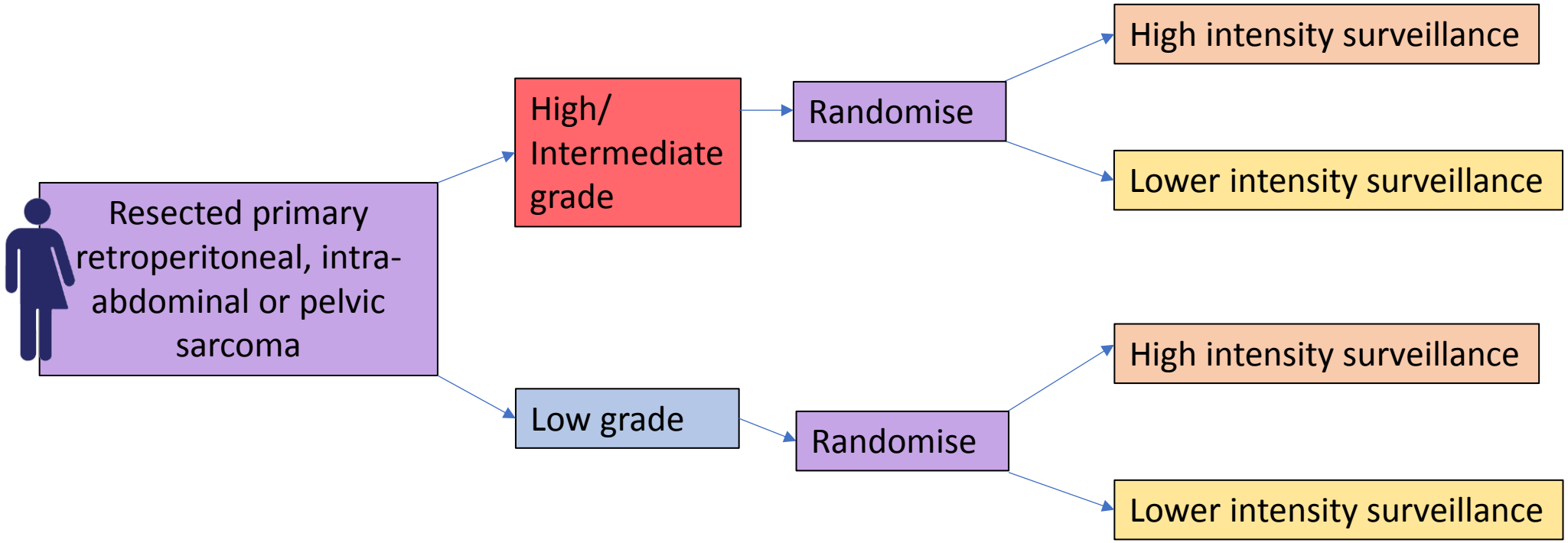
SARveillance Trial

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 Meeting Nov 2020

SARveillance Trial Schematic



Second Trial Development Group Meeting

26th October 2020

- **Attendees**
- Sam Ford (SF) – Birmingham, UK
- James Glasbey (JG) – Birmingham, UK
- Hannah Tattersall (HT) – Birmingham, UK
- Daniella Maes (DM) – Birmingham, UK
- Dirk Strauss (DS) – London, UK
- Alessandro Gronchi (AG) – Milan, Italy
- Dario Callegaro (DC) – Milan, Italy
- Roger Wilson (RW) – Patient representative - UK
- Emily Keung (EK) – TX, USA
- Tim Ramsay (TR) – Ottawa, Canada
- Bryde Fresque (BF) – Patient representative – Ottawa, Canada
- Sinziana Dumitra (SD) – Montreal, Canada

- **Apologies**
- Carolyn Nessim (CN) – Ottawa, Canada
- Winan van Houdt (WVH) – Amsterdam, Netherlands
- David Gyorki (DG) – Victoria, Australia
- Christina Roland (CR) – TX, USA
- Chandrajit Raut (CR) – MA, USA

Inclusion/exclusion criteria

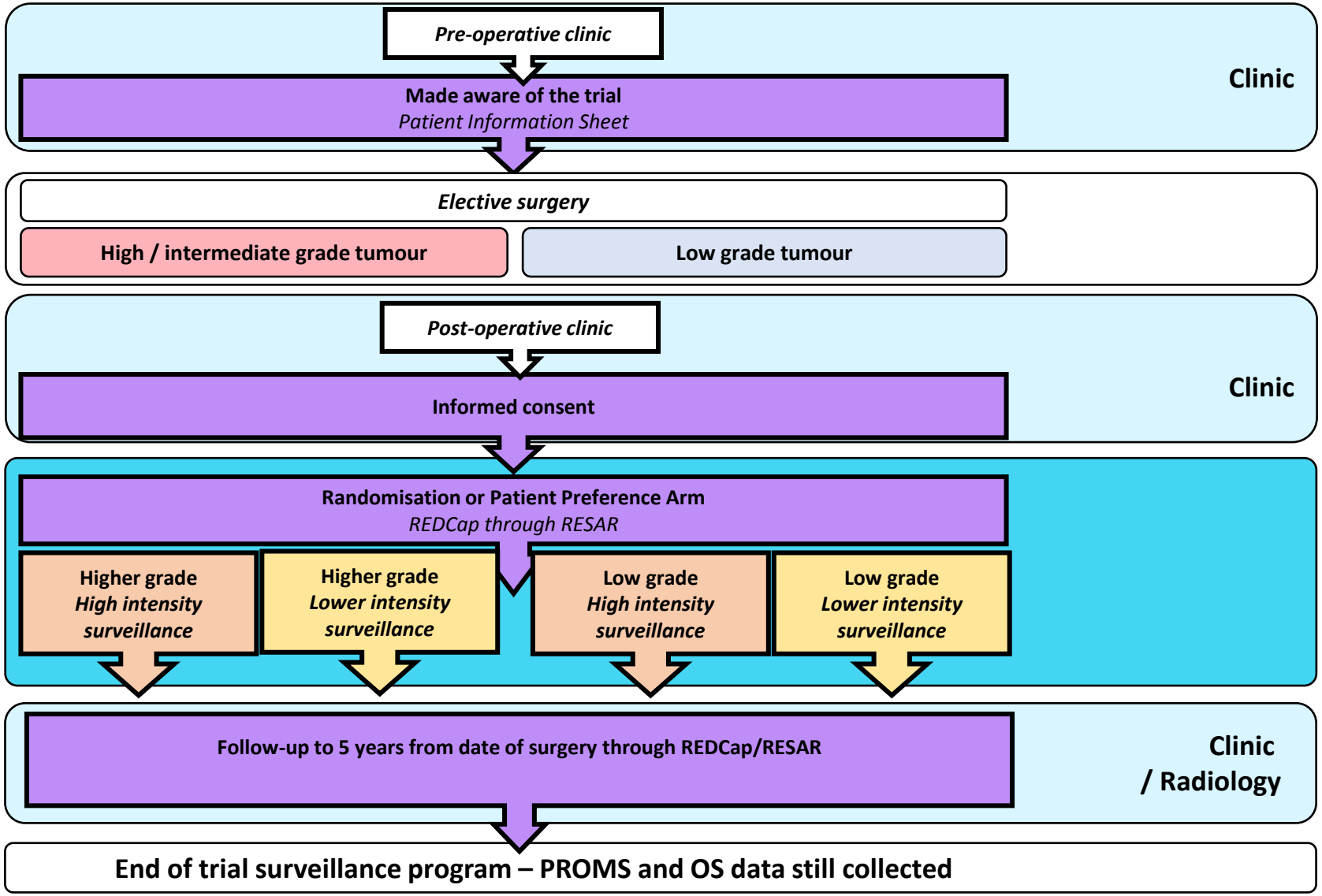
Inclusion criteria

- 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



Surveillance intensities – CT imaging

High-intensity radiological surveillance

- High/intermediate grade histology
  - 3-4 monthly CT scan up to 2-years postoperatively, 6-monthly CT scan from 2-5 years postoperatively
- Low grade histology
  - 6-monthly CT scan up to 2-years postoperatively, annual CT scan from 2-5 years postoperatively

Lower-intensity radiological surveillance

- High intermediate grade histology
  - 6-monthly CT scan up to 2-years postoperatively, annual CT scan from 2-5 years postoperatively
- Low grade histology
  - Annual CT scan up to 2-years postoperatively, biennial CT scan from 2-5 years postoperatively

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.

Endpoints

High/intermediate grade

- Co-primary endpoints – OS and PROM/QOL

Low grade

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

Recruitment

- 8 year trial = 3 years recruitment + 5 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 and 1/3 low grade)

Pre-defined secondary analysis

- Predefined secondary analysis comparing grade versus Sarculator-attributed risk would be feasible, and high impact (including prospective validation of Sarculator)

- Health-related quality of life: EORTC-sarcoma specific tool (extension to QLQC30) with Dr Olga Husson and Prof Winette van der Graaf - collaborate and prospectively validate the PROM within the trial (may open EORTC funding for trial PROMs)

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)

- Discussion around timing of introduction of the Patient Preference Arm to trial candidates – before or after offering randomisation? Overall, preference was for introduction if the patient declined randomisation – ethics?

Patient and public involvement

- Patient and public review group meetings – acceptability of study design and optimisation of PROs
  - Two or more patients from participating centres – to be Chaired by Mr Roger Wilson Jan 2021
  - Royal College of Surgeons Pump Priming Grant to fund this process

  - Mr Roger Wilson CBE (NCRI, President of Sarcoma Patients Euronet, Chair of EORTC Patient Panel, Founder of Sarcoma UK) review of protocol
    - Supportive of the trial
    - Highly supportive of the patient preference arm – not just QoL/PROs context – the high v low intensity choice could include an indication of intuitive acceptability of the high intensity approach and add to our understanding of patient perceptions
    - Having a non-randomised 'fall back' position will place a real challenge on the recruiting clinician to explain equipoise
    - Important issues – pain, social function and HRQoL
    - Suggestions for QoL/PROMs tools and contacts
    - Need for longitudinal data collection – area under the curve – spot trends

QoL/PROMS

- Critical to success of the trial in terms of funding and impact post-trial completion
- Extremely important for patients and may be more likely to hold significant differences than OS
- Likely to be highly influenced and shaped by patient and public involvement in the study design

- Collaboration with Prof Mel Calvert and Dr Lee Aiyegbusi – Centre for Patient Reported Outcome Measures, University of Birmingham
  - Very likely to be able to power the study for QoL / PROMs on the projected recruitment numbers – even for low grade
  - Recommended
    - Patient-Reported Outcomes Measurement Information System (PROMIS 29)
    - Hospital Anxiety and Depression Score (HADS)
  - No sarcoma specific QoL score is currently prospectively validated (sarcoma specific extension for EORTC QLQ-C30 potentially prospectively validated within the trial)
  - PROMs data should continue to be collected after the trial surveillance period ends
  - Timing of administration of PROMs remains problematic due to the differential in imaging intervals between the proposed trial arms (pre, post, interval in between imaging does not always a line – along with frequency) – more discussion planned for this!

Health economic analysis

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

- Collaboration with Prof Tracy Roberts and Dr Raymond Oppong, Institute of Applied Health Economics, University of Birmingham and Keele University
- Cost models proposed
  - Intervention costs
  - healthcare provider costs – including lost income
  - Patient level / societal costs / loss of productivity
  - Collect EQ-5D and derive QALYs
  - Would need to define and collect country specific data from the outset

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 need redefining before use in an RCT (on-going process) along with centralisation of data collection (Milan)

Mentoring, endorsements and co-enrolment

- Alessandro Gronchi has kindly agreed to support the trial as mentoring Chief Investigator
- EORTC - Soft Tissue and Bone Sarcoma Group has given preliminary endorsement / support for the trial
  - Supports application to University of Birmingham Cancer Research Clinical Trials Unit and applications to funding streams
- Co-enrolment
  - Co-enrolment with STRASS II is not practical
  - STRASS II well established at first SARveillance recruitment –unlikely to affect patient population within SARveillance

PhD program

- Funding for three year PhD program (Salary)
  - Danielle Maes – post CCT Orthopaedic Surgeon with an interest in sarcoma

- Possible outline
  - Protocol for randomised trial (or something to do with pragmatic/REACT implementation in the UK)
  - Retrospective study within RESAR – looking at imaging intervals for patients with recurrence (David Gyorki)
  - Qualitative exploration of patients attitudes to high and low intensity surveillance protocols for STS
  - Usability/validation of ePROs within an international trial

  Potential to develop a bone / extremity soft tissue sarcoma surveillance aspect to the trial – huge undertaking!

Next Steps

- QoL / PROMs PPI meetings – Chaired by Roger Wilson – two patients from each contributing centre
- QoL / PROMs protocol – further definition with Prof Mel Calvert
- Further letters of endorsement – Sarcoma UK, NCRI
- Engagement of CRCTU to assist in funding stream application (essential in UK) and refinement of formal protocol – new business case submitted
  - 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
- Ethics
- Movement towards centralisation of RESAR data / REDCap

Participation / questions / comments

Samuel.ford@uhb.nhs.uk