SARveillance Trial

An international, partially-randomised, patient-preference trial of high versus lower intensity radiological surveillance following primary resection of retroperitoneal, abdominal and pelvic soft tissue sarcoma

TARPSWG Meeting 17th March 2021

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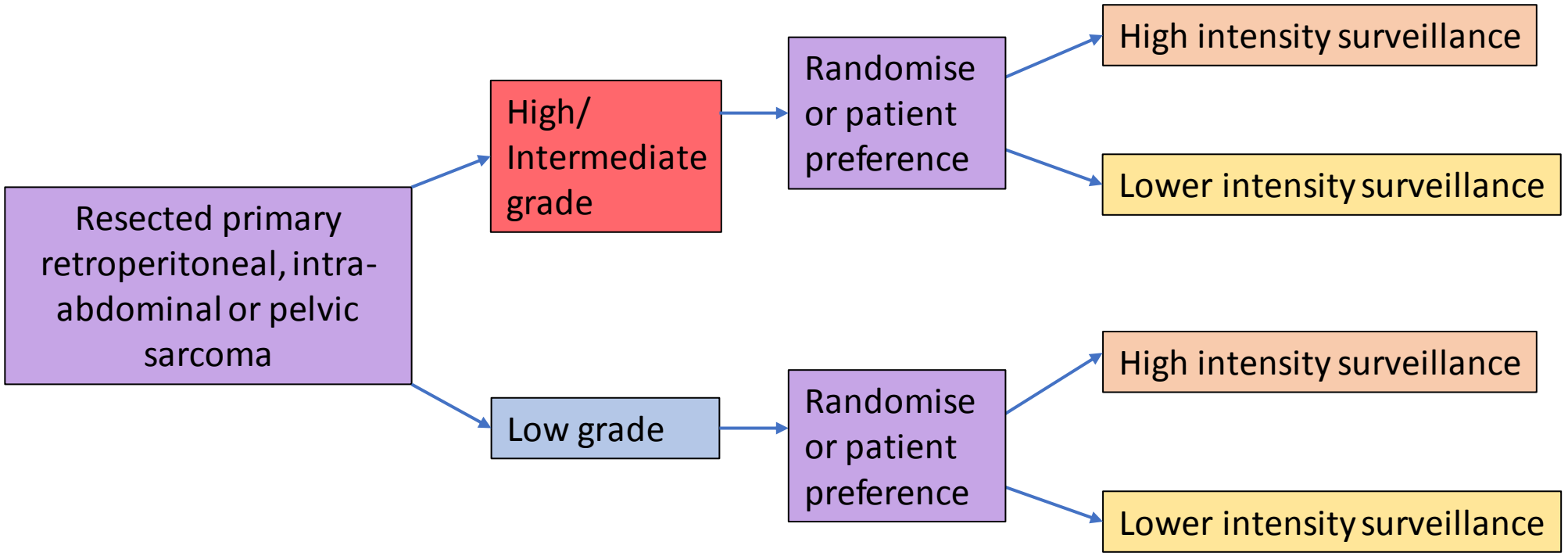


Efficient and pragmatic trial

- Trial within a registry (RESAR)
- *REthinking Clinical Trials (REaCT) pragmatic clinical trial design*
  - Trial methodology group in Ottawa, Canada
  - Patient centred, ultra-pragmatic trial design
  - Utilised where both treatment arms are currently standard of care
- No excess treatment costs anticipated
- Several pre-planned sub-studies
- PhD program

Multi-disciplinary trial development team

- Royal College of surgeons Pump Priming Development Grant

  - Second International Trial Development Group Meeting 22nd October 2020
  - Dedicated International Patient Advisory Group Meeting 11th January 2021
  - Centre for Patient Reported Outcomes Research (Prof Mel Calvert/Dr Aiyegbusi)
  - Health Economics (Dr Raymond Oppong) Institute of Applied Health Economics
  - REaCT trial methodology group (University of Ottawa)
  - 22 international high volume sarcoma centres have indicated interest (TARPSWG)
  - Alessandro Gronchi mentoring CI

Contributing specialist sarcoma centres

Contributing Specialist Sarcoma Centre	PI
UK	
Queen Elizabeth Hospital, Birmingham, UK	Mr Samuel J Ford
Royal Marsden Hospital, London, UK	Mr Dirk Strauss
EU	
Istituto Nazionale dei Tumori, Milan, Italy	Professor Alessandro Gronchi
University hospital of Padova	Dr Gaya Spolverato
Campus-Medico University, Rome, Italy	Dr Segio Valeri
Netherlands Cancer Institute, Amsterdam, The Netherlands	Dr Winan van Houdt
KU Leuven University, Leuven, Belgium	Professor Daphne Hompes
Ruprecht Karls University, Heidelberg, Germany	Professor Nikolaos Vassos
USA	
Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, USA	Professor Chandrajit Raut
Emory University Hospital. Atlanta, USA	Dr Ken Cardona
Mayo Clinic. Jacksonville, USA	Dr Sanjay Bagaria
University of Washington DC, USA	Dr Matt Spraker
Roxanne Moore University of Washington / Fred Hutchinson Seattle, USA	Michael J Wagner
Cleveland Clinic, Ohio, USA	Dr Daniel Joyce
MD Anderson, Texas, USA	Dr Christina Roland
University of Southern California, Los Angeles, USA	Dr William Tseng
Ohio State University, Ohio, USA	Dr Valerie Grignol
Canada	
Ottawa Hospital Research Institute, Ottawa, Canada	Dr Carolyn Nessim
McGill University, Montreal, Canada	Dr Sinziana Dumitra
Australia	
Peter MacCallum Cancer Centre, Melbourne, Australia	Professor David Gyorki
Royal Prince Albert Hospital, Sydney, Australia	Dr David Coker
Russia	
NN Blokhin Cancer Research Center for Oncology, Moscow, Russia	Dr Alex Kalinin

Potential contributing centres increased to 22

SARveillance adopted by CRCTU

- Cancer Research UK Clinical Trials Unit (CRCTU) meeting
  - Birmingham 11th March 2021 (supported by Roger Wilson Chair of PAG)

- The CRCTU University of Birmingham - have agreed to formally adopt SARveillance
  - Plan for NIHR HTA funding (attempt full international funding - September 2021)
  - Excellent track record with gaining international funding / co-ordinating international trials
  - Two thirds success rate – all funding submissions

- Stipulation
  - Change the primary outcome
    - From OS and QoL to quality-adjusted life years - QALYs
    - More attractive to funding streams / QALY data generated from PPA - potentially incorporated into RCT analysis if required (easier to power)
    - Need to incorporate into the protocol (CRCTU abbreviated protocol advanced draft)
    - Up-date the power calculation for QALY

Endpoints

High/intermediate grade

- Quality-adjusted life years (QALYs)

Low grade

- Quality-adjusted life years (QALYs)

Secondary endpoints

- Overall survival
- Quality of life
- Health economic analysis – cost per QALY
- Disease free survival (internal measure)
- Environmental impact

International Patient Advisory Group

- Developed a dedicated international Patient Advisory Group – PAG

- Chair - Mr Roger Wilson CBE (Member of the NCRI Board and chaired the national patient group in research, President of Sarcoma Patients Euronet, Chair of EORTC Patient Panel, Founder of Sarcoma UK)

- First meeting 11th January 2021 (23 patients)
- Highly supportive – especially the PPAs
- Will be instrumental in developing patient accessible information - recruitment
- Timing and administration of QoL instruments

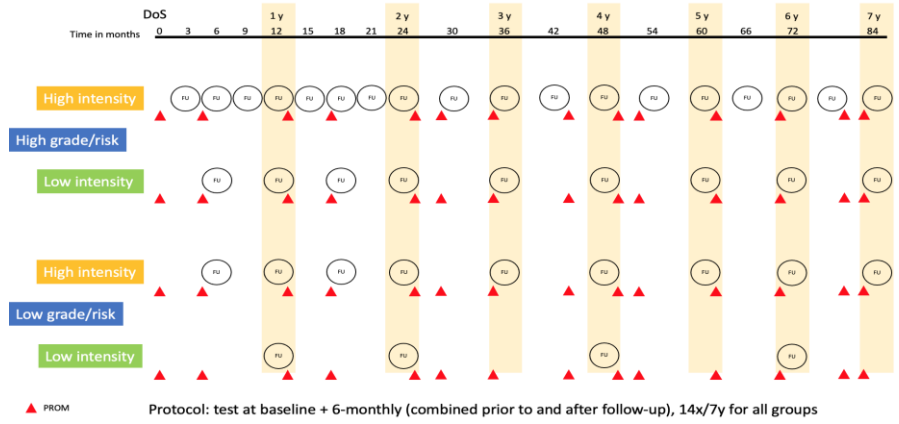
Patient preference arms

- Patients who decline to be randomised will be offered the opportunity to participate thorough the patient preference arms
  - Patients can choose to follow the high or lower intensity surveillance arms
  - Proposed as a way of retaining patients that decline to be randomised but still willing to participate in the trial within the preference based prospective cohort
  - Likely to yield insightful information on motivation for choosing surveillance intensity
  - QALY / QoL data will analysed and compared to the equivalent arms of the RCT to determine the impact of patient selection of surveillance strategy on their QALY / QoL versus randomisation
  - The patient advisory group is highly supportive of the PPAs and agree that it is ethically sound to introduce the PPAs after randomisation has been declined rather than before
- Internal pilot study
  - Proposed to be performed to refine study procedures including consent and rate of recruitment to the RCT and the PPAs

Quality of life

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

- Collaboration with Prof Mel Calvert and Dr Lee Aiyegbusi – Centre for Patient Reported Outcome Measures, University of Birmingham
  - Able to power the study for QoL on the projected recruitment numbers – even for low grade
  - Quality of life – EORTC QLQC30 plus four sarcoma specific questions from the EORTC Sarcoma Module
    - Have you been afraid of tumour progression?
    - Have you worried about recurrence of your disease?
    - Have you been watching yourself closely for any new symptoms?
    - Do you have worries and/or concerns about the future
  - QoL data should continue to be collected for two years after recurrence detected
  - Timing of administration of QoL instruments problematic
    - differential in imaging intervals between the proposed trial arms (pre, post, interval in between imaging does not always align)



Health economic analysis

- Much more prominent now QALY is proposed primary outcome

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

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

PhD program

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

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

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

Next steps

- Re-power for QALYs as primary endpoint (for both high/intermediate and low grade pathology)
- Adjust the CRCTU protocol to reflect change in primary outcome / change in power calculations
- Formalise potential number of cases per year for recruitment in contributing centres (retroperitoneal, abdominal and pelvic sarcoma resections)
- Review of the abbreviated CRCTU protocol by international Trial Development Group – before beginning formal extended CRCTU protocol / HTA application / site specific ethics

Questions and participation

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Surveillance intensities – CT TAP

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

Equipoise within the expert community
No excess treatment costs anticipated

Statistical power and recruitment

Power calculation for RCT component

- High/intermediate grade tumours (smallest meaningful difference in OS to change practice 10%)
- 5- year overall survival in group 1 (High intensity surveillance) - 53%.
- 5- year overall survival in group 2 (lower intensity surveillance) - 43%,

To power the study (high/intermediate grade sarcoma) for overall survival

- relative sample size of 1.0
- significance level at 0.05 and a power of 80%,
- A sample size of n=391 per group (n=781 total)

Low grade tumours

- The number of patients with low grade tumours coupled with a low event rate is too small to power for overall survival

Recruitment

- Total centres involved n=22
- Years of recruitment: 4
- Estimated candidates for recruitment: n=4580
- Assuming 60% recruitment to RCT n=2748
- Split 66% high/intermediate grade and 33% low grade

Best estimate recruitment assuming all centres participate

- *n=1813 patients over 4 years for high/intermediate grade*
- *n=935 patients over 4 years for low grade*