NCRI Bladder & Renal Group

Annual Report 2020 - 2021

NCRI Partners

NCRI is a UK-wide partnership between research funders working together to maximise the value and benefits of cancer research for the benefit of patients and the public. A key strength of the NCRI is our broad membership with representation across both charity and government funders as well as across all four nations in the United Kingdom.

List of Appendices

NCRI Bladder & Renal Group

Annual Report 2020-21

1. Top achievements in the reporting year (up to three)

Achievement 1 Presentation of initial results of the NAXIVA trial (oral presentation, ASCO GU, Feb 2021; GD Stewart et al.). This was the first trial to address the potential to use systemic therapy (in this case, axitinib) to reduce operative morbidity in patients with locally advanced renal cell cancer (RCC). The single-arm, phase II trial met its primary objective to demonstrate reduction in extent of venous invasion, and this resulted in less extensive surgery for some patients. New combination systemic therapies have higher response rates in advanced disease than axitinib, and so the Group now proposes to build on this finding.
Achievement 2 Successful completion of the feasibility stage of the BladderPath trial. The protracted timelines from referral to definitive treatment in muscle invasive bladder cancer are a cause of great concern to patients and clinicians and almost certainly a cause of excess morbidity and mortality. BladderPath seeks to address this by using early MR imaging to ascertain tumour staging prior to transurethral resection. During the reporting period, the study has successfully demonstrated feasibility of recruitment and randomisation. Published preliminary results suggest that MR is a suitably sensitive and specific test to enable early patient stratification and enable more rapid progression to definitive treatment for those with the more lethal muscle invasive form of the disease.
Achievement 3 Continued success in the area of rare cancers of the urinary tract. We've championed the impact of the POUT trial (adjuvant chemotherapy in upper tract urothelial cancer) in previous reports. The impact of this trial was enhanced during this reporting period by the publication of the primary results in the Lancet and also by the presentation of an updated analysis and final overall survival analysis (ASCO GU, poster discussion). Working with the International Rare Cancers Initiative we have also gained successful funding for a phase II trial in squamous urothelial cancer, building on the group's predecessor's previous success in publishing the only other prospective trial in this rare disease. We continue to lead innovative trials in penile cancer with the initiation of a prospective trial of an immune checkpoint inhibitor this year.

2. Structure of the Group

Membership rotation was suspended due to COVID-19. Consequently, there have been no changes to the membership or structure of the Group during this period.

Both our trainee members (Manon Pillai and Arabella Hunt) have come the end of their limited tenure during this reporting period.

See Appendix 1 for a list of Group members.

The Group is committed to multidisciplinary research, with nearly all of our studies involving more than one discipline. This is illustrated in our key highlights: NAXIVA was a highly successful collaboration which has initiated the development of a new paradigm in which drugs may one day be used to address a specific surgical problem and so bring down the morbidity and mortality associated with this form of surgery. BladderPath illustrates a key UK strength in aiming to establish an evidence-based approach to rationalising and accelerating the diagnostic pathway in the most lethal curable form of bladder cancer. This builds on previous UK success in using similar interventions in prostate cancer. In rare disease, the publication of the POUT trial demonstrated the ability of systemic therapy to improve outcomes from surgery, and ongoing work in Penile cancer (InPACT) aims to bring multimodality therapy to the forefront of treatment.

We thank the now departed trainee members for their contributions to the Group, particularly in helping drive the agenda to harness the power of patients and public in setting the Group's research agenda for the future. We wish them well in their senior careers as clinicians and researchers.

3. Bladder & Renal Group & Subgroup strategies

Bladder & Renal Group.

The current strategy of the Group was updated at a strategy review day in 2019. It has not changed during the reporting period. For the first time, we have been asked to provide metrics and timelines. In considering our response to this new request, the review panel should be mindful that these reporting elements were not considered at the time the strategic objectives were set by the Group, nor has the wider Group had the opportunity to review or discus these performance metrics.

We have five key domains within our strategy:

1. **Engaging with patients and the public in setting the research agenda**

Building on the formal Public and Patient Involvement (PPI) research conducted previously, the Group has continued to place Consumer involvement at the centre of its strategy. This research highlighted the particular priority placed by Consumers on translational research. Despite COVID-19, the early bladder cancer translational science 'spin off' group (now named 'BC-TraC') has continued to develop its membership and strategy and is moving towards funding applications. Our bladder cancer PPI rep continues to drive the strategy of this Group (Henry Scowcroft). These themes continue to underlie the wider work of the Group in other disease settings, although it has been highlighted that additional PPI resources are required to enable the Group to flourish in this ambition.

Metric:

1. Prioritisation process of research agenda with a broad PPI group.
2. Revised strategy of the Group to reflect this.
3. Delivery of that strategy.
4. Further review of research agenda prioritization with broad PPI group.

Timeline:

1. Complete 1Q 2019.
2. Complete April 2019 strategy review.
3. Ongoing without timeline for completion.
4. Prior to next strategy review (timeline to be set by NCRI executive, but usually quinquennially).

2. <u>Translational science</u>

Unfortunately, funding for the TransEASE work remains elusive in the current environment, but resources have been identified to allow appropriate samples to be collected to enable this work in the future. The purpose of this study is to better understand the underlying biology of small renal tumours with the ultimate goal of being able to distinguish tumours which benefit from early surgical intervention and those which do not. In upper urinary tract urothelial cell carcinoma (UTUC), funding has been obtained through commercial partnership to formally explore the relevance of fibroblast growth factor receptor (FGFR) aberrations using the POUT collection, and we hope this will lay the foundations for a future trial in this setting. Our precision medicine trial in advanced bladder cancer (ATLANTIS) trial has not been without its challenges, including slow recruitment and prolonged interruption due to COVID-19, specifically due to the extended 'pre-screening' phase increasing the effective period of suspension of randomization to the main trial. Furthermore, recent change in the standard of care (with the introduction of maintenance immunotherapy) has forced the closure of the enzalutamide component of the trial and the redesign of the other two current randomisations. The rucaparib randomization in patients with DNARD or high levels of LOH has now reached its required event number and analysis is ongoing, whilst the cabozantinib randomization has also closed as there are sufficient patients enrolled to meet the revised event count. The Group is in advanced discussion with an additional Pharma partner to enable the trial to resume with the inclusion of immunotherapy in all arms and has secured international partnership to enhance recruitment. Via the new 'BC-TraC' partner-group we are now working with a wider network of bladder cancer translational scientists in the UK and abroad.

Metric:

1. To instigate a network of translational scientists working in bladder cancer.
2. To instigate a network of translational scientists working in renal cancer.
3. To deliver tangible work packages in the area of translational science
4. Formulate and fund molecularly stratified trials.

Timeline:

1. 3Q 2020 (BC-TraC
2. By 1Q2022 (delayed)
3. Ongoing – see exemplars above
4. Ongoing – ATLANTIS and GUSTO as successful exemplars

3. <u>To build a stronger portfolio of trials of local treatments.</u>

The POUT group continues to explore options for a new trial in the management of upper tract urothelial cancer. A working party has been set up to explore options for a staging study with a view to enabling a future randomized trial exploring neo-adjuvant systemic therapy to bring knowledge gained in bladder cancer (where pre-operative systemic therapy is the standard of care) to UTUC, where accurate pre-operative staging and histology is, for most patients, elusive. In

bladder cancer, the iROC trial, randomizing between open and robotic cystectomy, has completed recruitment. The BladderPATH study (which aims to remove TURBT from the pathway altogether for patients with muscle-invasive disease), has successfully completed its feasibility phase during the reporting period and has recently published preliminary results from this phase. The BRAVO trial, which concluded that a randomised study between cystectomy and bacillus calmette-guerin (BCG) was unlikely to be feasible has now been published.

Metric:

1. Publication of POUT trial.
2. Formation of a programme of trials in all four disease areas (renal cancer, UTUC, bladder and penile).
3. Delivery of practice changing trials in all four disease areas

Timeline:

1. Complete 2Q 2020.
2. Complete and ongoing for quinquennial review (e.g. RAMPART+NAXIVA, POUT, IROC+BRAVO+BladderPATH, InPACT).
3. Complete and ongoing for quinquennial review

4. Radiotherapy

The Hybrid trial has been published this year. This randomized, multi-centre phase II trial demonstrated that adaptive ultrahypofractionated radiation therapy is deliverable with modest toxicity in an elderly, unfit population. The RAIDER phase II trial, which builds on the techniques used in HYBRID to enable dose intensification remains in follow up. Re-ARM, which exploits the abscopal effect in metastatic urothelial cancer, is fully funded but delayed in accrual due to COVID-19.

Metric:

1. To stimulate a coordinated approach to stereotactic radiotherapy in primary kidney cancer.

Timeline:

1. Still to be agreed (work delayed due to COVID-19).

5. Systemic therapy

In renal cancer, we published the final results of the SORCE adjuvant trial in renal cancer. This was one of 6 phase III trials exploring adjuvant vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs) in renal cancer, affirming 'no treatment' as the standard of care. This has impact, as the first trial comparing adjuvant immunotherapy with observation alone has now reported positive results. We also presented the final results of Naxiva, a novel trial exploring vascular endothelial growth factor receptors (VEGFR) TKIs to surgically downstage locally advanced renal cancers, (see achievement 1). A successor study is in development. We completed accrual into the PRISM trial, which focused on optimizing the tolerability profile of combination immunotherapy in advanced disease. This study also enabled UK patients to benefit from combination immunotherapy at a time where it was not available via standard NHS funding routes.

Rare tumours continue to be a focus for the Group. AURORA (a study of immunotherapy in squamous cancer) has now been funded.

COVID-19 has significantly delayed the opening of several key trials in the portfolio, among them GUSTO, Re-ARM and a phase II trial of cemiplimab in advanced penile cancer.

Metric:

1. To test 2 molecularly targeted therapies within the ATLANTIS platform.
2. Have 2 rare cancer systemic therapy trials open to recruitment.

Timeline:

1. Q1 2020. This has failed due to the premature closure of the enzalutamide randomization. Revised timeline 2Q 2022.
2. 1Q 2022.

Bladder Cancer Local Treatment Subgroup (Chair, Mr Param Mariappan)

The Subgroup aims to develop and support studies aiming to enhance the care of patients with non-metastatic bladder cancer. We will seek to improve the patient experience through the enhancement of cancer control and maximising quality of life.

Key targets areas of the Subgroup are:

1. To enhance the outcomes of patients with high risk non-muscle invasive bladder cancer (HR-NMIBC) through:
    a. Improved diagnostics utilising developments and knowledge in genomics and gene profiling.
    b. Optimised adjuvant therapies both intravesical and systemic.
    c. Exploration of the optimal approach to the use of radical surgery.
2. To develop improved bladder sparing approaches in muscle invasive bladder cancer (MIBC).
3. To work with the Bladder Cancer Systemic Treatment Subgroup to improve neo-adjuvant. Concomitant and adjuvant therapies for patients with MIBC.
4. To seek to understand better, and then improve, factors that impact on patient quality of life and experience of bladder cancer treatment.

We will seek to achieve these goals by utilising improved knowledge of tumour biology from translational research projects and through advances in drug development leading to enhanced treatment personalisation.

Progress towards strategic objectives:

<u>Enhance the outcomes of patients with HR-NMIBC</u>

The Bladder Cancer Local Treatment Subgroup continues to aspire towards 'a study for every patient' our 2019 strategy remains, focusing on the previously identified "gap analysis".

Central to the translational aspects of our strategy for HR-NMIBC has been the formation of the network, **BC-TRAC (Bladder Cancer Translational Research Consortium)** in April 2020 - this consortium is led by Mieke Van Hemelrijck (KCL), Rik Bryan (BCRC Birmingham), and Henry Scowcroft (NCRI Consumer Representative). BC-TRAC currently represents an informal multidisciplinary forum of European bladder cancer researchers (from fundamental urothelial biologists to clinical trialists) and patient representatives with the objective of forming new collaborations to address the research priorities for bladder cancer patients and healthcare professionals (Bessa A et al. *Eur Urol.* 2019; 76: 258-259). Meeting monthly by Zoom, the group have identified the top priority areas for future funding applications, including adjuvant therapies for HR-NMIBC, molecular subtype-stratified trials of current adjuvant therapies for HR-NMIBC, and sex differences in disease incidence and outcomes. During 2021, the group intend to secure funding to undertake such collaborative research projects. In addition, the group hope to formalise BC-TRAC through an MRC Partnership Grant application (submitted) focusing upon the development of a data science partnership and building capacity and sustainability (training, grant writing, dissemination), with the associated personnel and hardware and software infrastructure.

The **Scot BC Quality OPS** project is envisaged to create a platform of matching high quality prospective clinical data (building on unique national programmes of standardised treatment as well as surveillance) and biospecimens from HR-NMIBC patients, collected during routine care. This project will also feed into the BC-TRAC MRC Partnership application.

Whilst early radical surgery is felt to be a necessary alternative to BCG in some HR-NMIBC, the recent publication of results from **BRAVO** confirm that it is not feasible to recruit into a BCG v radical cystectomy trial in this setting. Better prognosis is required and a group from Edinburgh have submitted a proposal to CRUK to evaluate biomolecular (evaluating immune environment) - the Subgroup have reviewed the proposal and given feedback.

Several UK centres continue to participate in industry-driven I/O trials in HR-NMIBC (exploring alternatives to BCG), including:

(a) POTOMAC - phase 3 RCT evaluating the safety and efficacy of Durvalumab+BCG V BCG.
(b) CheckMate 9UT - Nivolumab Vs Nivolumab+experimental medication (BMS-986205) +/- BCG in BCG un-responsive HR-NMIBC.

We discussed and supported the **DETRUSOR** (DETermining Effectiveness of Repeat TURBT or mp-MRI in Staging and improving Outcomes in High Grade non-muscle invasive bladder cancer) trial proposal which aims to evaluate the accuracy of multiparametric- magnetic resonance imaging (mp-MRI) (and the VI-RADS scoring system as the bio-maker) excluding muscle invasive bladder cancer in patients with a transurethral resection of a bladder tumour (TURBT) detected HR-NMIBC, thereby potentially avoiding the routine re-TURBT and detrimental delays to definitive treatment.

Develop improved bladder sparing approaches in muscle invasive bladder disease

Bladder-Path, an HTA sponsored trial supported by the Subgroup that is designed to evaluate and transform the pathway to radical treatment of MIBC by the use of mp-MRI (and potentially avoid perceived delays with TURBT) continues to recruit.

The group from the ICR presented a proposal that we supported recently (**MRI to identify responders to treatment of MIBC**). The proposal being submitted to the CRUK Biomarker Project Award aims: (i) To determine and validate the use of quantitative diffusion-weighted imaging (DWI) biomarkers as a non-invasive alternative to cystoscopy and biopsy to assess treatment response, (ii) To determine and validate use of quantitative DWI biomarkers during treatment (diagnostic MRI +/- MR-Linac) to determine early responders and non-responders. The study is designed as a Phase II, single arm non-randomised control trial comparing the current standard of cystoscopy + biopsy against DWI-MRI assessment of response to radical radiotherapy. The primary endpoint is Sensitivity of DW-MRI signal change with pathological outcome. A suite of translational research and patient reported outcome measures (PROMS) are also being planned along with evaluation of cost-effectiveness.

Work with the Renal Cancer Systemic Treatment Subgroup Strategy to improve neo-adjuvant, concomitant and adjuvant therapies for patients with invasive urothelial cancer

Results of **NEOBLADE**, a phase 2 UK RCT of neoadjuvant treatment (comparison between Gem-Cis neoadjuvant chemotherapy and combination of chemotherapy and the Tyrosine Kinase Inhibitor, Nintedanib in MIBC) lead by the Bladder Cancer Systemic Treatment Subgroup Chair, Prof Syed Hussain, have been presented recently and has demonstrated efficacy in improving overall and progression free survival.

Several industry driven I/O trials in MIBC continue to run in the UK:

(a) **NIAGARA** - Phase 3 global RCT evaluating efficacy and safety of combined neoadjuvant Gem-Cis chemotherapy and Durvalumab with adjuvant Durvalumab V neoadjuvant Gem-Cis chemotherapy alone prior to radical surgery.

(b) **CheckMate 274** - phase 3 RCT evaluating disease-free survival (DFS) following adjuvant treatment with Nivolumab V placebo in patients with high risk of recurrence following radical surgery for bladder or upper tract urothelial carcinoma.

Seek to understand better and then improve, factors that impact on patient quality of life (QoL) and experience of bladder cancer treatment

The Yorkshire Bladder Screening Trial, led by Prof James Catto, has successfully received funding from Yorkshire Research. They plan to carry out a feasibility assessment for implementing a targeted study in populations with high disease specific mortality risk with the overall hypotheses:

(a) Screening for bladder cancer is effective and cost-effective applied to high-risk populations.
(b) Sufficiently high-risk populations can be identified using gender, age and prior geographical Bladder Cancer mortality demographics.

The Feasibility study hypotheses:

(a) Early detection is possible using urine dipstick self-testing at home
(b) Compliance is sufficient to justify a large phase 3 RCT
(c) Bladder cancer prevalence is sufficient to power a phase 3 RCT.

The **Q-ABC** study, evaluating QoL in patients undergoing treatment for MIBC, supported by the Subgroup and developed by a trainee member opened continues to recruit.

The Subgroup have emphasised the use of PROMS in all of the proposals reviewed and pleased to note the inclusion in the study design.

Our trainee member has worked hard recently to check (and make necessary corrections) the accuracy of the portfolio map for the Subgroup.

Bladder Cancer Systemic Treatment Subgroup (Chair, Professor Syed Hussain)

The Advanced Bladder Cancer Subgroup has been renamed to the Bladder Cancer Systemic Treatment Subgroup and leads our development of novel systemic therapies and combinations in bladder cancer.

Our Subgroup has successfully developed potentially practice changing clinical trials that are on the portfolio and meet regularly. During the last year COVID-19 had a significant impact on clinical trials set up and delivery across different tumour sites nationally as clinical research took a back seat. Our Subgroup continued to meet regularly through virtual meetings and supporting development and delivery of clinical projects. We are planning to build upon our success over the last couple of years with continued development of studies with new agents in areas of unmet clinical need. We also recognise the importance of development of predictive biomarkers of response and toxicity and will ensure activity in this area alongside our interventional studies. We wish to widen access to interventional clinical trials by developing more pragmatic studies that are deliverable in all centres across the network enabling access for a wider patient population. COVID-19 pandemic has helped us understand the impact of decreasing research funding from national bodies impacting negatively leading to decreased activity of clinical and translational research across siters nationally. There are few sites in UK delivering on academic and commercial studies in terms of recruitment of patients in clinical trials, this poor recruitment has further worsened with COVID-19 pandemic and as a Subgroup we are trying to find solutions to this serious issue through wider engagement with colleagues.

Progress towards strategic objectives:

Optimise systemic therapy by developing new drug hypotheses to test in MIBC

- ATLANTIS remains the Subgroup's key study in advanced disease. This is a precision medicine maintenance study which had 3 nested arms within the randomised phase II trial directed by molecular selection markers. The study is currently on hold for any new recruitment as we review our strategy and consider additional arms. ATLANTIS is being challenged in 2021 by the introduction of maintenance immunotherapy into routine practice sooner or later based on avelumab data in maintenance setting in advanced bladder cancer. We are therefore exploiting the adaptive nature of the trial to introduce new randomisations which contain immunotherapy in both arms. Discussion with Janssen for example are in advanced stage for a new maintenance arm investigating erdafitinib with Immunotherapy in both arms within selected biomarker positive patients. Within the NCRI Subgroup ATLANTIS draws huge interest as an important academic led study that was open to 28 sites before it was put on hold temporarily, as long as we can add new biomarker driven arms that remain pragmatic and deliverable.

- The GUSTO trial (funded by NIHR) will test the principle of using molecular stratification to determine choice of systemic therapy in the neoadjuvant setting. Protocol for this study is being finalised with the aim to start recruitment in early 2022.

- A randomised phase II study comparing 3 vs 6 cycles of platinum-based chemotherapy prior to maintenance avelumab in advanced urothelial cancer (DISCUS trial led by Prof. Tom Powles)

- We have reported two neo-adjuvant studies which our group was instrumental in setting-up (SPIRE and NeoBLADE trials).

- Since our last report, we have reported on QoL data on BC2001 patients and outcome of subset of patients who received neo-adjuvant chemotherapy within BC2001 trial. We reported individual patient data meta-analysis on BC2001 and BCON trials.

Delivery of potentially practice changing studies

- Following the success of the POUT study (reported previously), which defined the standard of care in the postoperative management of UTUC, we have continued to develop the successor study, and an outline application to CRUK was successful. We continue to work with pharmaceutical partners to develop a precision-medicine adjuvant therapy study in this niche, although progress has been slow.

- RADIO, an adaptive trial of systemic radiosensitizers in muscle invasive disease is investigating the addition of Durvalumab to concurrent chemoradiotherapy which is the follow-on study to the practice changing BC2001 trial now has started recruitment across a number of sites nationally.

- The Subgroup has partnered with the Canadian research group to take part in BL-13, which aims to prove the value of adjuvant immunochemotherapy following radical radiotherapy for muscle invasive bladder cancer.

- The Subgroup retains a leadership role in the IRCI rare urothelial cancers group are members). Within this group we continue to lead on the development of trials in rare histology (AURORA) and UTUC (POUT2).

Develop larger translational research programmes

- ATLANTIS continues to provide a rich source of tissue for translation research in advanced disease: we are now carrying out a broad-panel next generation sequencing (NGS) platform test on all patients which is providing rich information both at a descriptive level but also to leverage support from industry for discussing future trial options. In addition, samples from previous studies including LAMB, SPIRE, BC2001 and NEOBLADE will provide further opportunities to improve our understanding of predictive biomarkers.

Penile Subgroup (Chair, Dr Vincent Khoo)

The Penile Subgroup has had an exciting past 12 months. It has changed several coordinators, but members have maintained administration for the Subgroup. After setting its strategic objectives, it has covered most of its three main aims.

The first aim was to review its membership with the aim of providing representation from each of the supranetworks and ensuring participation of the research active members. The membership was renewed to include a most enthusiastic patient advocate with considerable experience in ethics committees as well as coverage of most oncology and surgical research active specialists in the UK. The Subgroup also gained a pathologist to replace a retired pathologist member. It has yet to recruit an appropriate imaging specialist. Future aims would be to developed partners for each member from their respective regions who can act as a substitute or replacement when the member is not available. A secondary aim for the partnership would be to provide mentorship of younger members for future involvement in the NCRI.

The InPACT trial is an International Rare Cancer initiative. It is a randomised phase III that incorporates two sequential randomisations (InPACT-neoadjuvant and InPACT-pelvis) in patients with squamous carcinoma of the penis who have inguinal lymph node metastases (i.e. locally advanced disease). InPACT trial seeks to determine if there is a role for neoadjuvant therapy in this patient group; and if prophylactic pelvic lymph node dissection (PLND) improves survival in patients at high risk of recurrence following inguinal lymph node dissection (ILND). This study is led by Dr Steve Nicholson and Prof Emma Hall.

This study had poor recruitment internationally during the early phase of the COVID-19 pandemic. Following submission to CRUK, the trial recruitment target was revised from 400 to 200. Immense work to enhance patient recruitment was undertaken to increase participation in more countries and more centres. In the UK, all participating UK centres have recruited at least 1 case. There has been a good level of recruitment in the past four months during the COVID-19 pandemic with a 40% increase in UK recruitment status. Steps are in place to maintain the momentum achieved in the last 6 months as well as grow recruitment levels.

In the setting of clinical studies, the evaluation of MRI-PET to assess its utility for inguinal lymph node staging has completed recruitment for the impalpable cohort. This study is led by Mr Asif Muneer. The results are being analysed with the aim of publication in 2021.

Three new studies are being developed with the aim of opening in the latter half of 2021. In the setting of diagnostics, the feasibility of utilising brushing cytology and dermoscopy (BRUCY) for diagnosing penile lesions and malignant status will be compared with the gold standard tissue biopsy. This study is led by Prof Vijay Sangar.

In the setting of operative optimisation, a study for pelvic lympadenectomy is being developed comparing a laparoscopic versus open approach (VELRAD) to assess for operative and patient related outcomes. This study is led by Mr Asif Muneer.

The last study is a prospective Phase I/II trial of standard of care (SOC) chemotherapy in combination with Immunotherapy (cemiplimab) in locally advanced or metastatic penile

carcinoma (EPIC). This is an investigator led study in collaboration with industry (Sanofi). It is intended to involve up to 10 UK centres with the aim of opening in the latter half of 2021. This study is led by Prof Amit Bahl.

Renal Cancer Local Treatment Subgroup (Chair, Mr Axel Bex)

Despite the COVID-19 pandemic the Subgroup managed to meet twice online on September 1st, 2020 and March 9th, 2021. The Subgroup continued to pursue the strategy listed below to engage with the British Association of Urological Surgeons (BAUS), develop relevant trials across all renal cancer disease stages as well as upper tract urothelial cell carcinoma and to set up neoadjuvant trials as sequel to the ongoing studies.

Regarding ongoing trials, the table provides the update for 2020-2021, listed from lower to higher stage disease:

Ongoing Trial	Status in 2020-2021
NEST, a cohort embedded trial to investigate feasibility of randomisation between cryotherapy and partial nephrectomy CI: Mrs Maxine Tran	The trial was on hold during the first surge, then resumed in September 2020. In March 2021 NEST was on target and is expected to finish recruitment in the next couple of months. 41 in randomisation cohort. 8 centres expressed interest to participate but currently single centre.
SESTAMIBI, a diagnostic feasibility study to detect oncocytomas non-invasively CI: Mrs Maxine Tran	The study had its TFC in March 2021, and currently 2 patients have been recruited at the Royal Free.
WIRE, a window of opportunity trial to test drug therapy in the waiting time for surgery in cT1b and higher renal cancer stages CI: Professor Grant Stewart	The trial opened at the time of the first surge and in March 2021 6 patients had been included and the Independent Data Monitoring Committee (IDMC) met for the first time.
NAXIVA, a single-arm phase 2 neoadjuvant trial to downsize renal cancer thrombi with axitinib CI: Professor Grant Stewart	The trial closed after successful accrual during the pandemic. Final clinical results have been reported in an oral presentation by Grant Stewart at GU ASCO in February and a manuscript is in preparation.
RAMPART, a randomised multi-arm adjuvant trial of durvalumab plus tremelimumab versus durvalumab versus observation in high-risk renal cancer Co-CI: Professor Grant Stewart	The trial was severely affected by closure during the first and second surge but accrual resumed in the interval of both surges as well as after the second surge. Accrual is behind schedule and opening of international centres in France and Spain have been delayed due to COVID-19 but are expected soon.
NEOAVAX, a single arm phase 2 trial of neoadjuvant avelumab plus axitinib in locally advanced renal cancer CI: Professor Axel Bex	The trial was closed for 3 months in 2020 but resumed accrual. Currently 35 of 40 projected patients are included and translational research has begun on sequential tissue samples in cooperation with Barts. On treatment changes of the immune-environment are presented at ASCO in June 2021.

In addition, a number of trials are in preparation to continue with the defined strategy. Their planning has been partly affected by COVID-19 but other factors have been involved which are summarised in the overview below. The sequence follows lower to higher disease stages. The status of the trial project in terms of a timeline is indicated by:

Stage 1: protocol drafting
Stage 2: acquisition of funding
Stage 3: ethics and other required approval
Stage 4: study initiation

Trials in preparation	Status in 2020-2021
Screening study for renal cancer CI: Professor Grant Stewart	**Stage 2:** Funding secured conjoined with lung cancer screening and is moving forward.
EASE, a European study of active surveillance for biopsy proven small renal cancers CI: Mr Stephen Bromage, Mr Cristopher Blick	**Stage 4:** In 2020-21 unfortunately not much to update from European partners, UK PI's had a video conference but accrual across Europe was severely affected by COVID-19. EASE is expected to open in April 2021 but the deadline has been extended. 8 centres in set up out of 20 who expressed interest. Sponsorship moved to Alessandro Volpe's University from previously the EAU Research Foundation. Unfortunately funding for **Trans-EASE**, a translational proposal to investigate predictors of progression was rejected by CRUK.
NEST-X, a feasibility study of SABRE CI: Dr Kate Fife	**Stage 2/3**: Originally planned as an extension of NEST, it was decided after discussion in the Subgroup to develop NEST-X as a Cambridge single-centre study and as a smaller trial with an MRI-based endpoint (MRI efficacy) with translational response endpoints. Hoping to set up in a year.
STARTs, a phase III study of stereotactic ablative radiotherapy for small renal tumours CI: Mr Alex Laird	**Stage 2:** The proposal was submitted pre-COVID-19 to CRUK and rejected. It is planned to resubmit to NIHR.
NEOCANI, a single-arm phase II study of Neoadjuvant Cabozantinib and Nivolumab in RCC for pre-operative venous tumour thrombus reduction CI: Alex Laird	**Stage 2**: Protocol has financial support from company and is moving forward.
CONCERT, a RECUR prospective study of optimised follow-up of RCC CI: Professor Axel Bex	**Stage 1:** Concerns from patient advocacy group regarding low frequency of imaging have been partly addressed by introducing additional imaging in the first year. Role of MRI brain has been discussed and concept needs endorsement by Kidney Cancer UK (KCUK).
RAVE– Renal Artery Vandetanib Embolization prior to surgery in locally advanced and metastatic ccRCC CI: Professor David Nicol	**Stage 1:** Unfortunately, the concept will not be supported by the company. Currently uncertain if this proposal will move forward.
EQUATOR - Evaluating the Use of Ablative Therapy to current management for Oligometastatic disease in RCC CI: Dr. Vincent Khoo	**Stage 1:** No funding secured yet.

PRIMER – a cohort embedded trial of deferred cytoreductive nephrectomy versus no nephrectomy after response to immune checkpoint inhibitor combination therapies CI: Professor Axel Bex	**Stage 1:** A protocol has been drafted and endorsed by KCUK.

In addition, projects for upper urinary tract urothelial cell carcinoma were discussed which are in an early stage of drafting:

Trials in preparation for upper urinary tract	Status in 2020-2021
Distal ureter management in UUTUCC CI: Mr Stephen Bromage	It was finally decided to move away from a prospective trial concept into a BAUS audit 2017-2019, preliminary data suggest there may be potentially 3000 cases to audit. Results may inform prospective trial designs.
Post-ureteroscopy for UUTUC mitomycin C study, ODMIT-C2 CI: Mr Raj Nair	**Stage 1:** this protocol is in drafting stage.

In summary, the short-term strategic goals have been met with the successful accrual in the ongoing studies – two of which have been set up during the pandemic - and the termination and presentation of the NAXIVA data at GU ASCO in February 2021. The wider strategy is continued through developing and attracting new trial proposals engaging multidisciplinary teams including radiotherapy and medical oncology as well as patients.

BAUS have set up their own trials unit and two of the above proposals (CONCERT and PRIMER) have been submitted through TUF (The Urology Foundation) for BAUS trials unit ideas during the annual BAUS conference in June 2021.

Renal Cancer Systemic Treatment Subgroup (Chair, Dr Tom Waddell)

Despite the challenging research environment of the past 18 months, the Renal Cancer Systemic Treatment Subgroup has still achieved a number of its planned objectives including:

- Development of new trial proposals including:
  - The REFINE trial in collaboration with Duncan Gilbert at MRC CTU
  - The NeoCaAT proposal with interest from both commercial partners (Roche for Atezolizumab, Ipsen for Cabozantinib)
- Set-up and opening of the CAPER trial to recruitment at 3 out of 4 planned UK centres. First patient recruited in May 2021 at the Christie.
- Successful ongoing recruitment to the multi-arm adjuvant RAMPART trial. There was a temporary pause on recruitment for a few months during lockdown 1 (Mar – Jul 2020) which was eased as the situation improved.
- Completion of recruitment to the CALYPSO trial (results expected later in 2021)
- Successful analysis of final results from previously recruited trials including PRISM and STAR. Both are planned for submission as late-breaking abstracts to the European Society for Medical Oncology (ESMO) Congress 2021
- Ongoing collection of translational samples within recruiting trials with minimal disruption.
- Early work to establish the planned translational working party by Dr Samra Turajlic.

We believe that the above demonstrates that the Subgroup is continuing to successfully achieve its planned objectives in trying to advance the systemic therapy treatment options

for patients living with RCC within the UK. Some outputs have undoubtedly been slowed by the events of the pandemic, but none have been completely derailed, meaning no lost opportunities for our patients.

4. Cross-cutting research

We continue to work with MRC-CTU to develop a pan-disease study which aims to optimize immunotherapy scheduling (REFINE) by reducing the frequency (and cost) of systemic immunotherapy in both renal and urothelial cancers.

The Group has not had any active 'task and finish' groups during the reporting year.

5. Funding applications in last year

Table 1 Funding submissions in the reporting year

Study	Committee & application type	CI	Outcome	Level of Group input	Funding amount
Cancer Research UK*					
March 2021					
AURORA: Atezolizumab in patients with squamous cell carcinoma of the bladder and urinary tract – a single arm, open label, multicentre, phase II trial	Clinical Trial Award	Dr Simon Crabb	Conditionally Supported		

**CRUK CRC applications for table 1 completed by NCRI Executive.*

6. Consumer involvement

Alison Fielding

The first piece of research that I was involved with as a Consumer and which involved Group members was presented at GU-ASCO. The NAXIVA trial looked at whether TKI drug therapy prior to surgery for those with IVC and renal vein invasion would make surgery safer. Having reported positive results, I have now joined a team (NeoCaAT) which will test a TKI/ immunotherapy combination in the same patient group.

There has been progress in becoming involved at an earlier stage and I have been assisting with discussions on scope, helping to promote other patient input by survey and focus groups, reviewing documents and, in the case of PROPER, becoming a co-applicant.

The NCRI Consumer Forum helped in getting COVID-19 information shared. I was involved in understanding how it was impacting kidney cancer patients generally and on trials. My involvement in patient online forums enabled me to see participants' concerns and alert the Rampart team (of which I am a TMG member) of the inconsistent messaging to patients. Information on the trial status and advice to patients was updated on the website and shared to researchers and patients.

After I raised a new project which enables making MRI for pacemaker/ICD patients safer and easier to arrange, I am pleased to have seen several research teams looking to expand their trial inclusion criteria.

I spoke at an NCRI Webinar on Demystifying PPI involvement and at an International Kidney Cancer Coalition Conference about how Consumer input might challenge norms.

Henry Scowcroft

The bulk of my work this year has been taken up with establishing the BC-TRaC translational research consortium, where I have played a leading role in organising/scheduling meetings, taking and circulating notes, suggesting topics for discussion and ensuring that the perspectives of patients and carers are represented in the group's work. This has allowed the consortium to gain sufficient momentum to apply for an MRC Partnership Grant to formally establish itself and set up a data-sharing system.

I played a key role in the programming of the annual KCL/Birmingham Bladder Cancer Translational Meeting, hosted virtually this year, where I pushed for the inclusion of a patient speaker in the running order, and helped find a speaker on the topic of eCigarettes. I also spoke at the World Bladder Cancer Patient Coalition's annual conference, about the importance of translational research, as well as doing numerous speaking events and interviews off the back of the publication of my book, Cross Everything, which is about my late partner's experience of bladder cancer.

Beyond this, I have continued to play an active role in the main Group and both bladder cancer subgroups, attending all but one meeting over the year, and contributing actively to discussions at each. Beyond my contribution to meetings, I have provided feedback over email and via Zoom on several project proposals, which I believe have resulted in substantive changes to subsequent plans. For example, Alison Fielding and I fed back, via the NCRI Consumer Forum's Dragon's Den, on a project looking at immunotherapy side effects, which we hope will lead to much improved PPI on that project going forward.

One thing that has gone less well this year has been collaborating with the Group's other Consumer members, Alison and Salena, on broader strategic issues relevant to the Group's work. This has partly been due to time pressures, and partly due to the lack of face-to-face contact as a result of the pandemic. I hope we can pick this work up again in the coming months as things return to something approaching normal.

Salena Mulhere

I am a member of the Systemic Treatment Subgroup and a Consumer member of the Rampart team and recently joined the CAPER team.

The NCRI Consumer Forum helped in getting COVID-19 information shared. I was involved in understanding how it was impacting kidney cancer patients generally and on trials. My involvement in patient online forums enabled me to see participants' concerns and discuss with the Rampart team of the inconsistent messaging to patients. Information on the trial status and advice to patients was updated on the website and shared to researchers and patients.

I have also participated in a piece of work that began with a Dragons Den at the last "in person" NCRI Conference which focused on Patient Reported Outcomes being designed into trials, and took part earlier this year in a follow up session focused on PROs in dose – setting trials.

I also have supported the development of the design of some research by the Translational Oncology and Urology (TOUR) group from Kings College London shaping a proposed study investigating the impact socioeconomics has in people with long term conditions presenting at a late stage.

The requirements of responding to the impact of COVID-19 directly in my day job has limited my ability to engage with additional activities over the last year as much as I would have liked.

7. Collaborative partnership studies with industry

The Group has several established academic/ commercial collaborations:

Renal
NAXIVA (Pfizer) – completed and first presentation of final data
RAMPART (AstraZeneca) – recruitment ongoing
SORCE (Bayer) – published
ASPEN (Pfizer / Novartis) – translational study published
PRISM (Bristol Myers Squibb) – completed accrual

Urothelial
SPIRE (Astex pharmaceuticals) – published
TOUCAN (AstraZeneca) – published
ATLANTIS (Clovis, Exelixis, Astellas) – completed accrual (Clovis and Exelixis), closed early (Astellas)
ATLANTIS (Janssen) – advanced discussions to open new randomisations using immunotherapy +/- novel targeted therapy
Re-ARM (Roche) – in set up
AURORA (Roche) – funded, in set up
POUT translational (Janssen) – funded
NeoBLADE (Boehringer) – end of trial (manuscript currently in preparation)

Penile

EPIC penile cancer (Janssen) – in set up

8. Priorities and challenges for the forthcoming year

Key Priority Transition to the new Group Structure (as proposed by NCRI Executive). The Group has generally welcomed the proposal for this new development, with the notion of focussed working groups addressing specific initiatives being appealing. We already have a number of similar initiatives working 'at arm's length' from the NCRI Group (e.g. BC-TraC; POUT2 working group), and this may enable better engagement with NCRI. There will be challenges, in particular the challenges of a portfolio in three largely unrelated diseases (bladder, kidney and penis), with limited opportunity for cross-cutting study development. The Group has also worked extensively to develop its PPI strategy in recent years, and it is important that this restructuring enables this opportunity to grow without investigator disengagement.
Priority 2 Consolidate plans for a viable successor to POUT. Although the focus to date has been on developing a successor drug trial, current developments in advanced urothelial cancer mean that this is complex and negotiations with drug companies have been slow because of these complexities. Whilst these discussions continue, the Group has initiated broader discussions to consider other opportunities for a trial in UTUC. POUT itself was born of similar discussions within the (then) Bladder Group.
Priority 3 Re-engagement with UK research sites in the post-COVID-19 world. This was problematic prior to COVID-19, but study set up and recruitment has been severely impacted.
Key Challenge Grant funding. The Group's work is funded by a diverse group of funders, including NIHR and MRC, but is heavily dependent on research charities (CRUK in particular). The funding climate is likely to remain compromised in the years ahead, and the Group needs to work with a broad range of funding bodies to enable trials which are deliverable across a network which is, itself, increasingly compromised for resources.
Challenge 2 Re-engagement with experienced investigators. The turnover and diversity of Group membership has, deliberately, increased in recent years. Whilst this is good, there is a risk that previous members are less involved in the work of the Group than was previously the case. This presents a specific challenge as we move toward the new Group structure.

Professor Robert Jones (Bladder & Renal Group Chair)

Appendix 1

Membership of the Bladder & Renal Group

Name	Specialism	Location
Dr Kate Fife	Clinical Oncologist	Cambridge
Dr Ann Henry	Clinical Oncologist	Leeds
Professor Peter Hoskin	Clinical Oncologist	Middlesex/ Manchester
Dr Vincent Khoo	Clinical Oncologist	London
Dr Mohini Varughese	Clinical Oncologist	Exeter
Dr Arabella Hunt*	Clinical Research Fellow	London
Ms Alison Fielding	Consumer	Surrey
Mrs Salena Mulhere	Consumer	London
Mr Henry Scowcroft	Consumer	London
Professor Syed Hussain	Medical Oncologist	Sheffield
Professor Robert Jones (Chair)	Medical Oncologist	Glasgow
Dr Lisa Pickering	Medical Oncologist	London
Dr Samra Turajlic	Medical Oncologist	London
Dr Tom Waddell	Medical Oncologist	London
Professor Hardev Singh Pandha	Medical Oncologist	Surrey
Dr Simon Crabb	Medical Oncologist	Southampton
Dr Manon Pillai*	Medical Oncology Specialist Trainee	Manchester
Dr Anne Warren	Pathologist	Cambridge
Professor Emma Hall	Statistician	London
Mr Christopher Blick	Surgeon	Oxford
Professor James Catto	Surgeon	Sheffield
Mr Param Mariappan	Surgeon	Edinburgh
Professor David Nicol	Surgeon	London
Dr Axel Bex	Surgeon	London

Consumer Representation

Name	Location
Ms Alison Fielding	Surrey
Mrs Salena Mulhere	London
Mr Henry Scowcroft	London

Trainee Members

Name	Specialism	Location
Dr Arabella Hunt	Clinical Research Fellow	London
Dr Manon Pillai	Medical Oncology Specialist Trainee	Manchester

Membership of the Subgroups

Bladder Cancer Local Treatment Subgroup		
Name	**Specialism**	**Location**
Dr Yvonne Rimmer**	Clinical Oncologist	Cambridge
Dr Ann Henry	Clinical Oncologist	Leeds
Dr Alison Birtle**	Clinical Oncologist	Lancashire
Dr Ashok Nikapota**	Clinical Oncologist	Sussex
Professor Robert Huddart	Clinical Oncologist	London
Dr Sally Appleyard**	Clinical Oncologist	Sussex
Dr Arabella Hunt*	Clinical Research Fellow	London
Mr Henry Scowcroft	Consumer	London
Dr Anne Warren	Pathologist	Cambridge
Dr Steven Kennish	Radiologist	Sheffield
Dr Simon Baker	Research Fellow	York
Dr Rik Bryan**	Research Fellow	Birmingham
Professor Emma Hall	Statistician	London
Mr Param Mariappan (Chair)	Surgeon	Edinburgh
Professor James Catto	Surgeon	Sheffield
Mr Ashwin Sridhar**	Surgeon	London
Mr Rajesh Nair**	Surgeon	London

Bladder Cancer Systemic Treatment Subgroup		
Name	**Specialism**	**Location**
Professor Robert Huddart	Clinical Oncologist	London
Dr Alison Birtle	Clinical Oncologist	Lancashire
Dr Ananya Choudhury	Clinical Oncologist	Manchester
Dr Sundar Santhanam	Clinical Oncologist	Nottingham
Mr Henry Scowcroft	Consumer	London
Professor Syed Hussain (Chair)	Medical Oncologist	Birmingham
Professor John Chester	Medical Oncologist	Cardiff
Professor Robert Jones	Medical Oncologist	Glasgow
Professor Thomas Powles	Medical Oncologist	London
Dr Naveed Sarwar	Medical Oncologist	London
Dr Maria De Santis	Medical Oncologist	Warwick
Professor Margaret Knowles**	Scientist	Leeds
Professor Gareth Griffiths	Statistician	Southampton

Penile Subgroup		
Name	**Specialism**	**Location**
Dr Jim Barber	Clinical Oncologist	Cardiff
Dr Tony Elliot	Clinical Oncologist	Manchester
Dr Vincent Khoo (Chair)	Clinical Oncologist	London
Dr Anita Mitra**	Clinical Oncologist	London
Dr Dan Ford	Clinical Oncologist	Birmingham
Dr Amit Bahl	Clinical Oncologist	Bristol
Mr Neil Walker	Consumer	Bristol

Mr David Wilkinson	Consumer	
Professor Dan Berney	Histopathologist	London
Dr Jon Oxley	Histopathologist	Bristol
Dr Steve Nicholson**	Medical Oncologist	London
Dr Constantine Alifrangis	Medical Oncologist	London
Dr Mark Callaway	Radiologist	Bristol
Dr Miles Walkden**	Radiologist	London
Professor Emma Hall	Statistician	London
Mr David Dickerson**	Surgeon	Somerset
Mr Asaf Muneer	Surgeon	London
Mr Matthew Perry**	Surgeon	London
Mr Vijay Sangar	Surgeon	Manchester
Mr Duncan Summerton	Surgeon	Leicester
Dr Nick Watkin**	Surgeon	London
Mr Roland Donat**	Urologist	Edinburgh
Mr Aditya Manjunath**	Urologist	Bristol
Mr Suks Minhas**	Urologist	London
Mr Ben Ayres	Urologist	London

Renal Cancer Local Treatment Subgroup		
Name	**Specialism**	**Location**
Dr Kate Fife	Clinical Oncologist	Cambridge
Dr Vincent Khoo	Clinical Oncologist	London
Mrs Alison Fielding	Consumer	Surrey
Mrs Rose Woodward	Consumer	Cornwall
Dr Anne Warren	Pathologist	Cambridge
Mr Axel Bex (Chair)	Surgeon	London
Mr Christopher Blick	Surgeon	Oxford
Mr Stephen Bromage	Surgeon	Manchester
Mr Tobias Klatte	Surgeon	Bournemouth
Mr Tom Mitchell	Surgeon	Cambridge
Mr Pieter Le Roux	Surgeon	London
Professor David Nicol	Surgeon	London
Mr Grenville Oades**	Surgeon	Glasgow
Miss Maxine Tran	Surgeon	London
Mr Mark Sullivan	Surgeon	Oxford
Mr Ravi Barod	Surgeon	London
Mr Satish Maddineni	Surgeon	Manchester
Mr Alex Laird	Surgeon	Edinburgh
Mr Simon Williams	Surgeon	Derby
Mr Rajesh Nair**	Surgeon	London

Renal Cancer Systemic Treatment Subgroup		
Name	**Specialism**	**Location**
Dr Natalie Charnley	Clinical Oncologist	Preston

Dr Bernadett Szabados	Clinical Research Fellow	London
Mrs Salena Mulhere	Consumer	
Dr Richard Griffiths	Medical Oncologist	Liverpool
Dr James Larkin**	Medical Oncologist	London
Dr Paul Nathan**	Medical Oncologist	Middlesex
Dr Lisa Pickering	Medical Oncologist	London
Professor Thomas Powles**	Medical Oncologist	London
Dr Christy Ralph	Medical Oncologist	Leeds
Dr Stefan Symeonides	Medical Oncologist	Edinburgh
Dr Samra Turajlic**	Medical Oncologist	London
Dr Balaji Venugopal	Medical Oncologist	Glasgow
Dr Tom Waddell (Chair)	Medical Oncologist	Manchester
Dr Anand Sharma**	Medical Oncologist	London
Professor Janet Brown**	Medical Oncologist	Sheffield
Dr Manon Pillai*	Medical Oncology Specialist Trainee	Manchester
Mr Grant Stewart**	Surgeon	Cambridge

* denotes trainee member
**denotes non-core member

Appendix 2

Bladder & Renal Group & Subgroup Strategies

A – Bladder and Renal Group Strategy

At our 2019 Strategy Day it was agreed that our overall aim will be:

Developing the highest quality clinical and translational research portfolio that integrates patient led priorities, improves patient outcomes and gives new insights into the diseases we treat.

We identified 5 areas that we wish to focus on to deliver this challenge. This strategy has not changed. Progress towards strategy in Section 3 of the report.

1. Engaging with patients and the public in setting the research agenda

The Group agreed that we should work to ensure that those areas of priority to our patients are reflected in our research development portfolio.

Our Bladder and Renal Group cancer patient representatives (Alison Fielding, Salena Mulhere, Henry Scowcroft) together with our trainee Dr Arabella Hunt, are building upon an RCC patient RCC gap analysis (led by Group members Mr Grant Stewart Dr Janet Brown and their teams in Cambridge and Sheffield) to identify patient priorities for research in both bladder cancer and renal cancer.

Preliminary conclusions indicate that patients want research to reveal a greater understanding of disease biology that will lead to novel treatments; develop improved screening, surveillance and diagnostic methods; and identify optimal sequences of treatments. These observations require substantiating in larger studies with broader engagement. We will therefore establish a Patient Priority Working Group to deliver a more data-led robust understanding of patient priorities. These will then instruct initiatives to ensure consumer priorities are reflected in the portfolio.

We are aware that there are many patients who are excluded from interventional clinical trials, frequently due to their co-morbidities or due to resource limitations at their treating centre. There are many issues regarding patient experience before, during and after treatment that we need to understand better. The patient priority working party will develop a program of qualitative research that aims to improve access to clinical trials for the majority of patients who are not able to contribute to current interventional studies.

2. Translational Science

It is a priority for the Group to ensure that we learn as much as possible from our clinical trial activity about the biology of the diseases we treat as well as the mechanisms of efficacy and toxicity of our treatments. We wish to avoid translational work that pays lip service to the expectation that clinical research requires a translational component. The reality is that a range of pre-clinical expertise will be required across our portfolio and that the breadth of skills required will not be reflected by the Group membership. We therefore wish to establish a Translational Working Party led by Dr Samra Turajlic that will identify a network of high quality translational scientists working in areas relevant to bladder and renal cancer pre-clinical research. This resource will ensure that relevant pre-clinical scientists are invited to contribute to projects in development at the earliest possible stage. The Working Group will also develop a generic component for trial consent forms, influenced by Dr Turajlic's experience with the TraceRx and PEACE

studies, that will ensure future-proofing for biological samples and data generated from our trial activity.

3. Local Treatments

The Group will be reorganised to have Bladder and Renal Local Treatment Subgroups. These will replace the current Bladder T2 & Below (TABS) and the Renal Surgical Subgroup. They will support study development with surgical and non-surgical local treatments including radiotherapy and other modalities such as RFA and cryotherapy. This clarifies the activities of the subgroups. Local treatments often provide rich opportunity for translational work given that acquisition of tumour material is frequently a standard of care. The membership of each local treatment subgroup will be reviewed to ensure that a translational scientist is a group member.

We believe there is opportunity for the many patients in the country who undergo surgical procedures and who are not eligible for studies on our interventional clinical trial portfolio to contribute to our understanding of their experiences through qualitative and semi-quantitative research. The local treatment subgroups will therefore explore whether there are opportunities with BAUS to develop studies that are relevant for a wider population of patients and the patient priority working party will develop activity in this area.

4. Radiotherapy

Radiotherapy is a mainstay of treatment for many bladder cancer patients. Efficacy needs to continue to be increased and toxicity decreased. Radiotherapy increasingly dovetails with other therapeutic modalities, and with the advent of new systemic therapies the role of combination systemic treatment and radiotherapy needs to be developed. The UK has led the world in the field of chemoradiotherapy in bladder cancer, and we intend to build on this success. The Group prioritises delivery of radiotherapy research in these areas and therefore will ensure clinical oncology expertise within our local and systemic treatment subgroups in bladder and RCC.

We will develop studies that a) continue to refine methodology with highly technical radiotherapy b) are pragmatic ensuring improvement of radiotherapy regimes that are current standards of care c) explore radiotherapy in combination with systemic treatments and d) address areas of high unmet clinical need including management of brain metastases.

5. Systemic Treatment

The Advanced Bladder Cancer Subgroup has been renamed to the Bladder Systemic Treatment Subgroup and, along with the Renal Cancer Systemic Treatments Subgroup, leads our development of novel systemic therapies and combinations in both diseases. Both groups are productive, have successfully developed potentially practice changing clinical trials that are on the portfolio and meet regularly. We plan to build upon this success with continued development of studies with new agents in areas of unmet clinical need. We also recognise the importance of development of predictive biomarkers of response and toxicity and will ensure activity in this area alongside our interventional studies. We wish to widen access to interventional clinical trials by developing more pragmatic studies that are deliverable in all centres across the network enabling access for a wider patient population.

B - Bladder Cancer Systemic Treatment Subgroup (Chair, Professor Syed Hussain)

Strategy has not changed. Progress towards strategy in Section 3 of the report.

- Optimise systemic therapy by developing new drug hypotheses to test in MIBC
- Delivery of potentially practice changing studies
- Develop larger translational research programmes

C - Penile Subgroup (Chair, Dr Vincent Khoo)

Strategy has not changed. Progress towards strategy in Section 3 of the report

- To ensure membership coverage for the Penile supranetworks including consumer representatives and to involve research active members across the specialities of surgery, oncology, imaging and pathology.
- To consolidate and support the International Rare Cancer initiative in penile cancer: InPact trial.
- To develop new studies incorporating surgical developments and new systemic therapies.

D - Renal Cancer Local Treatment Subgroup – (Chair, Prof Axel Bex)

Strategy has not changed. Progress towards strategy in Section 3 of the report

- Engage with BAUS and BAUS Oncology on promotion of their new trials
- Develop a range of surgery and radiotherapy relevant studies across all stages of renal cancer i.e. from screening to metastatic disease.
- Deliver and complete feasibility studies in contentious areas to prove recruitment can be achieved
- Liaise with oncologists for neoadjuvant trials

E - Bladder Cancer Local Treatment Subgroup (Chair, Mr Param Mariappan)

Strategy has not changed. Progress towards strategy in Section 3 of the report

- Enhance the outcomes of patients with high risk NMIBC (HR-NMIBC)
- Develop improved bladder sparing approaches in muscle invasive bladder disease
- Work with the Systemic Treatments Renal Cancer Working Party Strategy to improve neo-adjuvant, concomitant and adjuvant therapies for patients with invasive urothelial cancer
- Seek to understand better and then improve, factors that impact on patient quality of life and experience of bladder cancer treatment

F - Renal Cancer Systemic Treatment Subgroup (Chair, Dr Tom Waddell)

Strategy has been updated here.

<u>Optimisation of IO Therapies</u> The treatment landscape in patients with metastatic RCC (mRCC) continues to evolve rapidly, presenting opportunities and challenges in study development. In particular, immunotherapy-based combinations have revolutionised the first-line treatment

paradigm for most RCC patients. Despite impressive efficacy results, most patients will still not obtain durable remissions, and a key focus of the group is around optimisation of IO therapies, including:

1) Efforts to increase the volume of mRCC patients deriving benefit –

a) CALYPSO trial (led by Tom Powles) is evaluating Durvalumab in combination with MET inhibition (Savolitinib), plus specific evaluation in a non-clear cell RCC cohort. Recruitment has been successfully completed and results are awaited.
b) CAPER trial (led by Tom Waddell) evaluating modulation of immune micro-environment with cyclophosphamide combined with Pembrolizumab in patients refractory to prior IO therapy. This trial is now open to recruitment with 1st patient recruited.
c) Proposal in development to deliver SBRT to a targeted tumour area in combination with IO therapy (led by Nav Vasudev)

2) Efforts to reduce unwanted toxicities –

a) The PRISM trial (led by Nav Vasudev) has evaluated an alternative Ipi/Nivo schedule with the aim of reducing G3 AEs. Recruitment successfully completed ahead of schedule and results are expected later in 2021.
b) Ongoing national work evaluating late effects of IO therapies

3) Efforts to reduce frequency of administration –

a) The REFINE trial proposal is in set-up and the RCC cohort will evaluate reduced frequency of IO therapy administration in the maintenance setting (RCC cohort led by Lisa Pickering and Nav Vasudev)

4) Efforts to evaluate IO therapy in RCC beyond the metastatic setting –

a) Following on from the successfully reported NAXIVA trial, the NeoCaAT trial proposal (led by Stefan Symeonides) is currently in development to study neoadjuvant Cabozantinib + Atezolizumab
b) The RAMPART trial (led by James Larkin) is successfully recruiting Leibovich score ≥3 adjuvant RCC patients with randomisation to either surveillance, single agent Durvalumab, or combination therapy with Durvalumab + Tremelimumab

5) **Efforts to evaluate biomarkers of response / resistance –**

a) PET trial (led by Natalie Charnley) is evaluating tumour flare in association with early response to IO therapies
b) Blood and tissue biomarker work is ongoing within all of the above trial activity

Real-World Data Collection

Complementary to the above trials activity, a key focus of the RCC Systemic Treatment Subgroup is to develop a platform for better collection and collaboration across the UK in the real-world data space. This data is becoming increasingly important to support areas where RCT evidence is lacking. The goals of the group in this regard include:

1. Establish RWD infrastructure within the UK to support this work
2. Systematic review of current RWD (in progress)
3. Begin data collection in identified key areas of clinical interest / unmet need -
   a. Treatment sequencing / efficacy of options following failure of 1st-line IO combinations
   b. Outcomes in bone metastasis patients with current therapies
   c. Non-clear cell RCC outcomes

Develop high quality translational biobanks

At present, there are still no biomarkers in routine clinical use in patients with RCC. The establishment of high quality sample banks in the context of a changing treatment landscape remains a priority. As mentioned previously, all ongoing trials developed

through the subgroup have incorporated tissue and blood collection for biomarker substudies.

Recently, Samra Turajlic has led the establishment of a newly formed translational subgroup. This has started by identifying a network of translational scientists with an interest in RCC from across the UK. One of the key goals is to try to develop UK-wide protocols to ensure tissue and blood collection and preservation is harmonised. This will help to ensure that translational analyses, and subsequent validation of findings, can be easily replicated within different datasets or trial populations.

Appendix 3

Top 5 publications in the reporting year

Trial name & publication reference	Impact of the trial	CSG involvement in the trial
1. POUT: Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Birtle A, Johnson M, Chester J, Jones R, Dolling D, Bryan RT, Harris C, Winterbottom A, Blacker A, Catto JWF, Chakraborti P, Donovan JL, Elliott PA, French A, Jagdev S, Jenkins B, Keeley FX Jr, Kockelbergh R, Powles T, Wagstaff J, Wilson C, Todd R, Lewis R, Hall E. Lancet. 2020 Apr 18;395(10232):1268-1277	Global practice change. Adjuvant chemotherapy is now the global standard of care following nephroureterectomy. Adjuvant chemotherapy is now the control arm for future trials.	The need for a trial in UTUC was a key strategic objective of the predecessor Bladder Research Group. POUT was designed by a working part of that Group. Design and progress was constantly monitored and driven by the Bladder Research Group to completion. 11 of the authors have at some time been members of the Group or its predecessor.
2. BladderPATH Comparing an Imaging-guided Pathway with the Standard Pathway for Staging Muscle-invasive Bladder Cancer: Preliminary Data from the BladderPath Study. Bryan RT, Liu W, Pirrie SJ, Amir R, Gallagher J, Hughes AI, Jefferson KP, Knight A, Nanton V, Mintz HP, Pope AM, Catto JWF, Patel P, James ND.Eur Urol. 2021 Feb 27:S0302-2838(21)00141-X. doi: 10.1016/j.eururo. 2021.02.021. Online ahead of print.	BladderPATH continues to be funded as a phase III trial. If successful, this will have the impact of transforming the initial diagnostic pathway for early bladder cancer, in the same way that the pathway has been transformed for prostate cancer by similar work. This will result in more timely progress to definitive treatment for muscle-invasive bladder cancer and may thereby improve cure rates.	Reactive review and ascent. Provided support to the Chief Investigator in appealing to NIHR to continue funding beyond feasibility phase.
3. SORCE Adjuvant Sorafenib for Renal Cell Carcinoma at Intermediate or High Risk of Relapse: Results From the SORCE Randomized Phase III Intergroup Trial. Eisen T, Frangou E, Oza B, Ritchie AWS, Smith B, Kaplan R, Davis ID, Stockler MR,	Affirms that follow-up alone without treatment is the standard of care in the adjuvant treatment of renal cancer. There are multiple trials of immunotherapy ongoing (including RAMPART) all of which have intervention-free control arms. The first of these (pembrolizumab) has recently	Prioritisation output of previous Renal Research Group. Ongoing reactive review and ascent. 6 of the authors have been members of the Group or its predecessor.

Albiges L, Escudier B, Larkin J, Bex A, Joniau S, Hancock B, Hermann GG, Bellmunt J, Hodgkinson E, Stewart GD, Barber J, Brown J, McMenemin R, Nathan P, Pickering LM, Parmar MKB, Meade A.J Clin Oncol. 2020 Dec 1;38(34):4064-4075	been announced as positive and affirmation that the control arm is valid will support its pathway to impact.	
4. CALIBER: a phase II randomized feasibility trial of chemoablation with mitomycin-C vs surgical management in low-risk non-muscle-invasive bladder cancer. Mostafid AH, Porta N, Cresswell J, Griffiths TRL, Kelly JD, Penegar SR, Davenport K, McGrath JS, Campain N, Cooke P, Masood S, Knowles MA, Feber A, Knight A, Catto JWF, Lewis R, Hall E.BJU Int. 2020 Jun;125(6):817-826	There remains unmet need for new treatment to reduce the morbidity associated with surveillance for recurrence and its treatment in low risk NMIBC. The CALIBER trial efficiently affirmed that surgical management remains the standard of care and the control arm of future trials. Despite its popularity as a treatment, patients with this stage of the disease can be spared the additional morbidity and the health services can be spared the cost.	Fully prioritised, developed by and overseen by the Group. 7 of the authors have been members of the Group or its predecessor.
5. SPIRE Phase I Trial of DNA Methyltransferase Inhibitor Guadecitabine Combined with Cisplatin and Gemcitabine for Solid Malignancies Including Urothelial Carcinoma (SPIRE). Crabb SJ, Danson S, Catto JWF, Hussain S, Chan D, Dunkley D, Downs N, Marwood E, Day L, Saunders G, Light M, Whitehead A, Ellis D, Sarwar N, Enting D, Birtle A, Johnson B, Huddart R, Griffiths G.	The impact of phase I trials is always difficult to describe or measure. However, any framework for impact of drug trials would always have to consider that there can be no phase III trial without a phase I trial. Therefore, the impact of this trial is that a safe, tolerable and pharmacodynamically active dose of this three drug combination has been found in patients with urothelial cancer to permit further investigation.	This work grew out of the Advanced Disease/ Systemic Therapies/ Chemotherapy/ T2 and above Subgroup (as its name has changed over time) of the Group and the former Research Group. 7 former or current members of the Group are authors.

Appendix 4

Recruitment to the NIHR portfolio

Summary of patient recruitment by Interventional/Non-interventional and number of studies opened/closed.

Year	All participants		Cancer patients only*		Number of studies	
	Non-interventional	Interventional	Non-interventional	Interventional	Opened	Closed
2016/17	6105	1392	381	1026	40	23
2017/18	3796	1552	3237	1224	33	30
2018/19	1389	1720	1296	1342	31	31
2019/20	3290	1273	3654	922	21	31
2020/21	986	362	6645	195	14	19

*This data is based on a proxy from CPMS (the NIHR database used to collect patient recruitment data) and includes diagnostics, screening and prevention patients.

Appendix 5

Annual report feedback 2019-20

06 November 2020

Dear Rob

Re: NCRI Bladder & Renal Group Annual Report 2019-20

Thank you for submitting an annual report for the Bladder & Renal Group for 2019/20, especially given the challenges with the ongoing COVID-19 pandemic which will have impacted on both the Group and the report itself.

All the Group's annual reports were reviewed at a two-day meeting on the 12th and 13th October 2020 by a panel consisting of some former NCRI Group Chairs, NCRI CMPath Chair, former NCRI CTRad and the current NCRI Strategic Advisory Group (SAG) Chair, NCRI Head of Research Groups and representatives from the NIHR Cancer Coordinator Centre, NHS Cancer Alliances, epidemiology, CTU/basic science, allied health profession, NCRI Consumer Forum and the Canadian Cancer Clinical Trials Network.

We are writing to you now with a summary of the feedback which is based on the information provided in the report. It was noted that there is likely to be more activity taking place within the Group than is documented.

Please share the contents of this letter with your members for discussion at the next Group meeting.

Generic feedback for all the Groups

Strategic objectives and the impact of COVID 19

- Due to the research funding challenges and restrictions on NHS resources resulting from COVID 19, the Panel recommended the Groups evaluate their strategic objectives and focus on the most important priorities or questions that need to be answered as it would not be feasible for the Groups to be doing everything they planned or continue to "plug in the gaps." Additionally, the Panel suggested looking for more cost-efficient methods of working where they can.
- The Panel felt that the strategic objectives for most Groups were too broad especially in the current climate. The Groups were asked to provide specific, measurable aims for their strategic objective and attach timelines/metrics to them.

Multidisciplinary approach to research and membership

- The Panel noted the importance of collaborative and multidisciplinary working, especially in the current climate, and would encourage all Groups to continue to reach out to other relevant NCRI Groups and consider the NCRI strategic priorities where appropriate.

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Linking with the wider research community

- The Groups were asked to link with the wider research community and engage with relevant networks, in particular, with researchers who are developing or are running large national platform studies when there is one available in the disease site e.g. PrecisionPanc (Upper GI Group) and TRACERx (Lung Group). The NCRI recognised that there is a role for them to play in promoting collaboration and will be working with the partners to encourage greater interaction between the Groups and the networks in future.

Funding opportunities

- Given the potential decrease in funding opportunities, the Groups are encouraged to explore alternative funding sources and collaborations e.g. with industry, government funders, NHS Cancer Alliances etc.

Consumers involvement:

- The Panel encouraged Groups to integrate public and patient involvement (PPI) in all aspects of the Group's activities e.g. study design, proposal development, prioritisation of strategic areas etc.
- The Panel wanted to ensure that the consumer activity was captured throughout the report and not just in the consumer section, especially where the consumer reports are missing.

Specific feedback for the Bladder & Renal Group

Areas of strength:

- Very active Group with engaged members.
- The Panel thought the practise changing trial NEOBLADE was an important achievement.
- Linking with the new bladder cancer translational working party.
- Strong consumer involvement – the Panel was particularly impressed with how the consumer representative led the satellite meeting, which led to the development of the bladder translational working party.
- Good success rate with funding application submissions.

Areas which the Group need to consider:

- The Panel noted that while there was a lot of research activities taking place in the Group, it felt largely unfocussed and recommended the Group develop a clear joint strategy for bladder and renal cancers.
- There is a risk that the subgroups would end up working in silos in the new structure (the Advanced Disease and Localised Disease Subgroups across bladder and renal cancer). The Panel advised the respective chairs to keep a close eye on this to ensure joined up working is taking place across the Subgroups where possible.
- The Panel proposed a focus on discerning the immunological priorities with regards to tissue collection.
- The Panel highlighted that the InPACT study in penile cancer is recruiting poorly, with only 8 out of 200 patients recruited to date (closure date is in January 2021). They asked the Group to consider supporting the trial team to help improve recruitment.

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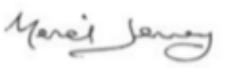
- There was mention of doing work on qualitative research and understanding patient priorities, but it was not clear if the Group was engaged with relevant cross cutting groups for example the NCRI Living With & Beyond Cancer (LWBC) Group or if there were representatives on the Group leading in this area.

Congratulations to you and your members for all your hard work and achievements in 2019/20.

If you have any comments on this year's process, please send them to Nanita Dalal (Nanita.Dalal@ncri.org.uk) for collation.

Best wishes,



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Appendix 6

Quinquennial review feedback - 2015

4. Comments and recommendations

The panel thanked the CSG team 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 which the Group need to consider:

Strengths

- A good report, although a little repetitive in parts
- Positive and enthusiastic engagement with the panel
- Progress since the last review on the points raised at that time
- A well-functioning Group with strong leadership and good interactions between individuals
- Impressive degree of involvement from the research community, particularly urology
- Audit of research networks
- Good exploitation of, and interactions with the NIHR CRN
- Planned roadshows to boost recruitment
- Involvement of trainees in the group's activities and bringing on the next generation of researchers
- Good consumer involvement
- Interactions with the other urological CSGs and joint annual trials meetings
- A full portfolio (though somewhat crowded in some indications)
- A clear vision for the future with the direction of travel good and well thought through

Issues for the CSG to consider

- The panel would like the CSG to clearly define and prioritise the top 5 (or so) research questions of importance in bladder cancer, and their strategy for addressing them.
- In doing this, attention should be paid to the major competitive strengths of the UK: our network capacity and coordination; uniformity of the NHS service; ability to perform trials with randomised designs, etc.
- The Group's translational research should be strengthened, with closer engagement with basic and translational research groups and clear translational research objectives in the group's strategy and research designs.
- However, the group should also continue to pursue its goals of including research which addresses health service questions and addresses the quality of patient experience.

Dr Birtle thanked the panel for their constructive feedback, indicating that it is helpful to know that the Group is moving in the right direction. In concluding the review the panel chair thanked CSG members, the panel for participating in the review, and the CSGs Secretariat for preparing the paperwork and organising the review.

The business of the meeting took 3 hours.

The Group will be reviewed in 5 year's time.

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Advancing Cancer Research Together

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