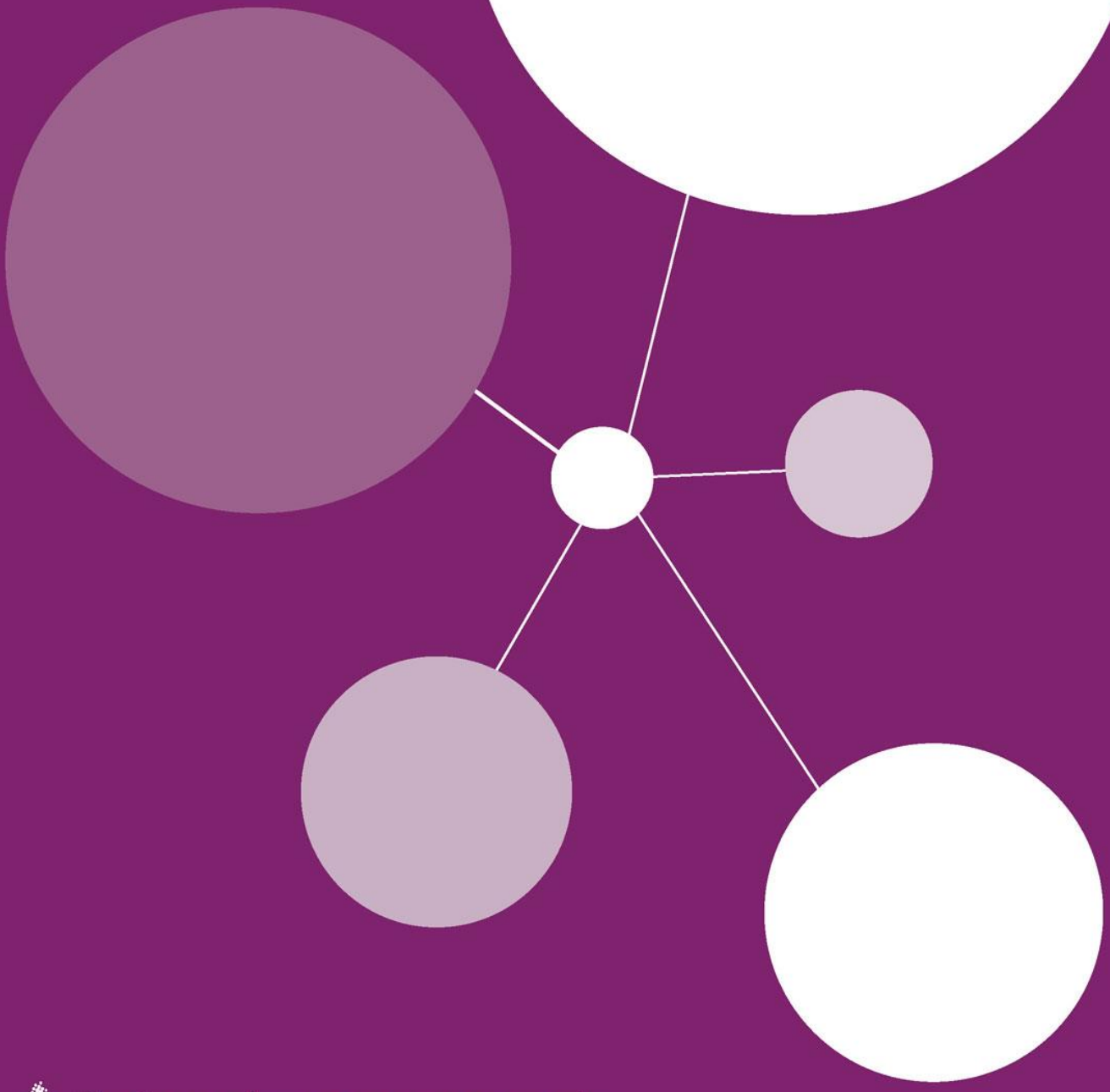
NCRI
National
Cancer
Research
Institute

NCRI Prostate Cancer Clinical Studies Group

Annual Report 2017-18



Partners in cancer research

NCRI Prostate Cancer CSG
Annual Report 2017-18

1. Top 3 achievements in the reporting year

Achievement 1 A thriving surgical trials portfolio in prostate cancer with 6 new surgical trials funded/commenced in the last 12 months following our strategic push to make this a high priority.
Achievement 2 Studies such as PROMIS and PRECISION in diagnosis of prostate cancer have made a major impact internationally and will significantly reduce rates of biopsies, and diagnosis of insignificant cancers. Significant cancers that were previously missed will also be detected early.
Achievement 3 STAMPEDE has reported on the abiraterone arm which will provide yet another impactful change in the management of advanced/metastatic prostate cancer.

2. Structure of the Group

The Prostate CSG continues to have two subgroups, Localised Disease Subgroup (chaired by Dr Rakesh Heer, Consultant Urologist) and the Advanced Disease Subgroup (chaired by Professor Robert Jones, Glasgow). The Localised Disease Subgroup was previously chaired by Professor Hashim Ahmed who took over from Dr Chris Parker as Prostate Cancer CSG Chair in August 2017. The previous Chair had instituted changes which gave subgroups the responsibility to design, develop and draft new clinical trials which will continue under the new Chair. In the coming year, a CSG strategy day will be held to determine whether this structure should continue and importantly, a decision will be made whether a further subgroup or working party will be required to take on issues around the translational interface, biomarker led studies and advanced imaging techniques. The Annual Report and QQR feedback will also be critical to this decision.

3. CSG & Subgroup strategies

Main CSG

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

This is our key priority and there are a number of gains we have made with this:

- PROMIS (National Institute for Health Research (NIHR) – Health Technology Assessment (HTA)), PRECISION (NIHR Fellowship) and PICTURE (US National Institutes of Health (NIH)) trials: proved use of MRI pre-biopsy to triage men to have a biopsy. Benefits: Reduced biopsies, reduced insignificant cancers diagnosed and treated, more significant cancers diagnosed (previously missed) and treated appropriately. Published and incorporated into National Health Service (NHS) England guidance for all Trusts to deliver within 1-2 years. NICE (National Institute for Health and Care Excellence) guidance pending but expected to support.
- SmartTarget Biopsy (Wellcome Trust) trial: improved detection of significant cancers using image-fusion targeted biopsies. Published
- CHHIP: reduced burden of radiotherapy for localised prostate cancer through hypofractionation
- Ongoing studies will aim to evaluate the role of
  - Personalised screening - PREDICT, Prostate Cancer UK (PCUK) TBC; and stratified diagnosis - re-IMAGINE, Medical Research Council (MRC)
  - Minimally invasive therapies to reduce treatment-related harms - INDEX (MRC), SmartTarget Therapy (Wellcome), PART (NIHR HTA), CHRONOS (PCUK)

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

The STAMPEDE RCT continues to make major inroads into this disease space with findings recently demonstrating benefit of abiraterone and prednisolone which confers fewer harms than docetaxel chemotherapy but similar benefit for cancer control.

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

- TROMBONE RCT of prostatectomy versus systemic therapy for oligometastatic prostate cancer (pilot funded by US Prostate Cancer Foundation (PCF))
- IP2-ATLANTA RCT of 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)
- CORE RCT of stereotactic radiotherapy for extracranial metastases in prostate cancer, breast and non-small cell lung cancer.
- 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

There has been success with young PIs in urology, specifically the surgical specialty, to engage with the CSG through mentorship, membership and guidance.

Mr Tom Leslie: co-applicant with Professor Freddie Hamdy: PART RCT of Focal HIFU versus surgery in localised prostate cancer. Funded by NIHR HTA: £0.5M.

Mr Greg Shaw: Neurosafe RCT of radical prostatectomy guided by Neurosafe method versus standard prostatectomy (pilot). Developed and discussed by the Localised Disease Subgroup and main CSG: Funded by NIHR Research for Patient Benefit (RfPB): £250K

Mr Prasanna Sooriakumaran: Trombone RCT of surgery versus standard care in patients with oligometastatic prostate cancer (pilot). Funded by Prostate Cancer Foundation: £100K

Mr Taimur Shah (Urology trainee representative of the CSG; mentored by Professor John Staffurth): co-lead applicant. Co-CI with Professor Ahmed. CHRONOS RCT evaluating innovative surgical approaches such as focal therapy and trial methodology (preference RCTs, multi-arm multi-arm) to treatment of localised prostate cancer (pilot). Funded by PCUK: £0.6M.

Promote international collaborations on prostate cancer trials

Discussions occurred with the Scandinavian Prostate Cancer Group in the past but competing trials such as CHHIP made this problematic.

Discussions formally continue with the European Organisation for Research and Treatment of Cancer (EORTC) and the PEACE group. However, due to competing recruitment to STAMPEDE further formal collaboration with EORTC or PEACE have not been fruitful

Current discussions are now at an advanced stage with CRUK and EORTC as well as the European Association of Urology Research Foundation about formal collaboration within the context of the CHRONOS RCT (detailed below). The CHRONOS RCT has fostered young PI involvement, led to engagement with PCUK, Cancer Research UK (CRUK) and EORTC as well as met the strategic aim of fostering surgical studies.

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

These links have been predominantly through specific studies, such as PACE-A to PACE-C, STAMPEDE, CHHIP, and CORE. Formal links through meetings have not occurred as they have not been felt to be required on a general basis.

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

Work with the Bladder & Renal CSG has predominantly been through the Royal College of Surgeons strategy to encourage surgical trials, National Cancer Research Institute (NCRI) Future of Surgery, led by Professor Richard Shaw (http://www.ncri.org.uk/accelerating-cancer-research/surgery/). There was good Prostate CSG representation at these workshops with

members of the Advanced Disease Subgroup and CSG attending. There have been no instances or appropriate reasons to work with the Teenage & Young Adults and Germ Cell Tumour (TYA & GCT) CSG so far.

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

There has been little work that the CSG itself has been doing towards this strategy. Whilst laudable in its aim, the multiple groups and funders as well as other national attempts to streamline this have been limited, this is a strategic aim that will likely be removed.

Nonetheless, that is not to say that the CSG does not think this area is important. The recently funded STRATOSPHERE bid to PCUK (Attard, £1.4M) and the re-IMAGINE proposal funded by MRC Stratified Medicine call (Emberton, Ahmed, Attard, van Hemelreijk; £5.5M) were both developed and worked up by the CSG and have at their core the principle of tissue and fluidic collection in parallel to a large clinical cohort undergoing interventions. The PCUK commissioned call on screening using multiplex panels will have a tissue and fluidic biobanking stream, if funded is confirmed. There are clearly established biobanks to link in with other studies such as STAMPEDE and PROMIS.

Support consumer involvement in clinical research and establishing links with the Prostate Cancer Support Federation

Our consumer representatives have been incorporated into the subgroups to facilitate this. Where appropriate and with discussion, representatives have been approached to be members of specific trial development and/or management groups. For instance, Mr Derek Price is a member of the IP1-PROSTAGRAM and IP2-ATLANTA trials.

The Prostate Cancer Support Federation is now known as Tackle Prostate Cancer. They are an umbrella organisation of a number of support groups around the country and as yet we have not found an appropriate need to formally engage with them. Nonetheless, in the coming year, the CSG will consider in what context a formal link might be needed or appropriate with this grouping.

Strengthen links with Prostate Cancer UK

PCUK are now invited to all CSG meetings and regularly attend with either the Director or their Deputy Director of Research being in attendance.

Further, we have worked with PCUK on specific commissioned calls of research in which PCUK have sought CSG input into the commissioned call wording. This has occurred twice.

First, the Stratified Medicine call. A CSG led application (Lead: Dr Gert Attard, Medical Oncology; £1.4M) in combination with the STAMPEDE team and with advisement from the Advanced Disease Subgroup was successful.

Second, a population-based next generation screening study evaluating the role of multiplex biomarkers with clinical variables to screen for significant prostate cancer. The CSG and in particular the Localised Disease Subgroup has provided advice during the commission development. The Localised Disease Subgroup and CSG then worked with Primary Care CSG and NCRI Screening, Prevention & Early Diagnosis (SPED) Advisory Group to submit an

application to the commissioned call. This has been through 4 reviews by the funding panel and a final decision is expected in the second or third week of July 2018 (Leads: Gabe and Ahmed, £4M).

Advanced Disease Subgroup (Chair, Dr Robert Jones)

Build on the success of STAMPEDE, introducing new treatment comparisons into the trial

This has been another landmark year for STAMPEDE, the biggest highlight being the publication of the abiraterone comparison - these were the first data to demonstrate a very large survival advantage with the use of abiraterone in men with newly diagnosed advanced prostate cancer. Other achievements included the presentation of Quality of Life and Health Economic data from the 'original' docetaxel comparison, presentation of a 'bonus' comparison between abiraterone and docetaxel in this setting and, in March 2018, the enrolment of the 10,000th patient.

The Subgroup has been specifically active in discussions around new arms - with extensive discussions around how best to include Radium and Pembrolizumab into the trial as well as discussions about a 'maximum treatment intensification' cohort for patients with locally advanced disease. Work is ongoing to open the first molecularly stratified arm with the expectation that genomically guided therapy will be introduced in 3Q 2018. The TROMBONE trial, a feasibility study of radical prostatectomy in oligometastatic disease, will complete accrual in 2Q 2018 and is likely to demonstrate good feasibility. Pending the upcoming results of M1 radiotherapy arm of STAMPEDE (due 3Q 2018), this will likely form the basis of a proposed new arm for STAMPEDE but will need to be discussed in main CSG in light of other RCTs starting that will ask this question (e.g., IP2-ATLANTA).

Identify intermediate endpoints to hasten clinical development of new agents

The Subgroup has been involved in discussions with the Attard group at University College London (UCL) to develop plasma tumour DNA as a novel response assessment biomarker in advanced prostate cancer. The CTC-STOP trial, which was developed in collaboration with the group – validating the role of circulating tumour cell measurements to enable therapeutic switches, opened to recruitment during the year.

Recognising the need to better understand the role of imaging in decision making in clinical practice, the Subgroup has now started working to better understand the availability of and current practices in this regard in advanced prostate cancer. The Subgroup proposes to build on this work to support the development of a research trial in the coming year.

Collaborate with the Supportive and Palliative Care CSG

This area of the strategy has not been developed in the current year.

Focus on translational science with an overarching focus to progress the theme of personalized medicine in advanced prostate cancer

Working with PCUK and CRUK, the Subgroup supported a successful grant application to support the translational programme which is being embedded in STAMPEDE to facilitate the expansion and development of the trial as a molecular stratified precision medicine platform (Attard et al.). In addition, the Subgroup has been involved in discussion with the Attard group regarding how to develop novel circulating biomarkers to enable precision medicine decision making in the future.

The TO-PARP trial, which was the first trial to demonstrate efficacy of PARP inhibitors in genomically selected prostate cancer patients has now nearly completed accrual to the second stage (a randomised phase II trial in patients selected for DNA repair deficiency). Knowledge gained in this trial has also informed the development of the first molecularly selected cohort within STAMPEDE which will open later in 2018 (exploring PARP inhibition in patients with DNA repair deficiency/loss of heterozygosity).

Within the TRAP trial (stereotactic radiotherapy in oligoprogressive disease), there are now plans to develop a biomarker to predict which patients are likely to benefit from this approach.

Engage with the Experimental Cancer Medicine Centres (ECMC) network

The Subgroup continues to work with the ECMCs to deliver a programme of innovative phase I/II trials in prostate cancer although no new trials have been added to this portfolio in the current year.

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: *MRC* RE-IMAGINE trial (Emberton); *Welcome* Screening MRI in the community (Professor Ahmed).

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

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:

- 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) (Dr Greg Shaw, UCL).
- SMART study - Using mpMRI after radiotherapy to predict long term failure. Pilot study funded to determine whether immediate post-radiotherapy mpMRI might predict long term outcomes and follow on study to be considered (Dr Anita Mitra, UCL).

New studies in development:

- MAMS Focal therapy study - A multi-arm, multi-stage, randomised controlled trial to assess failure free survival of focal therapy alone compared to focal therapy with neoadjuvant and adjuvant strategies in treating non-metastatic clinically significant prostate cancer (Professor Ahmed, Imperial).
- 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 (Professor Freddie Hamdy, Oxford).
- The 5-3-1 study - MR-guided adaptive radiotherapy trial (Dr Alison Tree, Institute of Cancer Research (ICR) and Dr Ananya Choudhury (NHS Christie)).
- Formal NIHR HTA application in development based on the NeuroSAFE PROOF study above (Greg Shaw, 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:

- PREVENT trial – Stockholm3 index validation study full submission to second round PCUK review – will include biobanking for biomarker studies (supporting potential follow on funding).
- 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 (Mr Shaw and Professor Jack Cuzick (UCL)).
- 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 (Professor Yong-Jie Lu and Dr Hayley Whitaker, Queen Mary and UCL).

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

Build on recent new additions to further strengthen the Subgroup to bring balance of new and young investigators and those with established expertise in translational, big data analyses and innovative trial designs.

The Localised Disease Subgroup has actively sought proposals to be discussed at meetings. The CSG and the Subgroup are seen as nurturing environments for study proposal discussions.

4. Task groups/Working parties

The Prostate Cancer CSG 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**
May 2017				
PROMPTS: A Prospective Randomised phase III study of Observation versus screening MRI and Pre-emptive Treatment in castrate resistant prostate cancer patients with Spinal metastasis	Full application (no-cost amendment)	Dr Emma Hall and Professor David Dearnaley	Supported	Discussed at idea stage and reviewed and discussed by Advanced Disease Subgroup and supported.
November 2017				
No applications submitted.				
Other committees				
Study	**Committee & application type**	**CI**	**Outcome**	**Level of CSG input**
Neurosafe: a pilot randomised controlled trial of standard care radical prostatectomy versus Neurosafe planned radical prostatectomy	NIHR RfPB	Mr Greg Shaw	Supported (£0.25M)	Developed and supported fully by Localised Disease Subgroup and main CSG from idea stage through to funding submission
IP3-CHRONOS: Comparative Health Research Outcomes of NOvel Surgery in prostate cancer	Prostate Cancer UK	Professor Hashim Ahmed and Mr Taimur Shah	Supported (£0.5M)	Developed and supported by the Localised Disease Subgroup and CSG from idea stage through to funding submission.
Re-IMAGINE - The exploitation of a novel image-based risk stratification tool in early prostate cancer	MRC (Personalised Medicine call)	Professor Mark Emberton (Site leads: Mieke van Hemelrijk []KCL], Gert Attard [ICR],	Funded (£5.5M)	Reviewed, developed and supported at Localised Disease Subgroup CSG meetings.

		Hashim Ahmed [Imperial])		
IP5-PREDICT - Prostate Risk Evaluation using Diagnostic Innovations in Community Testing	Prostate Cancer UK	Professor Hashim Ahmed and Dr Rhian Gabe (Primary Care CSG)	Awaited (three resubmissions asked for by funding panel) (£4.5M)	- Developed and supported by Localised Disease Subgroup and CSG from idea stage through to funding submission. - Commissioned call by PCUK was developed and advised upon by both the Primary Care CSG and Prostate Cancer CSG - Funding application initially submitted 2015/16 and then resubmitted August 2017 following review and then again third submission with changes Feb 2018. Pan-CSG bid with Primary Care, Prostate and SPED members involved. - Proposal discussed at Prostate and Primary Care CSGs.

6. Consumer involvement

Mr Derek Price and Ms Sue Duncombe have significant experience of volunteering as consumer members with PCUK and CRUK respectively. They were very pleased to be invited to join the CSG Localised and Advanced Disease Subgroups, respectively. They welcome the opportunity to be able to participate in discussions in the groups about potential studies and to provide patient perspectives.

They have both:

- Attended the NCRI Conference and Consumer Forum meetings
- Liaised with SPED consumer representatives regarding the current status of prostate screening and early diagnosis
- Had discussions with a University group on a research project concerned with specific prostate cancer survivorship issues

Sue Duncombe

- NCRI – input to 'Dragon's Den' prostate study proposal
- CRUK Campaigns Ambassador - campaigning actions in constituency with MP to support
- Clinical research in Brexit negotiations
- Government plans for improving diagnostic workforce capacity and development of local Cancer Alliance plan for diagnostic workforce
- Communications to lay audiences on benefits of clinical research through media activities and presentations
- CRUK Catalyst Expert Review Group meetings
- Input into numerous CRUK focus groups, workshops and sounding boards

Derek Price

- As a member of PCUK Grants Advisory Panel been involved in lay – reviewing grant applications for PCUK Research Innovation awards.
- Grants Advisory Panel representative on the PCUK Research Advisory Committee.
- Taken part in teleconferences as patient advocate on the CORE TMG and been involved in revising the Patient Information Sheets
- Has become a member of NIHR DC panel of expert commentators and has written a commentary on a paper for an NIHR Signal.
- Has been appointed as an NIHR public reviewer.
- Has been involved in prostate cancer awareness raising activities; these have included giving awareness talks and organising information stands and a focus group.
- Has become a member of Prostagram Clinical Trial Management Group.
- Has lay-reviewed patient information materials for PCUK
- Has attended local Prostate Support group meetings.

7. Priorities and challenges for the forthcoming year

Priority 1 Harnessing the opportunity presented by new imaging (e.g., PSMA PET). The CSG now believes that this imaging modality is likely to become more widely available across the UK. If this is the case, the UK will be uniquely positioned to conduct prospective trials exploring how best to use this efficiently for the best impact.
Priority 2 Evaluate the place of artificial intelligence in imaging and histological evaluation for diagnosing prostate cancer.
Priority 3 Evaluate novel screening strategies using clinical risk models, fluidic multiplex biomarkers and imaging.
Challenge 1 Supporting trials in the advanced disease space that might compete with STAMPEDE.
Challenge 2 Membership of CSG does not currently reflect priority 1 and priority 2 and might need co-opting expertise if experts in these fields do not apply for membership.
Challenge 3 Quinquennial review and CSG strategy day.

8. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies

A – Main CSG 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

Professor Hashim Ahmed (Prostate Cancer CSG Chair)

Appendix 1

Membership of the Prostate Cancer CSG

Name	Specialism	Location
Dr Suniel Jain	Clinical Oncologist	Belfast
Dr Alison Tree	Clinical Oncologist	London
Dr Nicholas van As	Clinical Oncologist	London
Dr Mohini Varughese	Clinical Oncologist	Somerset
Dr Phillip Turner*	Clinical Research Fellow	Belfast
Ms Sue Duncombe	Consumer	Childrey, Oxfordshire
Mr Derek Price	Consumer	Solihull
Professor Ros Eeles	Geneticist	London
Dr Simon Crabb	Medical Oncologist	Southampton
Dr Robert Jones	Medical Oncologist	Glasgow
Dr Simon Pacey	Medical Oncologist	Cambridge
Ms Vee Mapunde	NCRI Associate Consumer Lead	Leeds
Ms Kristina Duggleby	NIHR Cancer Research Network Manager	London
Professor Daniel Berney	Pathologist	London
Dr Tristan Barrett	Radiologist	Cambridge
Dr Richard Wagland	Senior Research Fellow	Southampton
Dr Fay Cafferty	Statistician	London
Professor Emma Hall	Statistician	London
Professor Hashim Ahmed (Chair)	Surgeon	London
Mr Rakesh Heer	Surgeon	Newcastle
Mr Tom Leslie	Surgeon	Oxford
Mr Sanjeev Madaan	Surgeon	Kent
Mr Greg Shaw	Surgeon	London
Professor Rob Bristow	Urologist	Manchester
Mr Taimur Shah*	Urologist	London

* 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 Philip Turner*	Clinical Research Fellow	Belfast
Dr Gerhardt Attard	Consultant	London
Ms Sue Duncombe	Consultant	Childrey
Professor David Waugh	Director, CCRCB	Belfast
Dr Simon Chowdhury	Medical Oncologist	London
Professor Robert Jones (Chair)	Medical Oncologist	Glasgow
Dr Jonathan Shamash	Medical Oncologist	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
Mr Taimur Shah*	Urology Specialist Registrar	London

* denotes trainee member
**denotes non-core member

Appendix 2

CSG & Subgroup Strategies

A – Main CSG 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 personalized 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: 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), are all working on an MAMS RCT design to evaluate neoadjuvant and adjuvant strategies with focal ablative therapy. The EORTC-GU group, the Anticancer Fund and the EAU Research Foundation are all actively involved

with commercial bodies to determine the best course and route towards funding. Discussions are ongoing with CRUK and commercial bodies as well as the Anticancer Fund about funding routes.

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)).

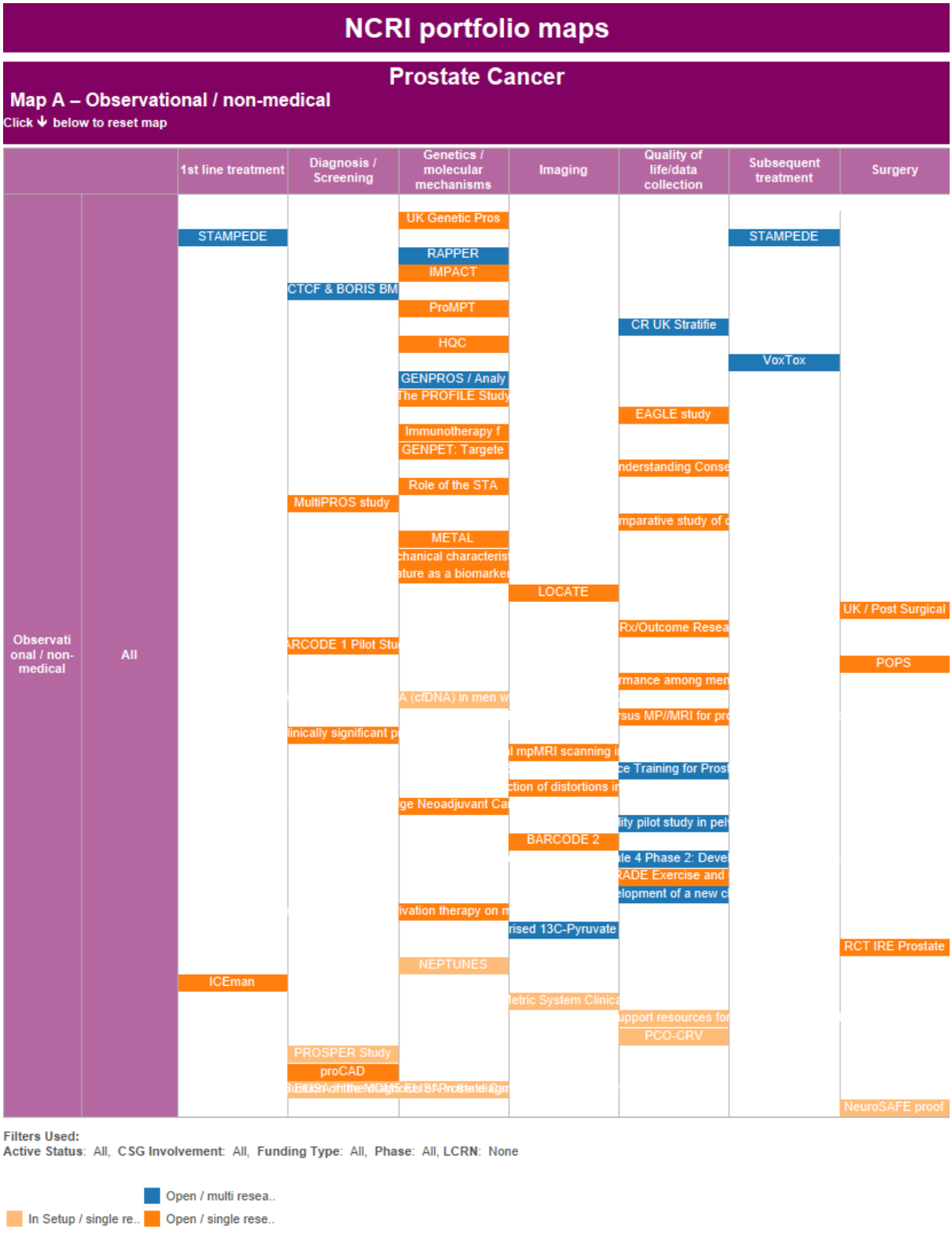
Project 3: CTC study
The exploration of novel non-invasive liquid biopsy approaches for prostate cancer diagnosis - aims to develop an efficient circulating biomarker model for non-invasive triage/diagnosis of clinically significant PCa. We will combine the CTC and CtRNA analyses in a same cohort of 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 Whitiker, 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

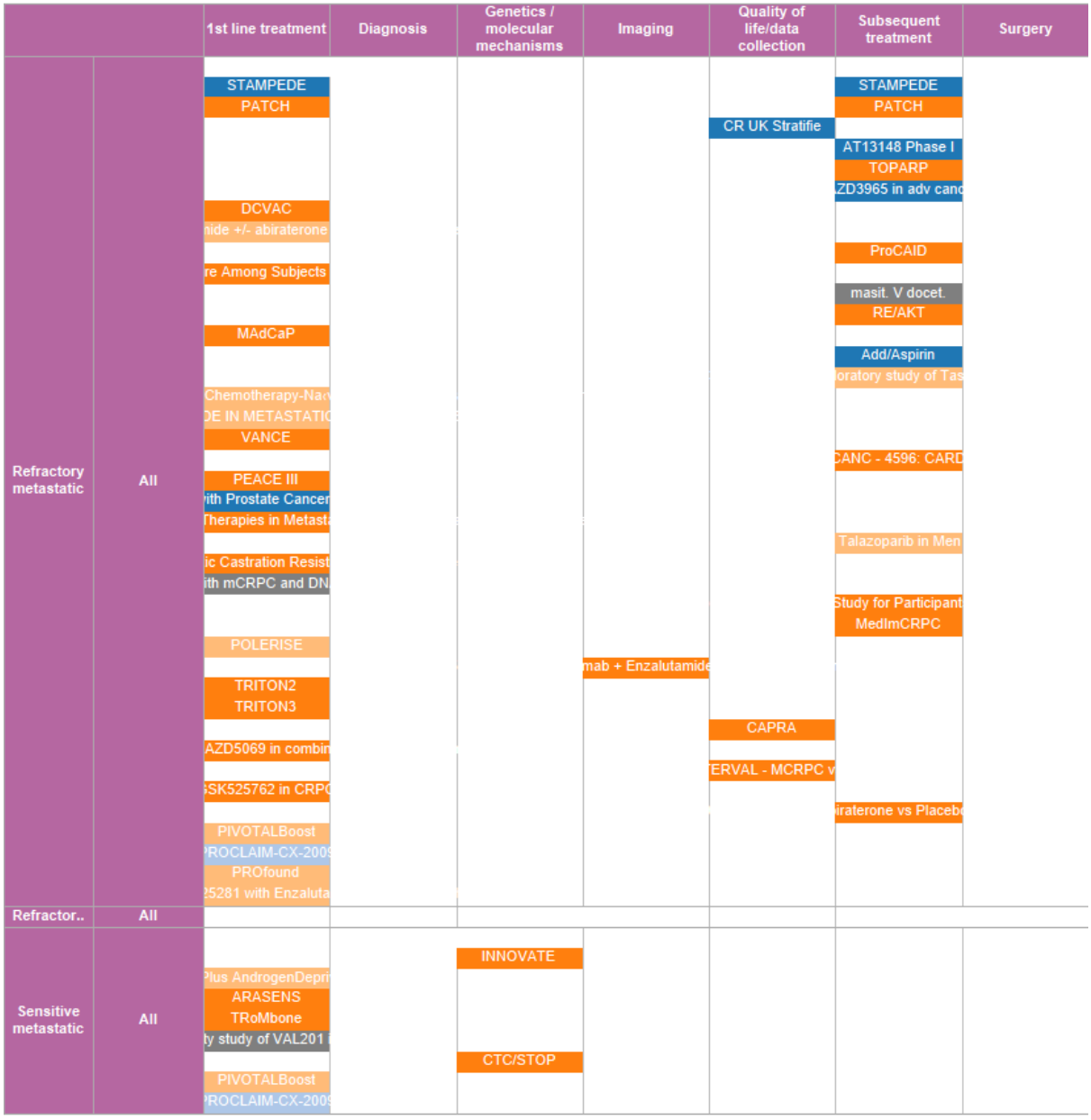


NCRI portfolio maps

Prostate Cancer

Map B – Metastatic

Click ↓ below to reset map



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..

NCRI National Cancer Research Institute

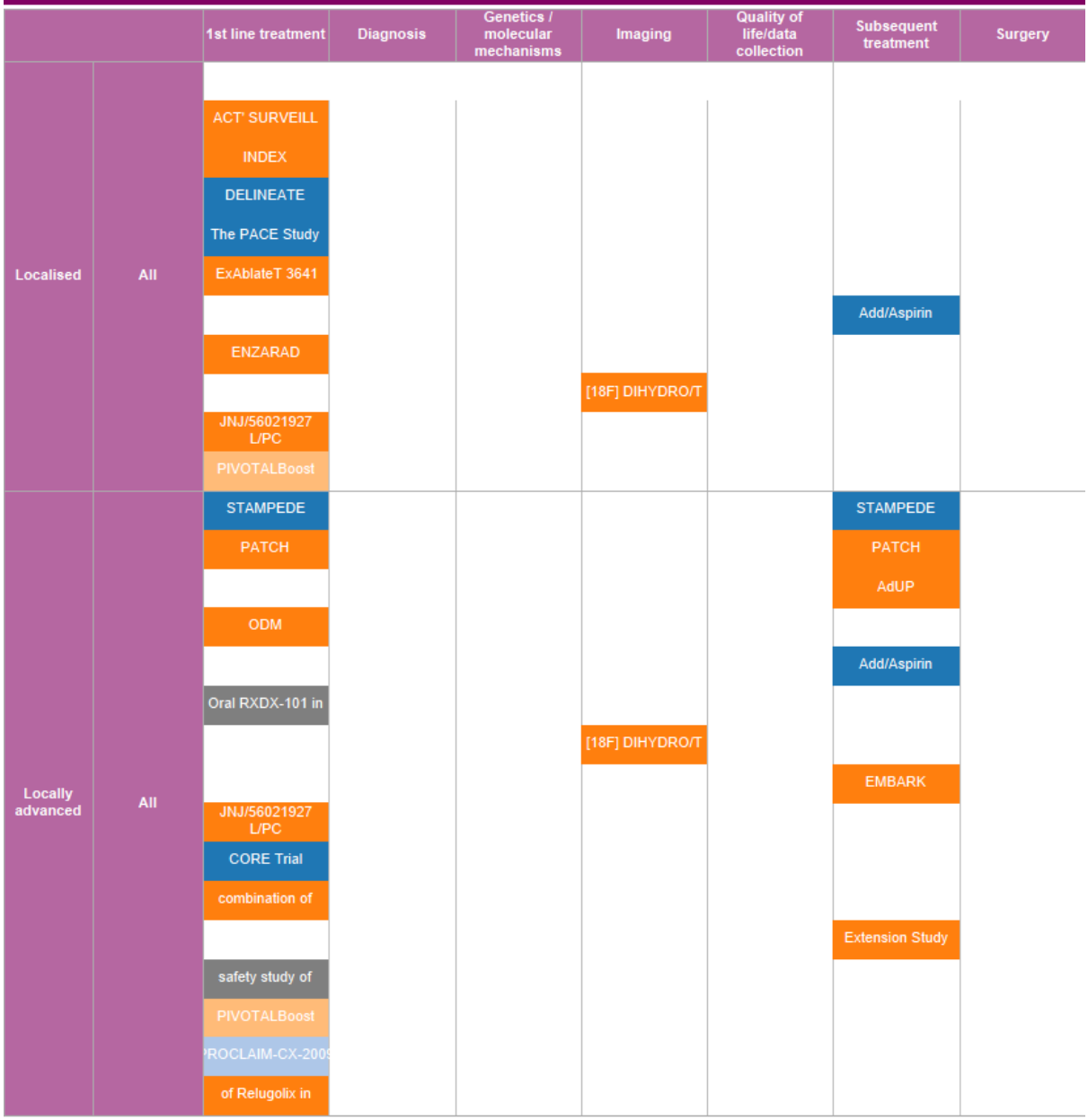
Designed and maintained by **NCRI Clinical Research Groups (CRGs)** & **NIHR**

NCRI portfolio maps

Prostate Cancer

Map C – Localised

Click ↓ below to reset map



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**

Appendix 4

Top 5 publications in the reporting year

Trial name & publication reference	Impact of the trial	CSG involvement in the trial
1. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. James ND et al, N Engl J Med. 2017 Jul 27;377(4):338-351.	NICE are currently considering their guidance on these findings.	CSG and Advanced Disease Subgroup fed into the TMG discussions around impact of results and generation of new arms to the trial.
2. Optimising the Diagnosis of Prostate Cancer in the Era of Multiparametric Magnetic Resonance Imaging: A Cost-effectiveness Analysis Based on the Prostate MR Imaging Study (PROMIS). Faria R et al, Eur Urol. 2018 Jan;73(1):23-30	As a result, over 100,000 men in the UK and hundreds of thousands around the world will have been impacted upon by this trial.	Full discussion of trial proposal and development at inception and through to funding application to NIHR-HTA. Main PROMIS trial report in The Lancet was published in the previous reporting year. NICE are currently considering their guidance on these findings as well as the PRECISION trial and main PROMIS trial report but NHS England have already issued guidance on the basis of PROMIS to all Trusts and Cancer Alliances in England to implement this important finding. https://www.england.nhs.uk/wp-content/uploads/2018/04/implementing-timed-prostate-cancer-diagnostic-pathway.pdf.
3. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm,	Feeds into the TMG discussions around impact of results, and generation of new arms to the trial.	CSG developed

multi-stage platform protocol. Sydes MR et al Annals of Oncology, Volume 29, Issue 5, 1 Feb 2018, Pages 1235–1248		

Appendix 5

Recruitment to the NIHR portfolio in the reporting year

In the Prostate Cancer CSG portfolio, 23 trials closed to recruitment and 24 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
2013/2014	3811	2826	3629	2826	9.0	7.0
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