How has CTRad addressed regulatory challenges in radiotherapy drug combination trials

Ruth Plummer

10th May 2017

Overview

- Radiotherapy historical perspective
- What is CTRad
- Regulatory positioning paper
- Next steps

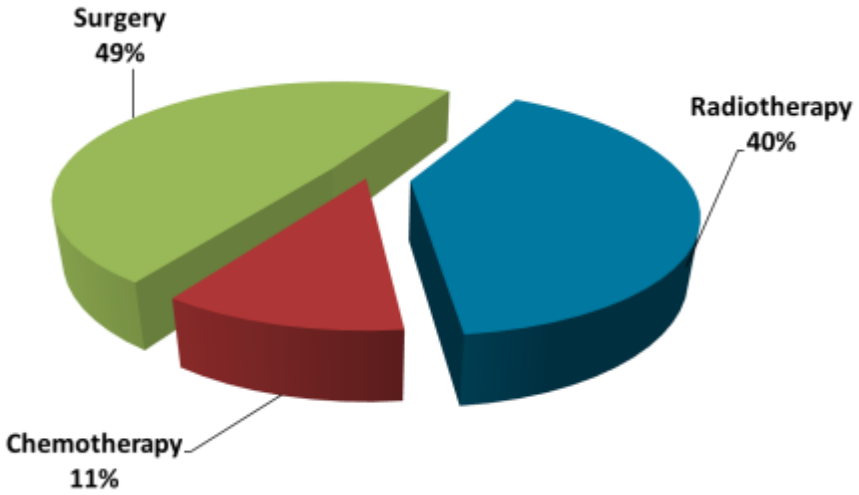
Clinical and Translational Radiotherapy
Research Working Group

Radiotherapy is a crucial, effective and cost–effective cancer treatment

- >50% of cancer patients require RT
- 60% treated with curative intent
- >100,000 UK patients receive RT with curative intent every year
- Across all tumour sites and different technology platforms

Huge scope to improve cure rates and/or reduce toxicity

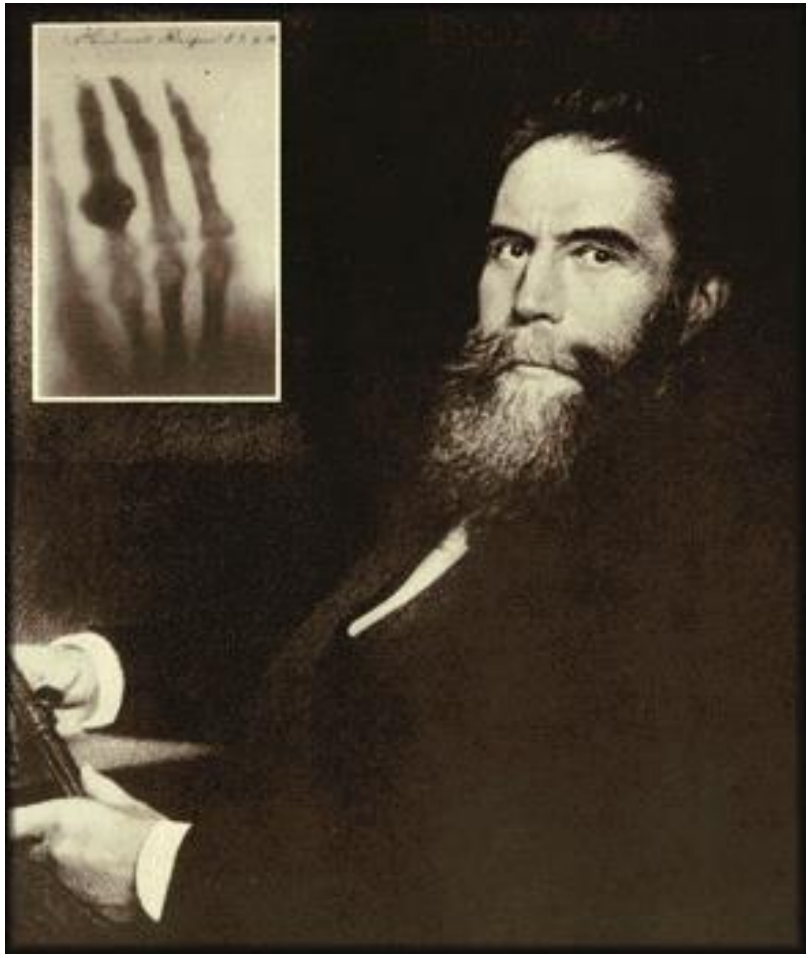
Curative treatment by modality



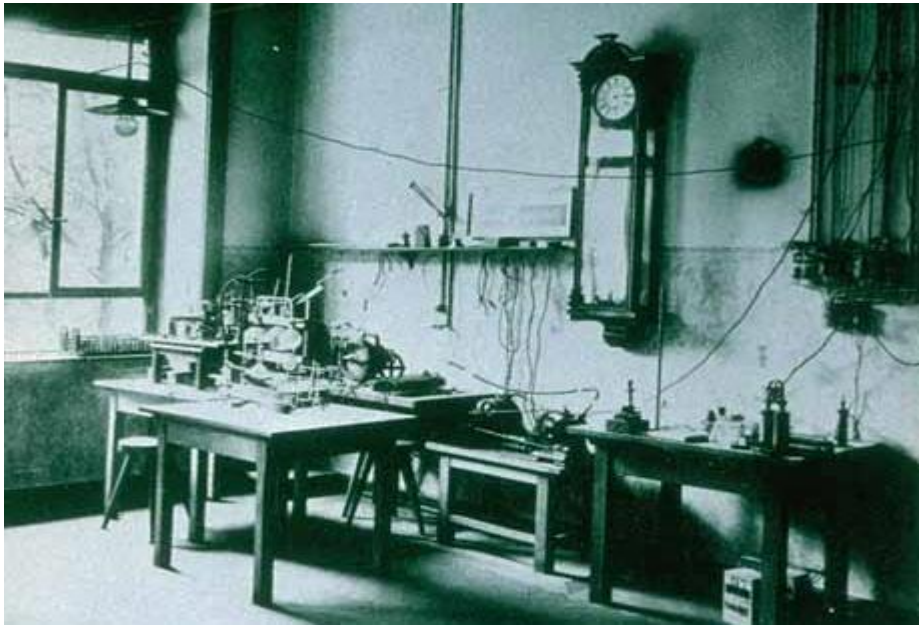
Treatment modality	Annual spend
Surgery	£2.1 billion
Chemotherapy	£1.7 billion
Radiotherapy	£0.5 billion

CRad
Clinical and Translational Radiotherapy
Research Working Group

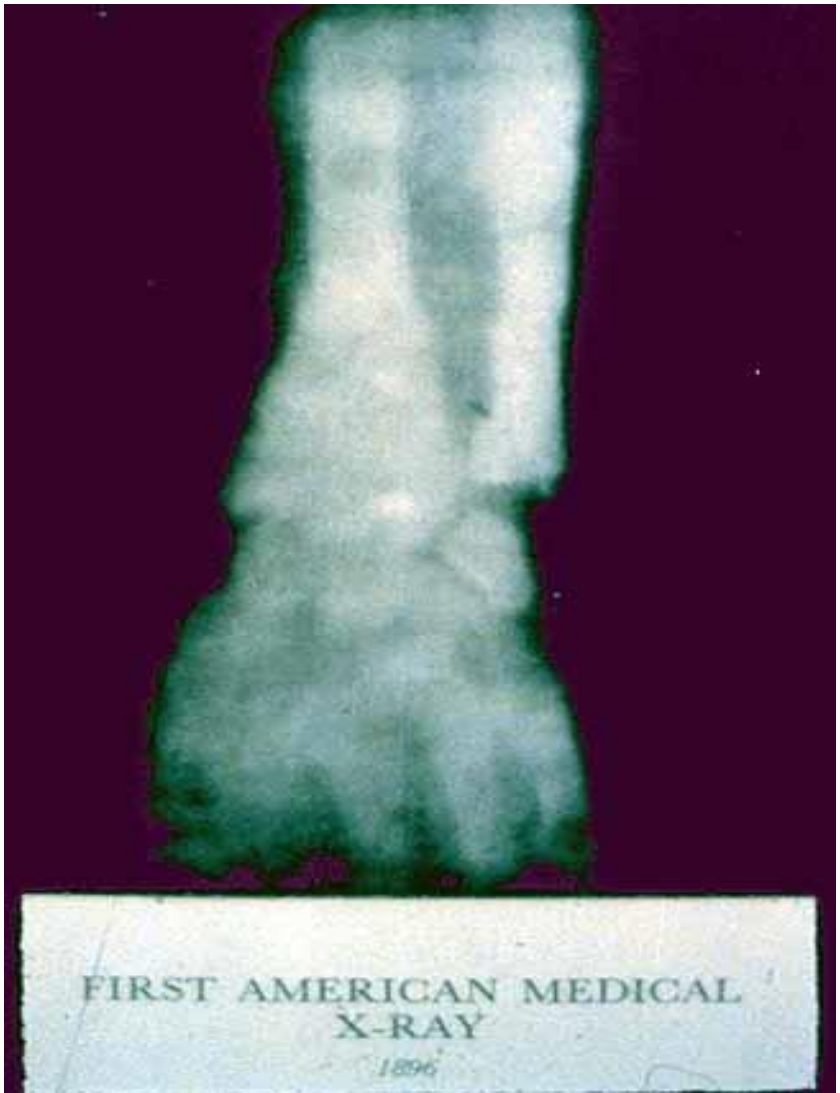
The discovery of X-rays



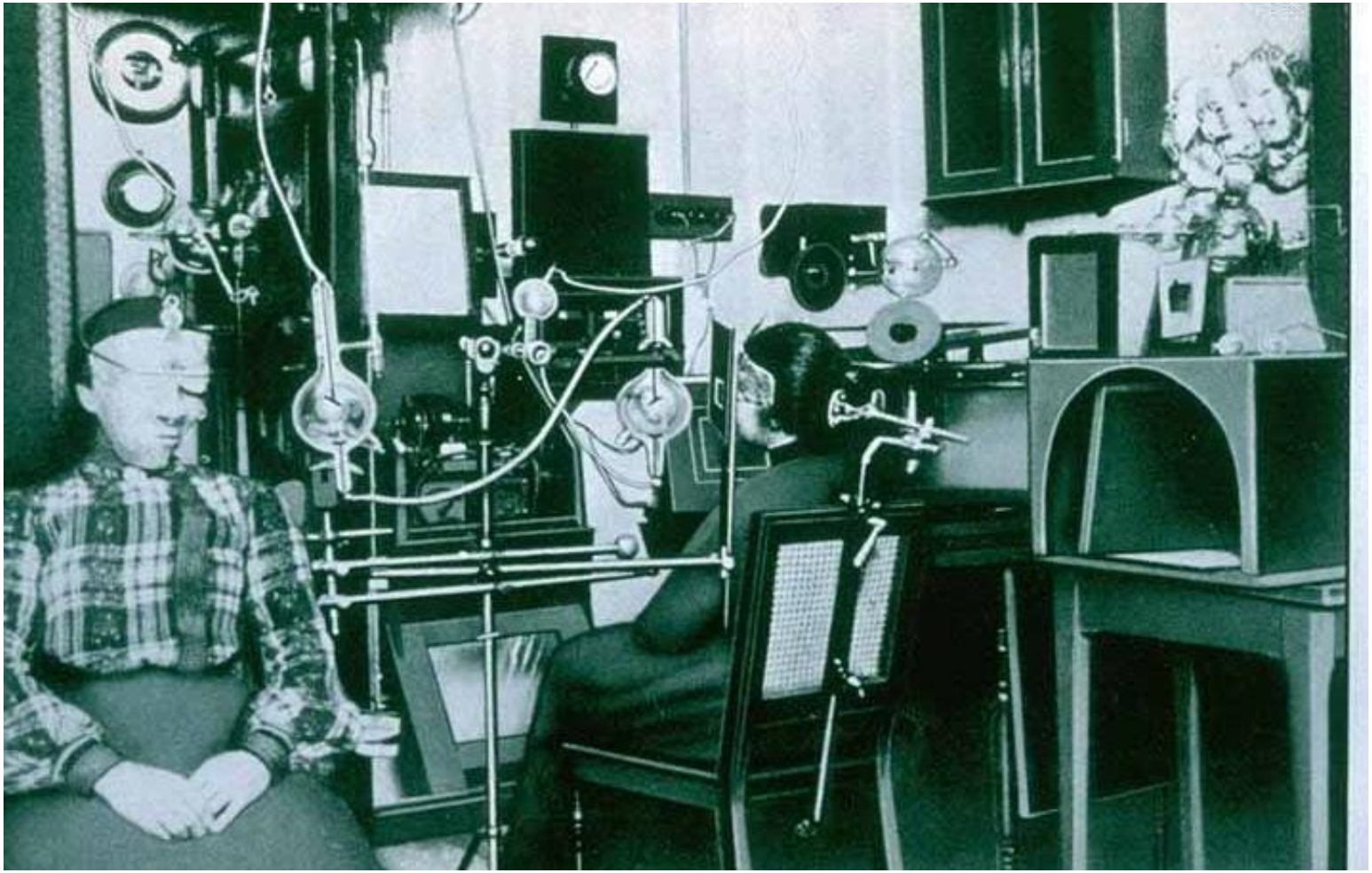
- Wilhelm Conrad Roentgen – 8th Nov 1895. Nobel prize
- First radiation therapy by Emile Grubbe on Jan 29TH 1896



First diagnostic X-ray 3rd Feb 1896 by Frost. Colles fracture

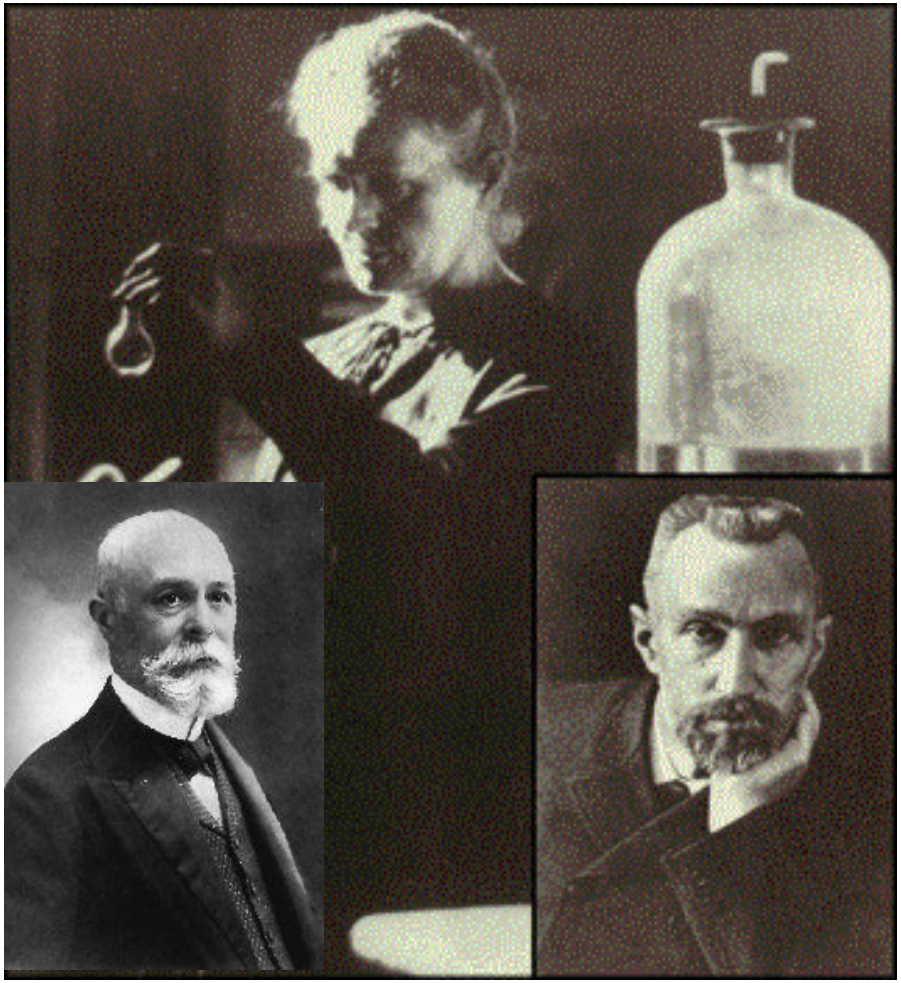


Early treatment lab

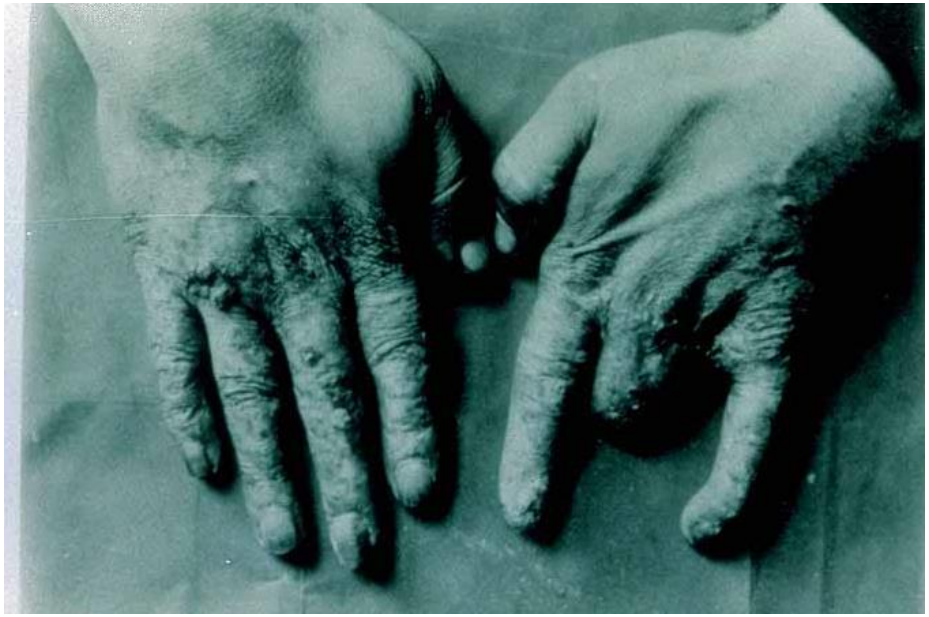


The Curies, Bequerel and Radium

- 1896. Bequerel discovers uranium salts produce a similar type of radiation to X-rays
- 1898. Curies isolate radium from pitchblende in a shed. Nobel prize 1903
- Pierre Curie developed an ulcer on his chest where he kept a sample of radium in his waistcoat! He suggested that radium could be used for cancer treatment - brachytherapy
- Original research papers remain radioactive!



Consequences for early radiation pioneers



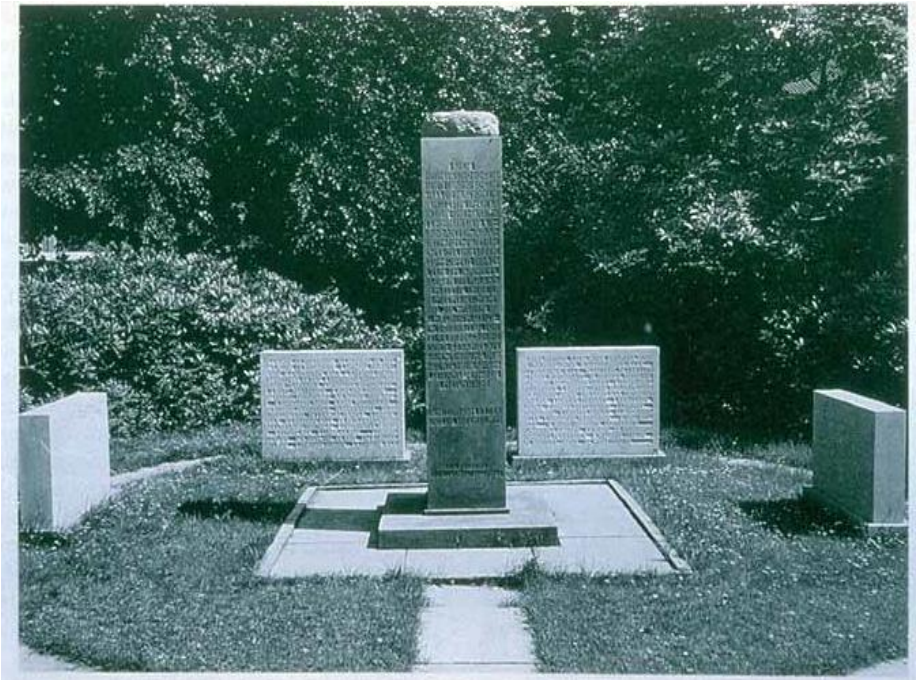
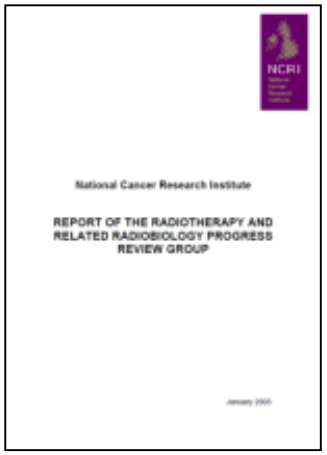


Fig. 12-8. The stelae honoring the pioneers who died victims of their exposures to radiations (1935).

Image-guided radiotherapy (*IGRT*) linacs 1990s-current

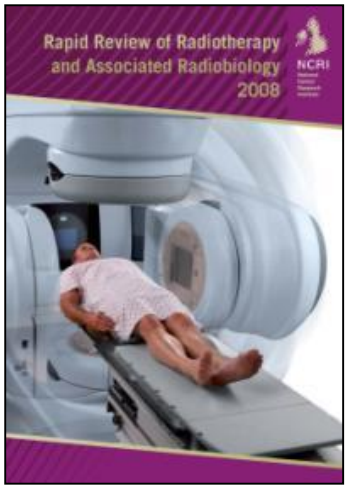
Stimulation to radiotherapy research in UK

Clinical and Translational Radiotherapy
Research Working Group



2003

NCRI identified RT as area of need



2008

Rapid Review

2006 Oxford Institute

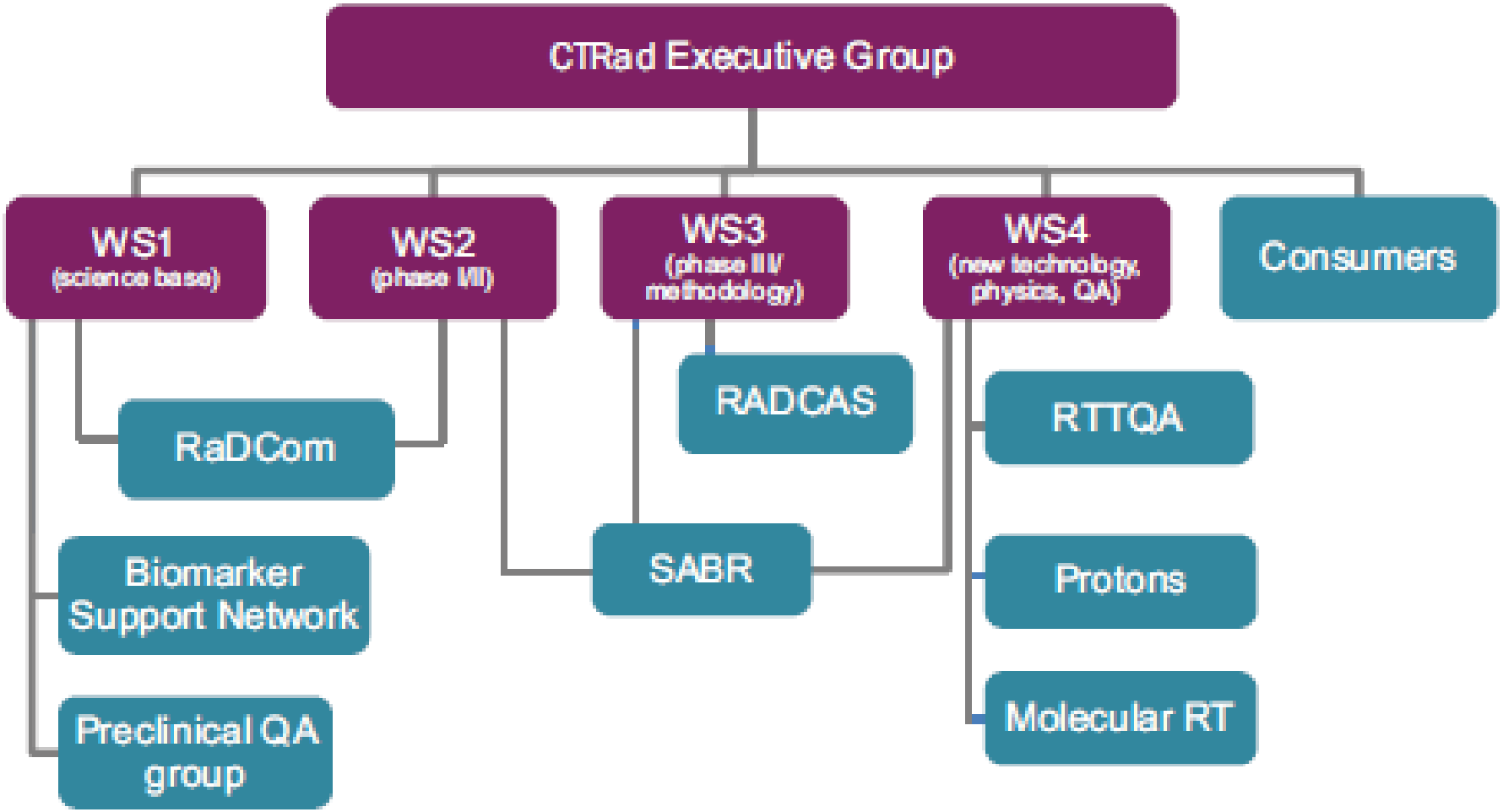
2009

CTRad launched

CTRad's strategic vision

- Lead the optimisation, implementation and evaluation of technological advances in radiotherapy
- Lead collaborative initiatives to realise the benefits of novel radiotherapy-drug combinations
- Build the academic radiotherapy research workforce through Centres of Excellence
- Lead the radiotherapy contribution to 'Precision Medicine'
- Be world leaders in the design and delivery of innovative, efficient and collaborative clinical trials

Clinical and Translational Radiotherapy Research Working Group



Academic work force development

RT-drug combinations

- Deliver strong collaborations with Pharma
  - Preclinical evaluation of novel combinations: RaDCom
- Biomarker driven early phase clinical trials
  - Novel clinical trial methodologies
- Rapid progression to practice-changing trials
  - Defining the route to registration: Nature Reviews Clinical Oncology consensus statement

Clinical and Translational Radiotherapy Research Working Group

Work stream 2 – early phase combination trials

- Original work stream leads – Kevin Harrington and Ruth Plummer,
  - Kevin moves to work stream 1 (radiation bioscience)
  - Ricky Sharma taking on WS2 lead

- 2013 – at WS 2 meeting Ozlem Ataman (industry member) expressed her frustration at the challenges of developing combination studies

- There was no “route to registration” where radiotherapy was involved
  - WS2 chairs proposed a workshop to CTRad exec

- A range of new agents are obvious radio-potentiators
  - PARPi
  - Other DDRi

Clinical and Translational Radiotherapy Research Working Group

2 round table meetings – September 2014 and 2015

- Who attended? – more than 40 people at both workshops
  - Clinical and medical oncologists
  - Industry representatives
  - PPI
  - Statisticians for trial design
  - CRUK team members
  - MHRA
  - Journal editor

Clinical and Translational Radiotherapy Research Working Group

Output is the Consensus statement

- 39 authors – buy-in from the whole workshop team
  - Key organising group and then alphabetical authorship
  - Industry felt this had to be academic-led or would have no traction
  - MHRA/EMA visitor happy to advise but challenging to be an author

- Where did they come from
  - 11 UK academic centres
  - 1 US academic centre
  - 12 different industry partners
  - CRUK, NCRI (including PPI)

Clinical and Translational Radiotherapy Research Working Group

Clinical and Translational Radiotherapy
Research Working Group

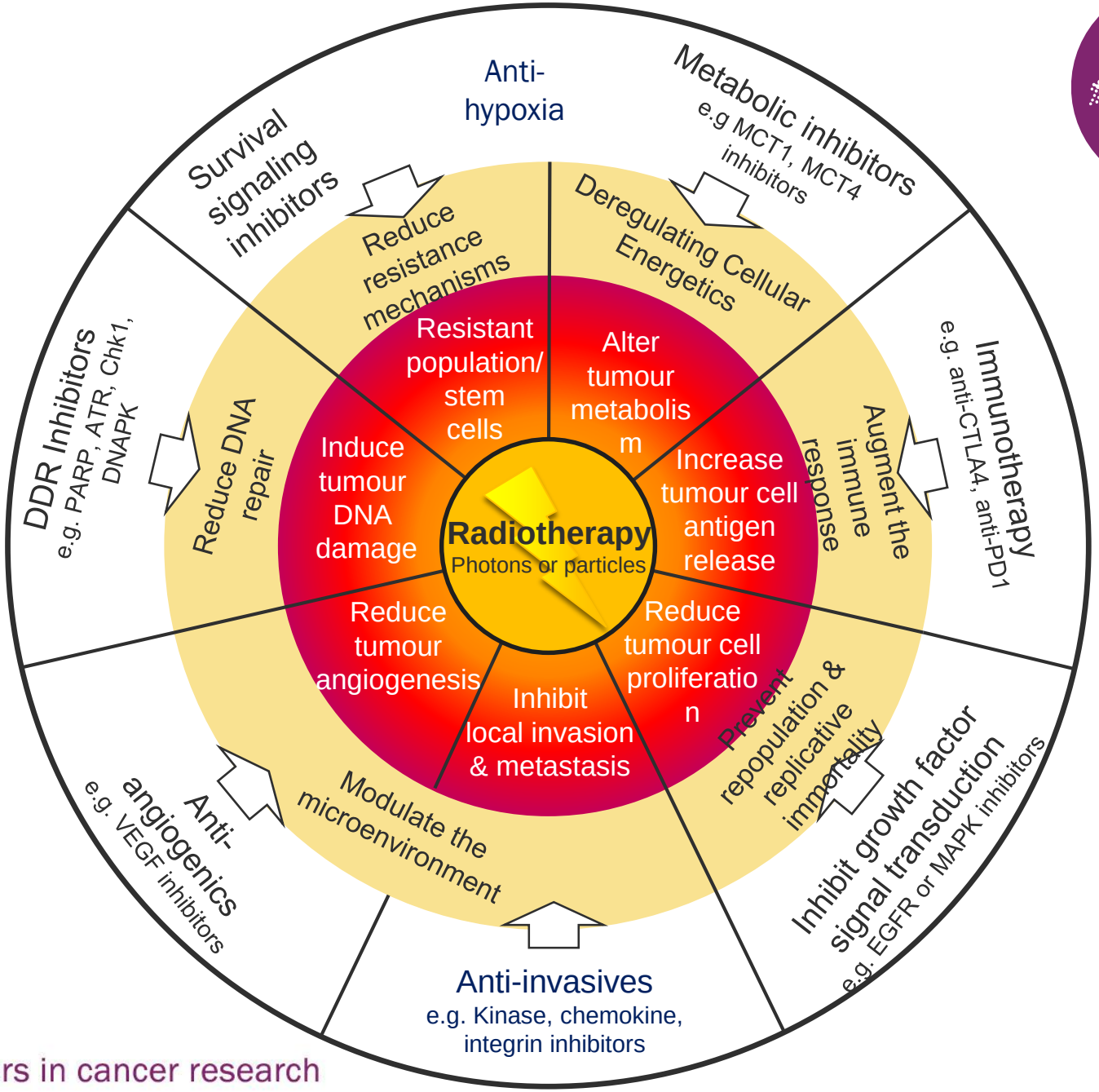
CONSENSUS STATEMENT

OPEN

Clinical development of new drug–radiotherapy combinations

Ricky A. Sharma[1], Ruth Plummer[2], Julie K. Stock[3], Tessa A. Greenhalgh[4], Ozlem Ataman[5], Stephen Kelly[6], Robert Clay[7], Richard A. Adams[8], Richard D. Baird[9], Lucinda Billingham[10], Sarah R. Brown[11], Sean Buckland[6], Helen Bulbeck[12], Anthony J. Chalmers[13], Glen Clack[14], Aaron N. Cranston[15], Lars Damstrup[16], Roberta Ferraldeschi[17], Martin D. Forster[1], Julian Golec[18], Russell M. Hagan[19], Emma Hall[20], Axel-R. Hanauske[21], Kevin J. Harrington[20], Tom Haswell[12], Maria A. Hawkins[4], Tim Illidge[22], Hazel Jones[3], Andrew S. Kennedy[23], Fiona McDonald[20], Thorsten Melcher[24], James P. B. O'Connor[22], John R. Pollard[18], Mark P. Saunders[22], David Sebag-Montefiore[11], Melanie Smitt[25], John Staffurth[8], Ian J. Stratford[22] and Stephen R. Wedge[2] on behalf of the NCRI CTRad Academia-Pharma Joint Working Group

Sharma *et al*, Nature Reviews Clinical Oncology, 2016



NCRI
National Cancer Research Institute

Partners in cancer research

Box 1 | **Consensus statements**

1. Drug–radiotherapy combinations

Approximately, 4 out of 10 patients with cancer who are cured by treatment receive radiotherapy. Combining novel drugs with radiotherapy has clear potential to significantly improve patient outcomes. When companies are considering testing a novel combination for an agent, they should consider drug–radiotherapy combinations as important as drug–drug combinations. Collaborative groups involving academia and pharmaceutical companies should prioritise the evaluation of appropriate novel drug–radiotherapy combinations early in the clinical development plan of a drug to potentially improve response and survival rates. Proposed combinations should have a sound scientific basis in radiobiology, immuno-oncology, molecular biology and pharmacology.

2. Route to registration

Currently, there are no published guidelines on how to design studies using novel drug–radiotherapy combinations and there is limited guidance on regulatory aspects. In the absence of specific guidance, drug–radiotherapy combinations should be viewed as similar in concept to novel drug–drug combinations. There should be a strong scientific rationale for the combination based on an understanding of mechanisms of action and a clear line of sight to registration for the combination, based on clinical need.

3. Clinical end points

Early communication between regulators and researchers with regard to the most meaningful clinical end point(s) for a specific tumour site and patient population will accelerate development of novel combination therapies. Inclusion of clinically relevant early and intermediate end points will accelerate clinical development by generating compelling data in a timely and cost-effective manner. Regulators should recognize that end points must be pragmatic, relevant to patients and applicable in a 'real world' setting, and should reflect (i) the important clinical benefits of durable locoregional control, and (ii) the balance of effects on tumour control and normal tissue toxicity. Composite or co-primary end points might be necessary or advantageous. Secondary end points should usually include assessment of effects on normal tissues.

4. Changing the standard of care

The treatment intent and the current standard of care for each disease being treated must be defined by the investigators, including any potential variation across countries. Potential changes in the standard of care must be predicted by clinical experts if the path to registration is to succeed.

5. Clinical trial methodology

Radiotherapy–combination research requires use of appropriate trial designs and robust statistical strategies based on appropriate end points at each stage in the development plan. Studies that take advantage of gaps between planning and starting radiotherapy, or between radiotherapy and surgery, are opportunities for early-phase trials and related pharmacokinetic, pharmacodynamic and imaging studies.

6. Radiotherapy quality assurance

Quality assured radiotherapy is critical to the success of drug-radiotherapy studies. The components include detailed development of the protocol resulting in a transparent description of the chosen technique. Target volume definition and the minimization of irradiation to surrounding normal tissues must be described. Pretrial and trial-specific review of radiotherapy treatment planning and treatment delivery is essential and should be determined for each study.

7. Preclinical dataset and target population

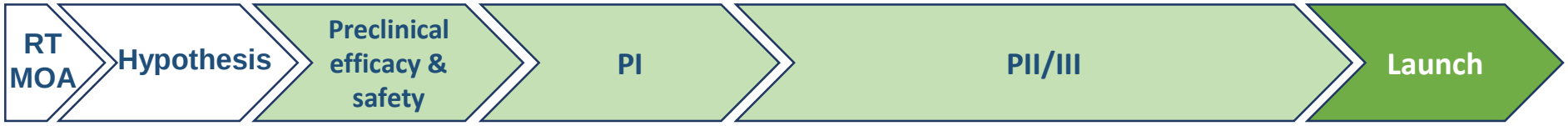
Similar to novel drug–drug combinations, a standard for a minimum preclinical dataset for justifying early-phase clinical development of a new drug–radiotherapy combination does not currently exist. However, it is recommended that the dataset should address four considerations: i) demonstrate that the novel drug improves the efficacy of radiotherapy in clinically relevant models; ii) define an effective dose schedule; iii) provide an assessment of normal tissue toxicity for the drug–radiotherapy combination to identify potential clinical risks; and iv) identify potential responsive patient subpopulations and the associated candidate biomarkers.

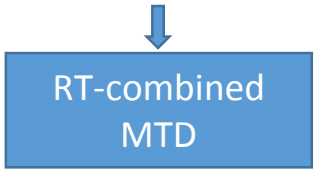
8. Patient and consumer involvement and raising awareness

Patients and consumer groups should be involved from the concept stage onwards for a clearer understanding of patient priorities and what will be considered acceptable by patients who may or may not wish to participate in a clinical trial. Efforts to raise public awareness of the efficacy of radiotherapy and drug–radiotherapy combinations should include clear statements of the potential benefits of the research to improve cancer treatment.

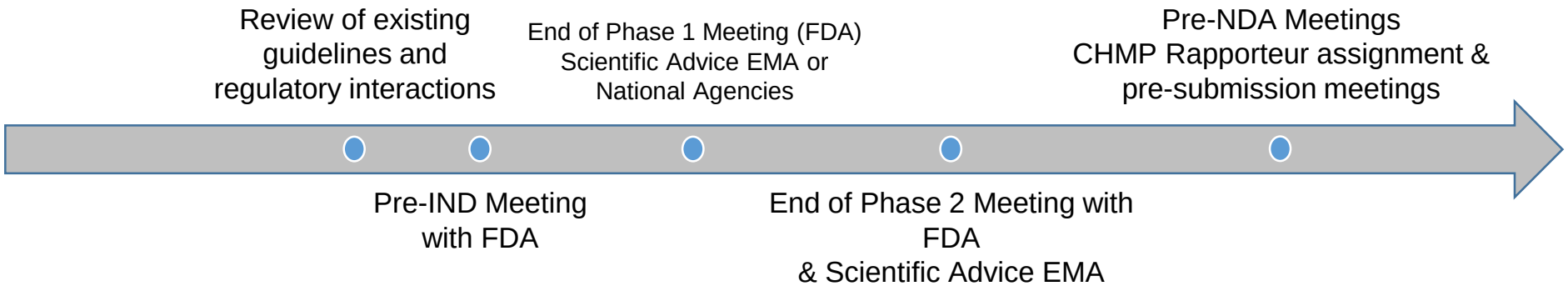
Core Programme

Radiotherapy Program

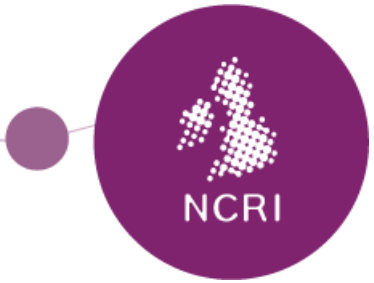




Potential Regulatory Interactions



Next steps


NCRI


Clinical and Translational Radiotherapy
Research Working Group

FDA interest!

- Discussions with FDA, EMA and MHRA over 2016 – led by Ricky and Julie Stock
- AACR to sponsor a workshop in 2018 with ASTRO as a potential co-sponsor
- NIH/FDA is going to propose the date for the workshop during the first two weeks of February 2018
- Aim is to produce a guidance document on drug-RT combinations either from FDA, or jointly with other regulatory agencies
- We are now thinking about attendees at this meeting

Clinical and Translational Radiotherapy Research Working Group

CONCORDE

NSCLC: Platform study of novel agents in **CO**mbinatio**N** with **CO**nventional **R**a**D**ioth**E**rapy in locally advanced disease

Gerry Hanna - Alastair Greystoke Sarah Brown

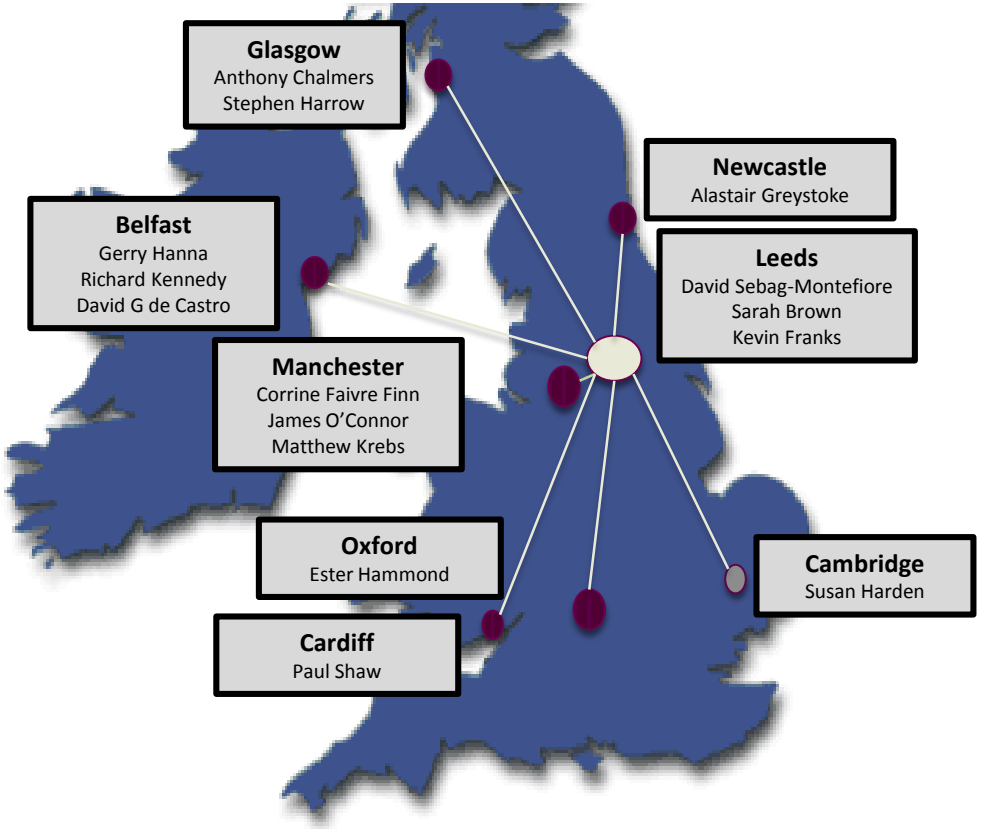
SPITFIRE

N**S**CLC: **P**latform study of **I**mmuno**T**herapy **F**or advanced disease **I**n combination with Stereotactic **R**adioth**E**rapy

Fiona McDonald - Martin Forster Emma Hall

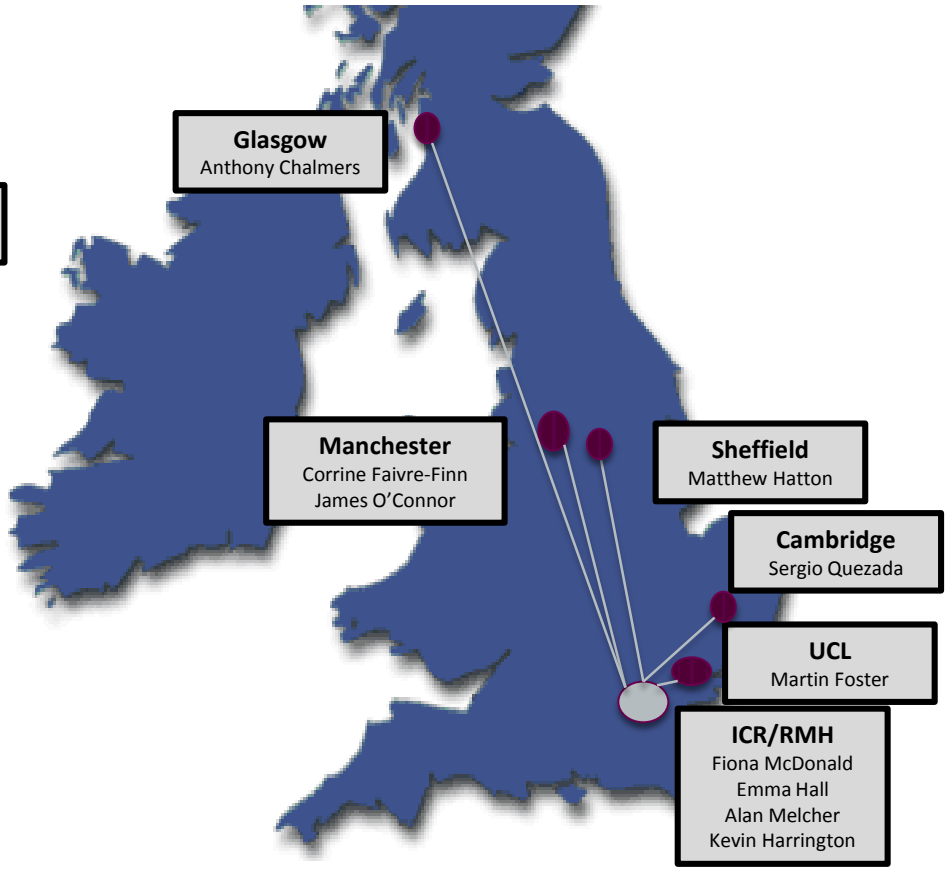
Queen's University Belfast · Newcastle University · ctru Leeds Institute of Clinical Trials Research · UNIVERSITY OF LEEDS · University of Glasgow · UNIVERSITY OF OXFORD · CARDIFF UNIVERSITY · PRIFYSGOL CAERDYDD · UNIVERSITY OF CAMBRIDGE · The Christie · UCL · ICR The Institute of Cancer Research · The ROYAL MARSDEN NHS Foundation Trust

CONCORDE -Stage III



Clinical and Translational Radiotherapy Research Working Group

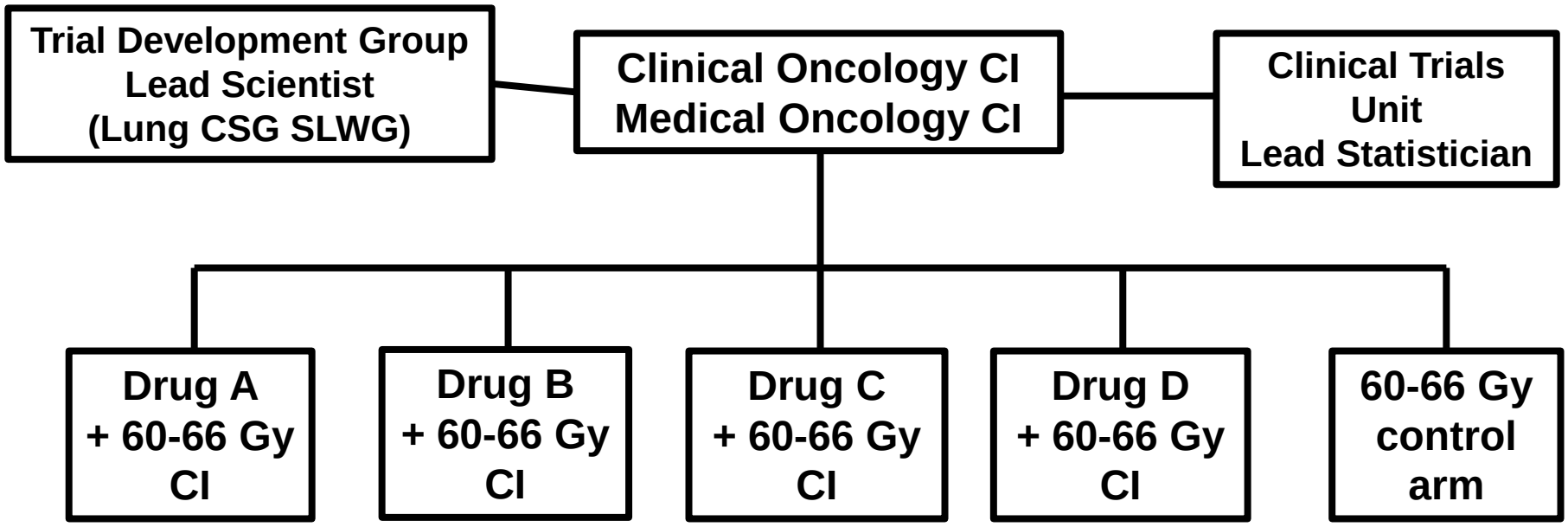
SPITFIRE - Stage IV



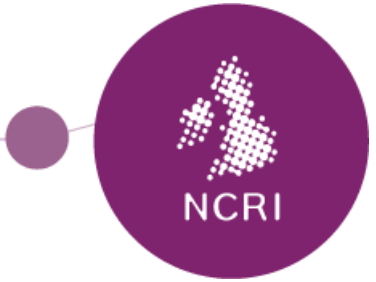
NCRI National Cancer Research Institute

Lung

Phase I multi-arm drug dose escalation study of molecularly targeted agents in combination with radical RT for stage III NSCLC



Thank you



CANCER RESEARCH UK

MRC Medical Research Council

CHIEF SCIENTIST OFFICE

Llywodraeth Cymru
Welsh Government

HSC Public Health Agency

Department of Health