SARveillance Trial

A multi-centre, international, parallel-arm, (stratified) randomised controlled trial of high versus lower intensity radiological surveillance following primary resection of retroperitoneal, abdominal and pelvic soft tissue sarcoma

TARPSWG Virtual Meeting – 17th July 2020

Overall objective

- Surveillance post retroperitoneal, abdominal and pelvic soft tissue sarcoma resection is highly resource intensive
  - Radiological resource
  - Clinical / nursing / administrative
  - Tumour board / MDT time for centralised review
  - Disruptive for patients
  - Anxiety inducing for some patients and reassuring for others
  - No clear evidence to support surveillance imaging or at least the intensity – although very likely to be of some benefit
  - Does it influence overall survival or QoL?
  - Here to stay – clear precedence set for surveillance imaging in specialist sarcoma centres across the world

- To improve the evidence base for surveillance of resected primary sarcomas of the retroperitoneum, abdomen and pelvis

  - Defined by outcomes that are important to our patients
    - Improve overall survival
    - Improve quality of life / minimise anxiety and depression

  - And to hospitals and health systems
    - Health resource usage
    - Cost-effectiveness

REVIEW Open Access

UK guidelines for the management of soft tissue sarcomas

Adam Dangoor[1*], Beatrice Seddon[2], Craig Gerrand[3], Robert Grimer[4], Jeremy Whelan[2] and Ian Judson[5]

ESMO

Annals of Oncology 0 (Supplement 0): iv1–iv17, 2018
doi:10.1093/annonc/mdy096

CLINICAL PRACTICE GUIDELINES

Soft tissue and visceral sarcomas: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†

P. G. Casali[1], N. Abecassis[2], S. Bauer[3], R. Biagini[4], S. Bielack[5], S. Bonvalot[6], I. Boukovinas[7], J. V. M. G. Bovee[8], T. Brodowicz[9], J. M. Broto[10], A. Buonadonna[11], E. De Álava[10], A. P. Dei Tos[12], X. G. Del Muro[13], P. Dileo[14], M. Eriksson[15], A. Fedenko[16], V. Ferraresi[17], A. Ferrari[18], S. Ferrari[19], A. M. Frezza[1], S. Gasperoni[20], H. Gelderblom[21], T. Gil[22], G. Grignani[23], A. Gronchi[1], A. Hannu[24], B. Hassan[25], P. Hohenberger[26], R. Issels[27], H. Joensuu[28], R. L. Jones[29], I. Judson[30], P. Jutte[31], S. Kaal[32], B. Kasper[26], K. Kopeckova[33], D. A. Krákorová[34], A. Le Cesne[35], I. Lugowska[36], O. Merimsky[37], M. Montemurro[38], M. A. Pantaleo[39], R. Piana[40], P. Picci[19], S. Piperno-Neumann[6], A. L. Pousa[41], P. Reichardt[42], M. H. Robinson[43], P. Rutkovski[36], A. A. Safwat[44], P. Schöffski[45], S. Sleijfer[46], S. Stacchiotti[47], K. Sundby Hall[48], M. Unk[49], F. Van Coevorden[50], W. Van der Graaf[29], J. Whelan[51], E. Wardelmann[52], O. Zaikova[53] & J. Y. Blay[54], on behalf of the ESMO Guidelines Committee and EURACAN*

Follow-up

There are few published data to indicate the optimal routine follow-up policy of surgically treated patients with localised disease [54].

The malignancy grade affects the likelihood and speed at which relapses may occur. The risk assessment, based on tumour grade, tumour size and tumour site, therefore helps in choosing a routine follow-up policy. High-risk patients generally relapse within 2–3 years, whereas low-risk patients may relapse later, although it is less likely. Relapses most often occur to the lungs. Early detection of local or metastatic recurrence to the lungs may have prognostic implications, and lung metastases are asymptomatic at a stage in which they are suitable for surgery. Therefore, routine follow-up may focus on these sites. Although the use of MRI to detect local relapse and CT to scan for lung metastases is likely to pick up recurrences earlier, it has not been demonstrated that this is beneficial, or cost effective, compared with the clinical assessment of the primary site and regular chest X-rays.

While prospective studies are needed, a practical approach in place at several institutions is as follows: surgically-treated intermediate-/high-grade patients may be followed every 3–4 months in the first 2–3 years, then twice a year up to the fifth year, and once a year thereafter; low-grade sarcoma patients may be followed for local relapse every 4–6 months, with chest X-rays or CT scan at longer intervals in the first 3–5 years, then annually.

Prognosis and follow-up for primary disease

1. It is recommended that patients with intermediate or high-grade sarcoma are followed up every 3–4 months for the first 2–3 years, then twice a year for up to 5 years, and annually thereafter for a total of 8–10 years.
2. Patients with low-grade sarcoma should be followed up every 4–6 months for 3–5 years, then annually.
3. Standard follow-up practice should consist of:
   a. Review of any new symptoms reported by the patient,
   b. Clinical examination to focus on local recurrence, with imaging follow-up where indicated by clinical suspicion,
   c. Routine chest X-ray to exclude pulmonary metastases.
   d. Monitoring for late-effects of treatment.
4. New models of follow-up warrant further investigation.

Single centre data – University Hospitals Birmingham – Queen Elizabeth Hospital

- Retrospective cohort study
- Primary resection of soft tissue sarcoma arising in the retroperitoneum, abdomen or pelvis
- Intensity of follow-up regimes were categorized as ESMO compliant (intensive), or non-ESMO compliant (less intensive)
- Primary outcome measure: overall survival
- Secondary outcome measures: disease-free survival, reoperation rate.
- Analyses were stratified by high (grade 2 or 3) or low (grade 1) tumour grade

Single centre retrospective data

- 168 patients
  - High/intermediate-grade: 67.1%, low-grade: 32.9%
- 40.0% of patients had ESMO-compliant radiological follow-up
  - High/intermediate-grade: 25.7%, low-grade: 66.7%

Univariable analysis

High/intermediate-grade tumours: ESMO compliance reduced DFS, no impact on overall survival OS. Trend towards increased reoperation rate with ESMO-compliant follow-up

Low-grade tumours: ESMO compliance significantly reduced DFS, but without effecting OS

Multivariable analysis

High/intermediate-grade tumours: ESMO compliance follow-up was associated with reduced OS and no difference in DFS

Low-grade tumours: no association between overall ESMO compliance and OS or DFS

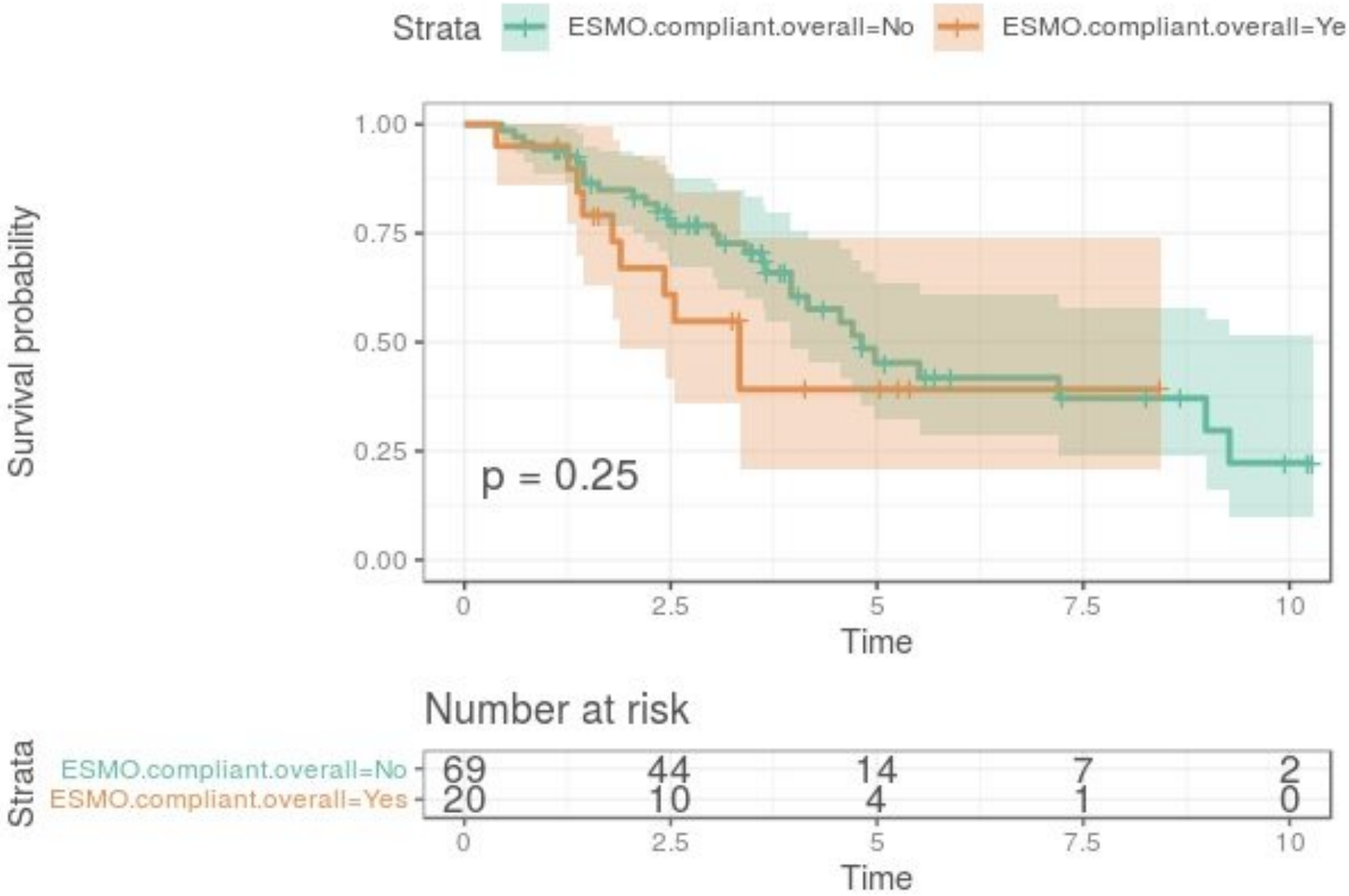


Figure. Kaplan-Meier plot showing differences in overall survival between high-grade tumours with ESMO-compliant (intensive) and non ESMO-compliant (less intensive) radiological follow-up

Evidence from other solid organ tumours

Cochrane Systematic Review

Follow up strategies for patients treated with non-metastatic colorectal cancer

Jeffery M, Hickey B, Hider P, See A

5403 patients, 15 RCTs

Comparing different follow up strategies for patients with non- metastatic colorectal cancer treated with curative intent

Overall survival (OS) – No statistical effect with intensive follow up, HR 0.90 (p=0.45)

Disease specific survival – No difference with intensive follow up, HR 0.93 (p=0.45)

Intensive follow up did not appear to affect quality of life, anxiety or depression

The FACS Randomized Clinical Trial
Effect of 3 to 5 Years of Scheduled CEA and CT Follow-up to Detect Recurrence of Colorectal Cancer
Primrose J, Perera R, Gray A et al

Methods: 39 UK centres, 1202 participants who had undergone curative treatment for primary colorectal cancer

Assigned to CEA, CT, CT + CEA or minimum FU

Primary outcome – Surgical treatment of recurrence with curative intent

Secondary outcomes – OS, DFS

Results - OS and DFS not significantly different when comparing intensive vs minimum follow up

ESMO Guidelines
Renal Cell Carcinoma

B. Escudier, C.Porta, M. Schmidinger, N.Rioux-Leclerq, A. Bex, V. Khoo, V. Gruenwald, S. Gillessen and A. Horwich

Limited evidence base, no RCTs

No evidence that follow-up protocol influences the outcome in early or advanced RCC.

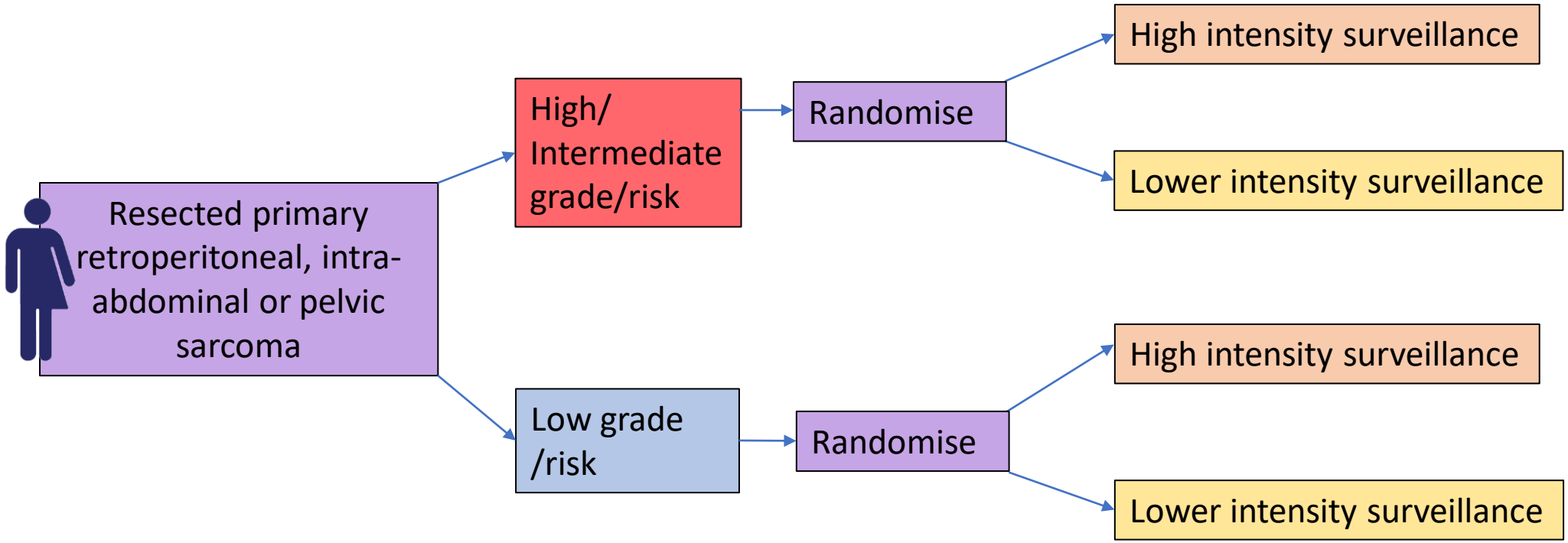
Recommendation (expert opinion) - CT scans every 3–6 months in high-risk patients for the first 2 years

Annual CT scan probably sufficient in low risk patients

Long term follow-up carried out by some institutions, however benefit has never been demonstrated (1)

(1) Dabestani S, Beisland C, Stewart GD et al. Long-term outcomes of follow-up for initially localised clear cell renal cell carcinoma: RECUR database analysis. Eur Urol Focus 2018

SARveillance Trial Schematic



Trial Development Group – 30th Jan 2020 Ottawa, Canada

Attendees

Surgical oncologists

Samuel Ford **(SF)** (University Hospitals Birmingham, Birmingham, UK)

James Glasbey **(JG)** (University Hospitals Birmingham, Birmingham, UK)

Hannah Tattersall **(HT)** (University Hospitals Birmingham, Birmingham, UK)

Carolyn Nessim **(CM)** (Ottawa Hospital, Ottawa, Canada)

Emily Keung **(EK)** (MD Anderson Cancer Centre, Texas, USA)

Sinziana Dumitra **(SD)** (McGill University, Montreal, Canada)

Chandrajit Raut **(CR)** (via videoconference) (Brigham and women's Hospital, Boston, USA)

Dario Callegaro **(DC)** (via videoconference) (IRCSS, Milan, Italy)

Marco Fiore **(MF)** (via videoconference) (IRCSS, Milan, Italy)

Oncologists

Mark Clement **(MC)** (Ottawa Hospital, Ottawa, Canada)

Patient representative

Bryde Fresque **(BF)** (Patient Representative, Ottawa, Canada)

Trial statisticians and epidemiologists

Tim Ramsay **(TR)** (Ottawa Hospital, Ottawa, Canada)

Apologies

Surgical oncologists

Dirk Strauss (Royal Marsden Hospital, London, UK)

Alessandro Gronchi (IRCSS, Milan, Italy)

Winan van Houdt (Netherland Cancer Institute, Amsterdam, the Netherlands)

David Gyorki (Peter MacCallum Cancer Centre, Melbourne, Australia)

Christina Roland (MD Anderson Cancer Center, Houston, Texas, USA)

Statistician

James Hodson (University Hospitals Birmingham, Birmingham, UK)

Sarcoma UK
The bone & soft tissue cancer charity

Key objectives – Trial Design Group meeting Ottawa Jan 2020

- Finalise inclusion and exclusion criteria for trial entry (**Patients**)
- Review variability in current follow-up protocols & agree acceptable limits for high- and lower-intensity surveillance regimes (**Intervention/Comparator**)
- Determine which primary & secondary outcome(s) should be evaluated, and are feasible within sample size constraints (**Outcomes**)
- Agree on overall design schema for the proposed trial (including any **stratification**, method and timing of randomisation, feasibility/pilot data)
- Agree a strategy for identifying and obtaining major competitive external **funding**

Inclusion/exclusion criteria

Inclusion criteria

- Adult patients (greater than 18 years)
- Primary resection
- Histologically confirmed retroperitoneal, intraabdominal or pelvic soft tissue sarcoma
- R0/R1 resection
- +/- neoadjuvant treatment

Exclusion criteria

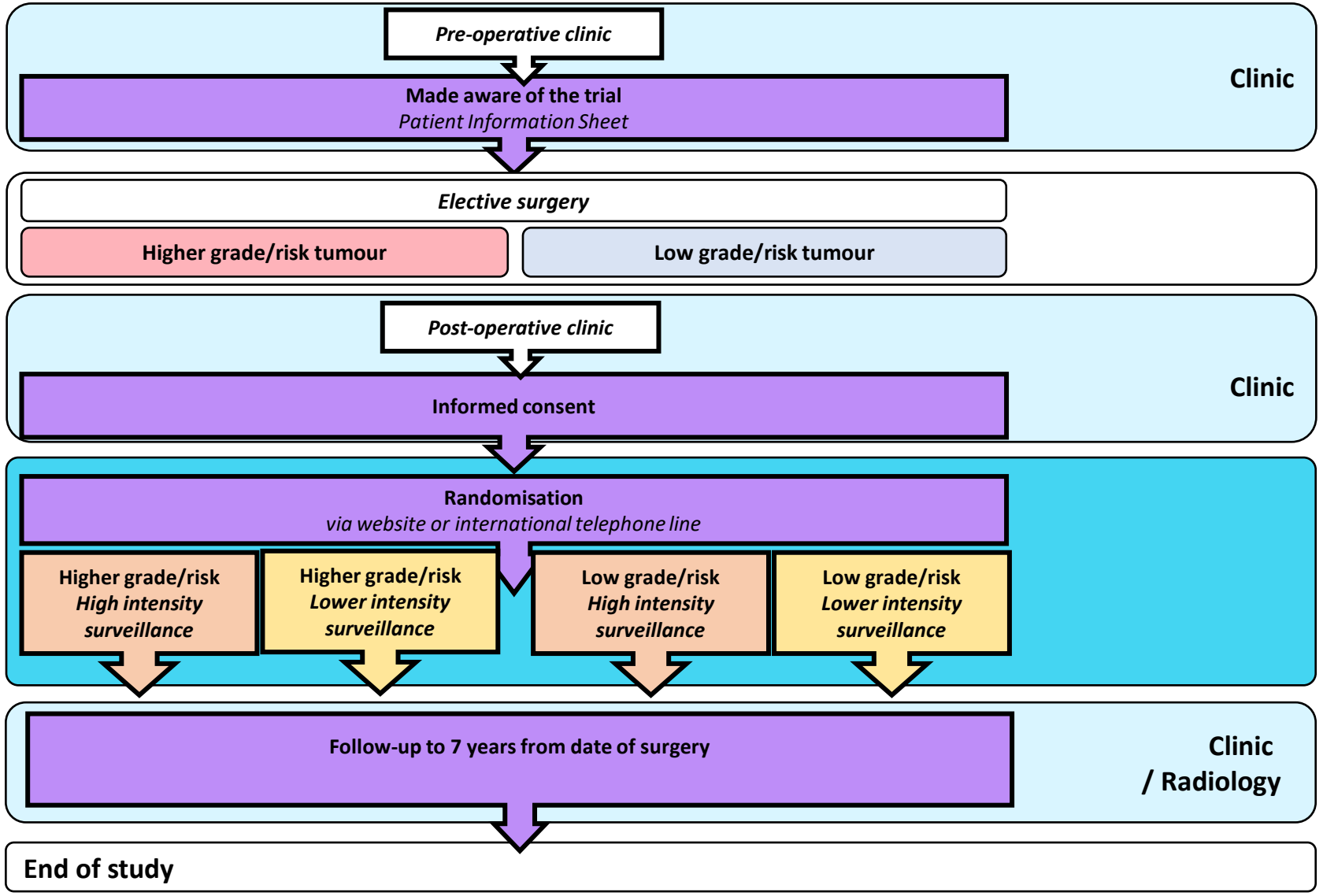
- Metastatic disease at time of randomisation
- Reoperation for recurrent soft tissue sarcoma
- Re-resection following previous inadequate surgery
- R2 resection
- Uterine sarcomas, extraskeletal Ewing's Sarcoma, Gastrointestinal stromal tumour (GIST), rhabdomyosarcomas, primitive neuroectodermal tumour (PNET) or other small round blue cells sarcoma, PEComa, osteosarcoma, chondrosarcoma, fibromatosis, epithelial tumours, multifocal disease

Patient pathway

Patient identification, recruitment and timing of randomisation

- Provide all potential trial candidates with an information sheet preoperatively
- Discussion of histology - Tumour Board/MDT based stratification
- Recruited and randomised at first postoperative outpatient appointment (website or international telephone line)
- Commence radiological surveillance (high or lower intensity)
- In the event of recurrence, the trial surveillance protocol would no longer apply as the patient would enter a treatment phase (active or monitoring / best supportive care)
    - PROM/QoL outcome data would cease, data on would OS continued to be collected

Patient pathway



Surveillance intensity - intervention / comparator

Discussion points

- How to define high and lower intensity surveillance
- Acceptability to all stakeholders
  - Patients
  - Clinicians
  - Institutions
- Imaging modality
- Feasibility of co-enrolment (STRASS II)?

Current follow-up protocols: Most intensive

		Y1	Y2	Y3	Y4	Y5	Y5-10
QEHB, Birmingham	High grade (II-III)	6m	6m	1y	1y	1y	Patient/clinician preference
	Low grade (I)	6m	6m	1y	1y	1y	Patient/clinician preference
IRCCS, Milan	High grade (III)	4m	4m	6m	6m	6m	1y
	Low grade (I-II)	6m	6m	6m	6m	6m	1y
Brigham, Boston	**All other/high grade**	**3-4m**	**3-4m**	**6m**	**6m**	**6m**	**1y**
	WDLPS	6m	6m	~6m-1y	~6m-1y	~6m-1y	1y
NCI, Amsterdam	High grade	4m	4m	6m	6m	6m	1y
	Low grade	6m	6m	6m	6m	6m	1y
MD Anderson, Texas	**High grade**	**3m**	**3m**	**6m**	**6m**	**6m**	**1y**
	Low grade	**3-4m**	**3-4m**	**6m**	**6m**	**6m**	**1y**
Peter MacCullum, Sydney	**High grade**	**3-4m**	**3-4m**	**6m**	**6m**	**6m**	**1y**
	Low grade	6m	6m	6m	6m	6m	1y
McGill, Montreal	**High grade**	**3m**	**3m**	**6m**	**6m**	**6m**	**1y**
	Low grade	4m	4m	6m	6m	6m	1y
Ottawa Hospital, Ottawa	DDLPS/LMS	4-6m	4-6m	6m	6m	6m	1y
	WDLPS/SFT	6m	6m	1y	1y	1y	2y

Current follow-up protocols: Least intensive

		Y1	Y2	Y3	Y4	Y5	Y5-10
QEHB, Birmingham	**High grade (II-III)**	**6m**	**6m**	**1y**	**1y**	**1y**	**Patient/clinician preference**
	Low grade (I)	**6m**	**6m**	**1y**	**1y**	**1y**	**Patient/clinician preference**
IRCCS, Milan	High grade (III)	4m	4m	6m	6m	6m	1y
	Low grade (I-II)	6m	6m	6m	6m	6m	1y
Brigham, Boston	All other/high grade	3-4m	3-4m	6m	6m	6m	1y
	WDLPS	6m	6m	~6m-1y	~6m-1y	~6m-1y	1y
NCI, Amsterdam	High grade	4m	4m	6m	6m	6m	1y
	Low grade	6m	6m	6m	6m	6m	1y
MD Anderson, Texas	High grade	3m	3m	6m	6m	6m	1y
	Low grade	3-4m	3-4m	6m	6m	6m	1y
Peter MacCullum, Sydney	High grade	3-4m	3-4m	6m	6m	6m	1y
	Low grade	6m	6m	6m	6m	6m	1y
McGill, Montreal	High grade	3m	3m	6m	6m	6m	1y
	Low grade	4m	4m	6m	6m	6m	1y
Ottawa Hospital, Ottawa	DDLPS/LMS	4-6m	4-6m	6m	6m	6m	1y
	WDLPS/SFT	**6m**	**6m**	**1y**	**1y**	**1y**	**2y**

Surveillance imaging considerations

- CT chest, abdomen and pelvis at each surveillance point
  - Tolerance for MRI if CT contraindicated
- High and low intensity follow up would be the highest and lowest intensity follow up currently performed across the TDG sites
  - Effectively demonstrates equipoise within the 'expert community' - Significant enough variability to see potential change in outcomes, without increasing treatment costs excessively or being unacceptably low intensity
- Not to exceed ESMO guidelines

- co-enrolment with STRASS II is not practical and a request for official amendment of the STRASS II Trial protocol to allow co-enrolment is likely to be rejected

Proposed surveillance intensities

High-intensity radiological surveillance

- High/intermediate grade/risk histology: 3-4 monthly CT scan up to 2-years postoperatively, 6-monthly CT scan from 2-7 years postoperatively
- Low grade/risk histology: 6-monthly CT scan up to 2-years postoperatively, annual CT scan from 2-7 years postoperatively

Lower-intensity radiological surveillance

- High intermediate grade/risk histology: 6-monthly CT scan up to 2-years postoperatively, annual CT scan from 2-7 years postoperatively
- Low grade/risk histology: annual CT scan up to 2-years postoperatively, biennial CT scan from 2-7 years postoperatively

Outcome considerations

OS

- Possible to power high/intermediate grade/risk group for OS with a 20-30% relative risk reduction (350-165 patients per arm)
- Unlikely to be able to power for low grade/risk group

DFS

- Not particularly useful as directly linked to surveillance intensity
- Still worth including as a process measure

Sample size considerations – powering trial for overall survival

Tumour Type	Proportion of Patients	Five Year Mortality	Sample Size per Arm for Relative Risk Reduction of:		
			20%	25%	30%
All	-	40%	600	**375**	**260**
High Grade	66%	53%	**350**	**250**	**165**
Low Grade	33%	18%	1700	1080	750

Statistical power

Sample sizes are the requirements to detect the stated minimal detectable risk reduction in five-year mortality in the high intensity vs. lower intensity radiological surveillance arms.
Calculations are based on a chi-square test of five-year mortality, with 80% power and 5% alpha.
Distributions of patients between risk groups and mortality rates are from previously published data.

Outcome considerations

PROMs/QoL

- Critical to success of trial in terms of funding and impact post-trial completion
- Extremely important for patients and may be more likely to hold significant differences that OS

- Patient numbers required to power trial for PROMs?
- How many surveys per year would be acceptable to patients?
- Appropriate timing to administer surveys?

- No conclusion on the most appropriate PROM to use
  - HRQOL, anxiety and depression, health utility measures
  - No sarcoma specific QOL score exists
  - STRASS I used EORTC OLQ-C30
  - Need to be validated and available in multiple languages

Endpoint conclusions

High/intermediate grade/risk

- Co-primary endpoints – OS and PROM/QOL

Low grade/risk

- Primary endpoint – PROM/QOL
- Secondary endpoint – OS

Recruitment

- 10 year trial = 3 years recruitment + 7 years surveillance
- 9 centres have indicated participation (Canada, USA, Europe and Australia)
- Estimated 650 patients recruited per year based on 60% recruitment rate (2/3 high/intermediate grade/risk and 1/3 low grade/risk)

Stratification

- Long discussion at Trial Development Group meeting in Ottawa
  - Stratification according to tumour grade or predictive nomogram (risk) (Sarculator)

- Current ESMO guidelines stratify according to grade
  - High / intermediate grade (2/3), low grade (1)

Stratification points / statements considered

- Sarculator is a powerful and useful tool for predicting outcome - retrospectively externally validated
- Sarculator would accurately predict DFS and OS on an individual basis – can it be used to risk stratify in to groups?
- Stratification by histological grade may better predict the pattern of disease recurrence (DM / LR) and therefore be more pertinent to surveillance and subsequent management?
- Precedent is currently set from ESMO guidelines to use grade – although makes reference to risk assessment
- “cut-off” values (for DFS/OS derived from Sarculator) for assigning to high/intermediate and low risk strata are not prospectively defined at present
- Use of the sarculator would necessitate follow-up out to 7 years post randomisation – may not be acceptable to funders (10 year study)
- The dynamic-Sarculator could be used within the trial to stratify risk at baseline and then re-calculate risk at each follow up – but would make statistical analysis too complicated
- Significant support in the TDG to prospectively validate Sarculator in the RCT to optimise “cut-off” values for a future study
- Predefined secondary analysis comparing grade versus Sarculator-attributed risk would be feasible, and high impact

- Overall the weight of opinion was in favour of using histological tumour grade for stratification

Patient preference arm?

- Proposed as a way of retaining patients that decline to be randomised but still willing to participate in follow-up during the study in a parallel prospective cohort study
  - Similar to current sarcoma trials (e.g. SACRO)

- This would allow for the patient to select a surveillance intensity arm. This “preference-based cohort study” might yield insightful information for QoL/PROMs and information on motivation for selecting intensive versus less intensive surveillance

- The QoL/PROMs outcome may be affected by including the “preference cohort” within the RCT analysis – therefore, restrict primary analysis to randomised patients and potentially utilise the “preference cohort” for additional statistical additional power if required (e.g. within a Bayesian analysis)

RESAR / Data Sharing Agreements

- “Trial within a registry” – could RESAR be utilised?
  - clear cost efficiency and potentially be attractive for funding streams - ‘efficient’ trial design
- RESAR would need to be augmented with additional data fields for those enrolled in SARveillance
  - Feasible via the RESAR steering group
- Not all participating centres contribute to RESAR
  - Currently a differential in the mix of cases submitted to RESAR (some including pelvic sarcoma and intra-abdominal sarcoma and others only RPS) - could be standardised if there was support for utilising RESAR data base
- RESAR data sharing agreements would ned redefining before use in an RCT

Health economic analysis

- Health economic models will differ between countries
  - Specific national level analyses to be considered

- Cost models proposed
  - Patient level cost of follow up
  - Cost effectiveness (QALYs/health utility measures)
  - Cost to healthcare providers – including lost income

Funding

- NIHR, CRUK are potential sources of funding available in the UK who would consider funding an international trial
- Country specific funding
  - Possible advantage to matched funding from different organisations

- REACT pragmatic clinical trials to answer important trial questions where the two intervention arms are currently within routine practice

Action points arising from Ottawa

- Meet with experts regarding PROMs/QOL scores and how to power to detect change in multiple sequential PROM measures
- Discuss different trial designs – preference based prospective cohort studies and using this data within Bayesian analysis of subgroups
- Involve Birmingham Clinical Trials Unit in order to prepare the draft protocol to prepare for funding applications and local ethics approval
- Consult health economists (country specific)
- Appraise RESAR requirements to potentially allow for ‘a RCT within the registry’
- Arrange 2-3 patient and public involvement group meetings
- Explore/apply for NIHR/CRUK funding and any other applicable international funding streams

Pump Priming Grant

- Successful application for a Pump-Priming Grant from the Royal College of Surgeons England to support patient and public involvement meetings
  - UK/Canadian based panel assembled – needs extending to other participating countries

Participation / questions / comments

Samuel.ford@uhb.nhs.uk