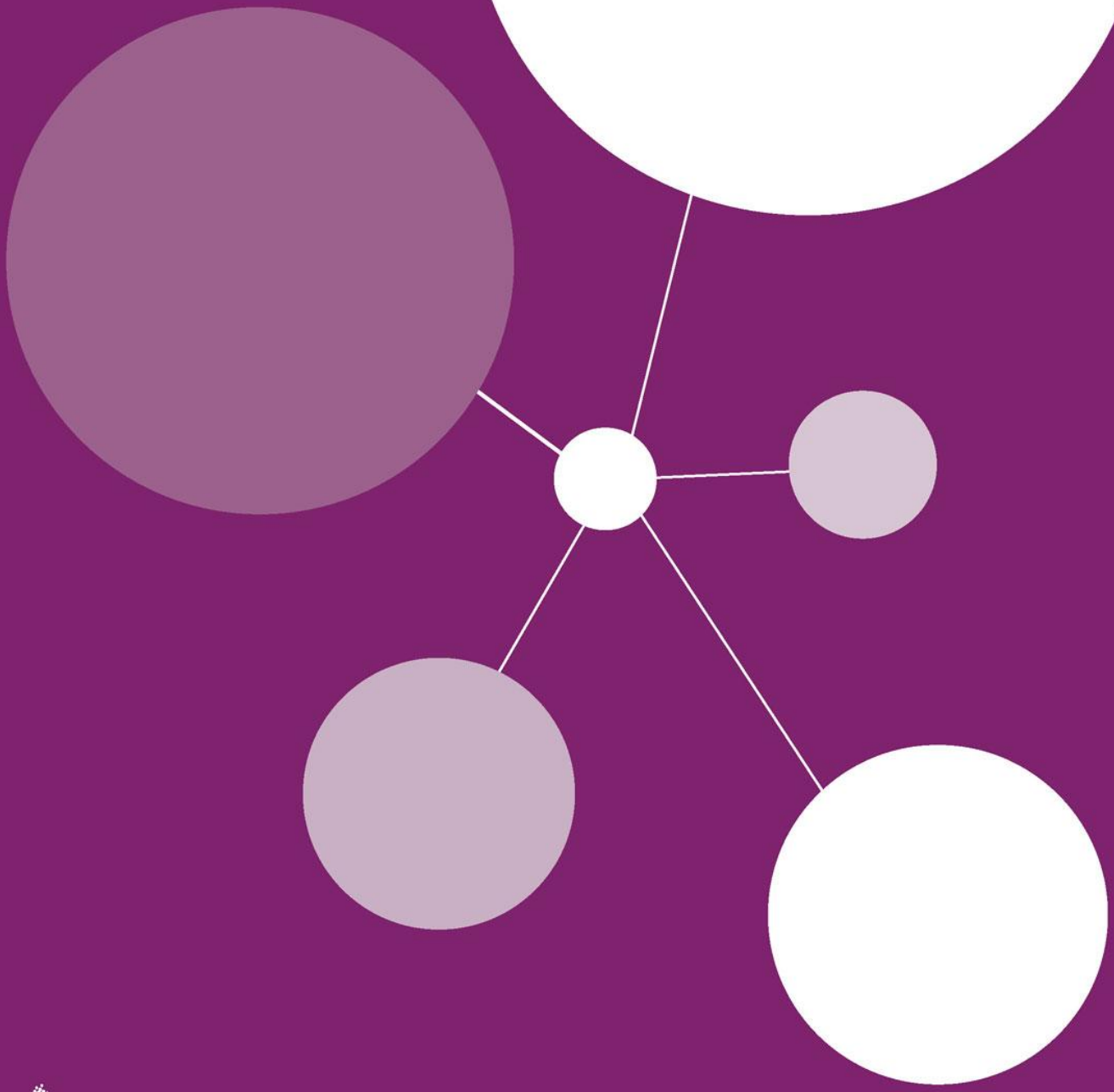
NCRI
National
Cancer
Research
Institute

NCRI Testis Cancer Clinical Studies Group

Annual Report 2014/2015



Partners in cancer research

NCRI Testis Cancer CSG Annual Report 2014/15

1. Executive Summary (including top 3 achievements in the year)

The Testis CSG represents a single uncommon cancer site with approximately 2000 new patients registered per year within the UK. The vast majority of cancers are germ-cell tumours (GCTs). Germ Cell tumours of the testis are increasing in frequency with the life-time risk in men being approximately 1:200 having been 1:400 20 years ago. There is increasing interest in exploring the environmental causes of testicular GCTs as well as the definite genetic predispositions.

The CSG, and its predecessor, the MRC Testis Clinical Trials Group, have been international leaders in the development of studies in GCTs that have defined and, often, redefined international standards of care for this disease over the last 30 years.

Our recently closed studies in early stage disease promises to reset again the standards of care for stage I seminoma and non-seminoma, and our current international collaborations in poor prognosis and relapsed disease may also take us forward for the first time in over 10 years in these patient groups.

Developing studies in advanced disease is challenging for the group since the patient numbers, particularly in poorer prognosis groups and refractory/relapsed patients are small. Additionally there is little support from the pharmaceutical industry for studies in our patients, since the potential for incremental improvements in outcome are small, there are few patients in whom to recoup drug developments costs and much of the focus in developing treatment strategies in testis cancer relates to issues of survivorship, late toxicities and understanding of basic biology and prognostic factors.

In the last year we have achieved international funding for the first time for a global study in relapsed patients, we have international agreement for the development of a poor and intermediate study and have advanced plans for an innovative first-line UK-based study in good prognosis patients.

The 3 main achievements of the Testis CSG in the last year are:

- Completion of recruitment to the TE24 study in Stage I seminoma. This is the largest ever prospective study in surveillance of stage I seminoma and the first randomised study in this patient population. Its outcomes will have applicability for imaging in other cancers.

- Completion of recruitment to the 111 study in stage I non-seminoma. This study will influence practice in the UK and if positive will bring health economic benefits as well as clinical benefits in this important group of cured young patients.
- Funding of the Accelerated BEP study in Poor Prognosis NSGCT and the TIGER study in relapsed disease, both of which representing major achievements in global cooperation.

2. Structure of the Group

The current structure of the CSG, we believe, represents an appropriate balance of members with the skills to take forward our current portfolio and develop new initiatives in line with our aims and objectives. We have a multi-disciplinary structure comprising clinical and medical oncologists, pathologist and translational scientists, nursing expertise, radiology and patient representatives.

In the last year we have been very pleased to recruit two new consumers, a new paediatric oncologist with an international standing as a basic and translational scientist, and, for the first time in some years, a new and very senior surgical representative with close links to BASO. We have also recruited two oncology trainees to the group this year and will continue to offer these placements to young investigators.

We no longer have a statistician as member, however, we are maintaining strong links with statisticians in a number of trials units, although access to a trials unit with QOL and survivorship interests remains a challenge.

We have just had agreement to co-opt our previous paediatric oncology member Dr Sara Stoneham onto the group so that we maintain joint membership with the Malignant germ Cell Tumour International consortium of investigators (MaGIC).

Our subgroup has recruited a health economist which will directly address some of the strategic needs identified within our progress review.

The CSG Chair, Professor Joffe, is due to stand down later this year after two terms in post.

3. CSG & Subgroup strategies

Main CSG

Generic Strategy:

- Maintaining membership of our main group and subgroup that will deliver our strategy
- Developing a system of time-limited task and finish groups to address specific studies or other needs.
- Co-opt additional expertise where required and work with cross-cutting groups and other CSGs to achieve our aims.
- Arrange a strategic time out to develop our strategic plans.
- Work towards the broader strategic needs identified in the Strategic Aims Document (see Appendix 2A)

Quality of Life (QoL) Subgroup (Chair, Dr Danish Mazhar)

The Quality of Life (QoL) Subgroup of the Testis CSG has a remit to provide an oversight on studies involving testis cancer patients (current and past) which focus on survivorship, treatment toxicities and quality of life issues. The further development of the QoL portfolio of studies is a key theme within the Testis CSG's overall strategy. The Subgroup has a multidisciplinary membership and has developed colloborative links other CSGs and subgroups (including the Psychosocial CSG and its survivorship subgroup). Danish Mazhar has been Chair of the subgroup since July 2011. In the last year, Ed Wilson who is a Health Economist based in the University of East Anglia has joined the subgroup.

Top achievements in the year include:

- Completion of recruitment to the TRYMS trial
- The leading role played by members of the subgroup in the development of quality of life sub-studies to run alongside large international collaborative studies in germ cell tumour patients (e.g. P3BEP and the MaGIC consortium study).

The Subgroup strategy for the next year can be seen in Appendix 2B.

4. Task groups/Working parties

We have attempted to follow this method of working over the last year and it has not been successful. The study concepts and ideas that have been discussed at CSG meetings have often not been followed up on, and as a result progress in developing new studies has been slow. Going forward, developing working groups to take forward specific projects with clear targets will be essential. This is recognised as an essential part of our developmental strategy.

5. Patient recruitment summary for last 5 years

For the last 5 years we have continued to recruit a very high proportion of our incident and prevalent patient populations into studies. We have a low incidence rate but high prevalence rates in so much as most of our patients are cured.

In a patient group with small numbers opening and closing of individual studies has huge impact on recruitment numbers to interventional studies, thus our numbers have fallen in the last year with completion of successful recruitment to TE24 and 111. These numbers will improve again with development of new studies. The UK Genetics of Testicular Cancer Study continues to recruit well though, and we have successfully completed recruitment to two important Quality of Life Studies, TRYMMS and RESTART.

We have a very high proportion of our incident populations but there are opportunities to develop studies that will utilise more of our surviving patients, their relatives and controls. Our aim of developing studies with the NCIN will support this.

In the Testis CSG portfolio, 3 trials closed to recruitment and 0 opened.

Table 1 Summary of patient recruitment by RCT/Non-RCT

Year	All subjects		Cancer patients only		% of cancer patients relative to incidence	
	Non-RCT	RCT	Non-RCT	RCT	Non-RCT	RCT
2010/2011	849	106	804	106	42.3	5.6
2011/2012	847	121	844	121	44.4	6.4

Table 2 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
2012/2013	1342	277	1335	259	59.8	12.4
2013/2014	1639	290	1495	290	67.0	13.0
2014/2015	1349	140	1269	140	56.9	6.3

6. Links to other CSGs, international groups and network subspecialty leads

We have representation on our group from the paediatric and TYA communities in the membership of Dr Stoneham in our main CSG and also Dr Dan Stark on our QoL Subgroup.

Dr Huddart is a member of the Bladder CSG and CTRad and also the NCIN Urology Group. Drs Stoneham, Dr Stark and Dr Murray are members of the International MaGIC consortium.

Drs Huddart and Mazhar have represented the group in the international collaborations supporting the TIGER study of salvage therapy in relapsed patients and the Accelerated BEP (P3BEP) study in first-line therapy of poor prognosis patients. Both of these studies have required considerable negotiation with international collaborators, all of whom have had to make compromises with respect to their own preferred agendas for investigation. The TIGER study has also had to overcome organisational and regulatory barriers regarding the use of high dose chemotherapy, and also challenges in terms of pan-European sponsorship.

Dr Huddart and Professor Joffe have been members of the European Germ Cell Cancer Collaborative Group since its formation.

We have a need to develop closer working with network subspecialty leads with the Gynae CSG. For the Urological CSGs interaction with subspecialty leads is challenging since there is just one lead for all of urology in each network. They cannot, therefore, be fully cognisant of issues for each CSG as they are unlikely to have in-depth clinical knowledge of all urological cancers, particularly testis cancer, which is increasingly managed in isolation from other urological malignancies.

In gynaecological cancer there is a pressing need for someone to take a lead in the investigation of female germ-cell tumours and stromal-cell tumours of the ovary (dysgerminomas). Our CSG would wish to develop that leadership function.

In addition to the Subgroup's interaction with other CSGs and cross-cutting groups, our CSG and subgroup member, Mrs Sue Brand, has been instrumental in the establishment of UKONS Germ-cell Forum, a group of specialist nurses working within the umbrella of the UK Oncology Nurses Society, to develop collaboration in management, audit and research in testicular cancer and germ-cell tumours.

7. Funding applications in last year

Table 3 Funding submissions in the reporting year

Clinical Trials Advisory and Awards Committee (CTAAC)			
Study	**Application type**	**CI**	**Outcome**
July 2014			
P3BEP: Phase 3 Accelerated BEP trial: A randomised phase 3 trial of accelerated versus standard BEP chemotherapy for patients with intermediate and poor-risk metastatic germ cell tumours	Full Application	Dr Danish Mazhar	Not funded
November 2014			
None			
March 2015			
P3BEP: Phase 3 Accelerated BEP trial: A randomised phase 3 trial of accelerated versus standard BEP chemotherapy for patients with intermediate and poor-risk metastatic germ cell tumours	Full Application *Appeal*	Dr Danish Mazhar	Funded

8. Collaborative partnership studies with industry

As indicated in the introduction, testis cancer has not been seen as an interesting tumour type for investment by the pharmaceutical industry. We have actively participated in the industry/NCRI workshops but have not been able to interest the pharmaceutical collaborators in supporting any studies within our patient population.

One study was put forward for consideration by Novartis (international, not UK) for an investigational agent in teratoma (differentiated or mature teratoma [TD]) in advanced disease. We felt that the study population proposed was too small even on a national basis and made what we thought were constructive recommendations about the study design, extending it to the much commoner situation of resectable TD following chemotherapy, with enthusiasm for participating in a modified study. The sponsors chose to go ahead with the original design in one UK centre only, which to the best of our knowledge has not been able to open.

9. Impact of CSG activities

The current standards of care in the UK, particularly in early stage disease, are based on studies completed by the group and the previous MRC Testicular Cancer Group. The TE19 study defined the role of Carboplatin in stage I seminoma, which has now been taken up internationally to a very large scale, replacing adjuvant radiotherapy in stage I seminoma.

Undertaking the TE24 study has promoted the use of surveillance in stage I seminoma and we have published audit National work demonstrating this.

If TE24 achieves its main outcomes then it will demonstrate the safest schedules and modalities for surveillance in stage I seminoma and will influence practice internationally. It will also have applicability to imaging of the retroperitoneum in other malignancies.

111 has the potential to influence National and international practice in stage I NSGCT.

The Chair of the CSG has undertaken a number of funding reviews and provided report to the following:

- CTAAC
- HTA
- French National Cancer Institute

10. Consumer involvement

The Group has struggled to maintain consumer involvement over the last two years due to outside pressures on our previous members. We are delighted that we have been able to welcome our two new consumers to the group last year. They have already made significant contributions to discussions at CSG meetings, and will be engaging also in the work of the QoL Subgroup. We look forward to supporting their participation in all of our activities.

11. Open meetings/annual trials days/strategy days

The Testis CSG has collaborated with the other urological CSGs over the last 4 years in the Urological Trials Meeting where we have given overviews of our portfolio and contributed to the development of the scientific program of the meeting.

The feedback has been increasingly positive, as we have gradually changed the format of the meeting in response to feedback, making it both more focussed and more academic, which has resulted on an even higher approval rating.

12. Progress towards achieving the CSG's 3 year strategy

In our last annual report we outlined our 3 year strategy including the following three main themes:

- Development of our translational study portfolio
- Development of our survivorship and QOL portfolio
- Development of viable studies in poor prognosis and relapsed patient group through international collaboration

We believe that we have made excellent progress towards the second and third of those aims, however, following our Progress Review last year we have a need to redefine our strategy. The change of CSG Chair expected later this year will provide a new opportunity to take this forward.

13. Priorities and challenges for the forthcoming year

The 3 Priorities for the forthcoming years are also the main challenges for the Group:

- To ensure a smooth hand-over between the outgoing and new Chair and the development of a coherent strategic plan for the next 3 years for the group

- To ensure the successful recruitment to our existing funded studies in poor prognosis and relapsed patients and to ensure that our other planned studies are developed quickly so that they can be funded and opened by the time of the next annual report.
- Address the challenges of developing new areas of work outlined in our progress review and those arising from the changing demographics of testicular cancer, such as in health service research, population research and environmental causes of testicular cancer, female germ cell tumours and non-germ-cell tumours.

14. Concluding remarks

As outlined in our last annual report, the Testis CSG has been an active and dynamic group that aims to continue to deliver and develop practice-changing clinical studies of international relevance. Although small, we believe that we punch above our weight both in comparison with other clinical groups within the UK and within the international testicular cancer community. Although we have successfully opened and completed a number of studies, the responsibility for this has fallen on a relatively small number of members. This has led to a weakness in that we have been unable to take forward projects in different areas at the same time, leading to gaps in our portfolio. Going forward we will need to change the way that we plan and delegate our work.

There are almost unique challenges in testis cancer because of the very high cure rate that is already seen in most of our patient populations and in the small numbers of patients within many of our patient groups. However, these also provide opportunities for new areas of work, particularly in survivorship and understanding of basic biology and aetiology of testicular malignancy.

Incremental improvements in outcomes are challenging both clinically and in terms of funding opportunities since our studies cost as much as many in larger populations of poorer prognosis patients and take longer to recruit and to report.

The focus will appropriately remain on survivorship issues as well as in understanding of biology that will allow us to concentrate effort on developing novel therapies for those patients who may not be cured through current treatment strategies and protect those who will be cured from the risks of unnecessary treatment, prolonged follow-up and over-investigation.

15. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies
A – Main CSG Strategy
B – Quality of Life (QoL) Subgroup Strategy

Appendix 3 - Portfolio Maps

Appendix 4 - Publications in previous year

Appendix 5 - Major international presentations in previous year

Appendix 6 – Strengths & Weaknesses from the Testis CSG 2014 Progress Review

Professor Johnathan Joffe (Testis CSG Chair)

Appendix 1

Membership of the Testis CSG

Name	Specialism	Location
Dr Rob Huddart	Clinical Oncologist	London
Mr Stephen Francis Thomas	Consumer	Cardiff
Mr Vincent Wolverson	Consumer	Norwich
Dr Linda Evans	Medical Oncologist	Sheffield
Professor Johnathan Joffe (Chair)	Medical Oncologist	Huddersfield
Dr Satish Kumar	Medical Oncologist	Cardiff
Dr Danish Mazhar	Medical Oncologist	Cambridge
Dr Matthew Murray	Paediatric Oncologist and Translational Scientist	Cambridge
Dr Andrew Protheroe	Medical Oncologist	Oxford
Dr Jonathan Shamash	Medical Oncologist	London
Professor Nick Stuart	Medical Oncologist	Gwynedd
Dr Matthew Wheater	Medical Oncologist	Southampton
Dr Jeff White	Medical Oncologist	Glasgow
Dr Benjamin Fairfax*	Medical Oncology Trainee	Oxford
Dr Hayley McKenzie*	Medical Oncology Trainee	Southampton
Mrs Sue Brand	Nurse	Bristol
Dr Clare Verrill	Pathologist	Oxford
Mr Matthew Hayes	Surgeon	Hampshire

* denotes trainee

Membership of the Subgroups

Quality of Life (QoL) Subgroup		
Name	**Specialism**	**Location**
Dr Rob Huddart	Clinical Oncologist	London
Mr James Ashton	Consumer	
Dr Danish Mazhar (Chair)	Medical Oncologist	Cambridge
Dr Dan Stark	Medical Oncologist	Leeds
Dr Jeff White	Medical Oncologist	Glasgow
Mrs Sue Brand	Nurse	Bristol
Ms Nicola Thomson	Nurse	Glasgow
Dr Sara Stoneham	Paediatric Oncologist	London

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

In taking forward the successes and challenges identified at the 2014 Progress Review (detailed in Appendix 6), the CSG recognises the need for the following generic areas for strategic development:

- Maintaining membership of our main group and subgroup that will deliver our strategy
- Developing a system of time-limited task and finish groups to address specific studies or other needs.
- Co-opt additional expertise where required and work with cross-cutting groups and other CSGs to achieve our aims.
- Arrange a strategic time-out for the group to develop firm objectives

Suggested aims for 2014 – 2015:

- Identify a small group of members to work with past Chief investigators to ensure all outstanding results are published
- Develop a Task and Finish Group to develop a strategy for translational work
- Discuss female germ cell tumours with the Gynaecological CSG and consider developing a joint sub-group or other mechanism for closer collaboration
- Establish an on-going collaboration with the NCIN to investigate population trends in germ-cell and rare tumour types and support work in genetic and environmental studies
- Continue to work towards developing studies in rare GCT groups and non-GCT testicular cancers through international collaboration and the IRCI.

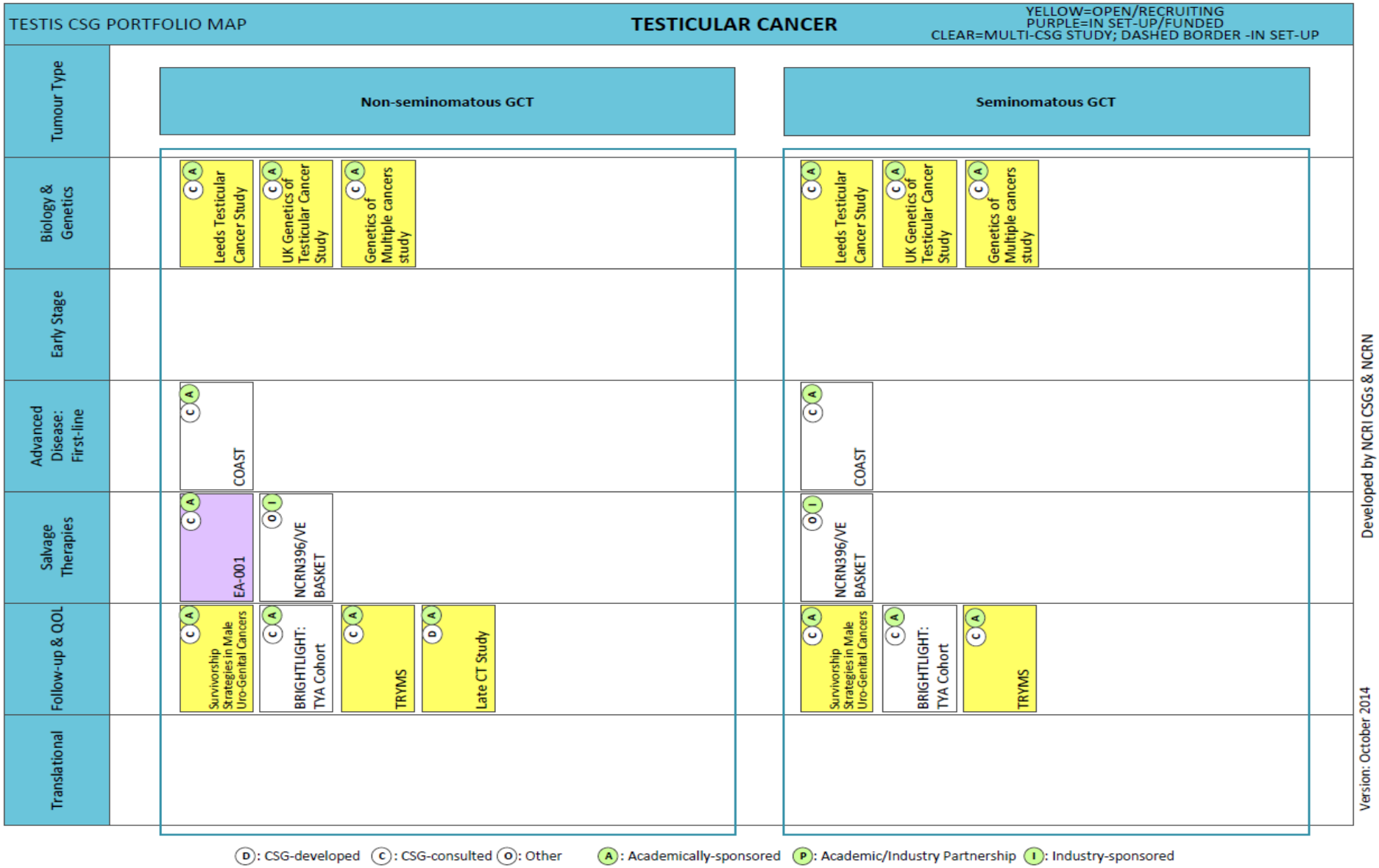
B – Quality of Life (QoL0 Subgroup Strategy

Aims for the next year include:

- To report on an on-going survey directed at Specialist Teams treating germ cell tumours regarding the provision for late effects monitoring and attitudes towards follow-up in testis cancer survivors. The subgroup has collaborated with the newly formed UKONS Germ Cell Forum to gain the views of testis cancer specialist nurses
- To develop a study examining attitudes of testis cancer survivors towards follow-up. Patient focus groups are being arranged in 3 locations (in Bristol, Oxford and Cambridge) to establish the issues relevant to patients. The information gathered at these focus groups will potentially inform the design of a study concept examining alternative forms of patient follow-up
- To develop a design for a randomised Phase II/III trial following on from the RESTART pilot study and submit for funding
- A further aim will be to engage with one or more trials units with experience of and interest in survivorship and QOL studies. This may also help to address the challenges of grant application in studies in these areas

Appendix 3

Portfolio maps



Appendix 4

Publications in the reporting year

UK testis genetics protocol

Litchfield K, Summersgill B, Yost S, Sultana R, Labreche K, Dudakia D, Renwick A, Seal S, Al-Saadi R, Broderick P, Turner NC, Houlston RS, Huddart R, Shipley J, Turnbull C. Whole-exome sequencing reveals the mutational spectrum of testicular germ cell tumours. *Nat Commun*. 2015 Jan 22;6:5973. doi: 10.1038/ncomms6973. PubMed PMID: 25609015; PubMed Central PMCID: PMC4338546.

Huddart R. New insight into the aetiology of testicular germ cell tumours. *Eur Urol*. 2015 Apr;67(4):702-3. doi: 10.1016/j.eururo.2014.11.032. Epub 2014 Dec 9. PubMed PMID: 25497430.

Litchfield K, Sultana R, Renwick A, Dudakia D, Seal S, Ramsay E, Powell S, Elliott A, Warren-Perry M, Eeles R, Peto J, Kote-Jarai Z, Muir K, Nsengimana J; UKTCC, Stratton MR, Easton DF, Bishop DT, Huddart RA, Rahman N, Turnbull C; UKTCC. Multi-stage genome-wide association study identifies new susceptibility locus for testicular germ cell tumour on chromosome 3q25. *Hum Mol Genet*. 2015 Feb 15;24(4):1169-76. doi: 10.1093/hmg/ddu511. Epub 2014 Oct 3. PubMed PMID: 25281660; PubMed Central PMCID: PMC4375409.

TE23 trial

Huddart RA, Gabe R, Cafferty FH, Pollock P, White JD, Shamash J, Cullen MH, Stenning SP; TE23 Trial Management Group and Collaborators and the National Cancer Research Institute Testis Cancer Clinical Studies Group. A Randomised Phase 2 Trial of Intensive Induction Chemotherapy (CBOP/BEP) and Standard BEP in Poor-prognosis Germ Cell Tumours (MRC TE23, CRUK 05/014, ISRCTN 53643604). *Eur Urol*. 2015 Mar;67(3):534-43. doi: 10.1016/j.eururo.2014.06.034. Epub 2014 Jul 4. PubMed PMID: 25001888.

Appendix 5

Major international presentations in the reporting year

Gem-TIP trial

Wheater, MJ., Huddart, RA., White, JD., Rustin, GJS., Hennig, IM., Cozens, K., Bowers, M., Cross, N., Mead, G. Salvage chemotherapy for relapsed germ cell tumors: A phase II trial of gemcitabine, paclitaxel, ifosfamide, and cisplatin (Gem-TIP). *J Clin Oncol* 32:5s, 2014 (suppl; abstr 4560)' – ASCO 2014

Appendix 6

Strengths & weaknesses from the 2014 Progress Review

Strengths:

- Good international reputation and international leadership
- Successes in delivering internationally practise changing trials
- Good number of publications in high profile journals
- Number of trials about to mature and a number of good ideas for future trials
- Good links with the paediatric, TYA and international communities through their germ cell work
- Good links with POS CSG through their work on survivorship

Issues for the CSG to consider:

- Giving urgent and due consideration as to how it maintains momentum, drive things forward and continues to do great work
- How to reduce focussing around one or two individuals and that little happens between CSG meetings
- Tasking new members with specific activities/projects e.g. writing up trial results, developing a specific trial, the idea for which may have been originated by someone else, and be expected to report back at regular teleconferences, as a tool to move things forward
- Establishing of a working party to look at follow up with clear focus, remit and timescales
- Opportunities for health services research and whether individuals with this expertise need to be co-opted onto the Group
- Filling gaps in their membership such as translational and basic research, pathology and statistics
- Exploring with the CSGs Secretariat how best consumers can be recruited and retained
- Maximising the synergy between the two genetics study in their portfolio and consider international collaboration on late effects