PROJECT DELIVERABLE

Project acronym: **REQUITE**	GA number: **601826**
Project title: **Validating predictive models and biomarkers of radiotherapy toxicity to reduce side-effects and improve quality-of-life in cancer survivors**	
Funding Scheme: **Collaborative Project (FP7-HEALTH-2013-INNOVATION-1)**	
Project start date: **01 October 2013**	Duration: **60 months**
Project's coordinator: **Prof Catharine West (University of Manchester, UK)**	

Deliverable no.: **D2.6**	Title: **Report on all recruited patients placed on REQUITE website**	
Due date: **Month 60 (30 September 2018)**	Actual date: **Month 62 (23 November 2018)**	
Aim of the Deliverable: To report on final recruitment to the observational study, and provide an update on the associated REQUITE resource namely collection of longitudinal, standardised radiotherapy toxicity and quality of life data, physics data and associated biobank. **Deliverable D2.5 has been achieved in full**.		
Lead beneficiary for this deliverable: **Jenny Chang-Claude (B2)**		
Personnel involved: **Catharine West, Rebecca Elliott, Debbie Payne, Antony Payton (B1); Petra Seibold, Kerstin Pieper, Anusha Müller (B2), Liv Veldeman (B3); Adam Webb, Paul Symonds, Chris Talbot (B4); Dirk De Ruysscher (B5, B13); David Azria (B7, B15); Tiziana Rancati, Riccardo Valdagni (B8); Ana Vega, Sara Gutierrez Enriquez (B9); Ananya Choudhury (B1, B10); Barry Rosenstein (B12); Sylvie Canisius (B13); Frederik Wenz (B14).**		

Dissemination level:		
PU	Public	**X**
PP	Restricted to other programme participants (within the Commission)	
RE	Restricted to a group defined by the consortium (including the Commission)	
CO	Confidential, only for members of the consortium (including the Commission)	

1. Why REQUITE?

REQUITE worked to address an ambitious and urgent need to reduce long-term side effects and improve health-related quality-of-life in cancer survivors who received radiotherapy. The motivation for the project was the need to move away from a one-size-fits-all approach to treatment. Survivorship issues are particularly relevant for radiotherapy as it is an important potentially curative treatment in many cancers. Although many models and biomarkers have been developed that appear to identify patients with an increased risk of long-term side-effects, validation is rare. Progress is hampered because data and samples are not generally collected in routine clinical practice and any datasets available are heterogeneous. Missing and harmonisation of existing data are problematic. The main achievement of REQUITE was completing an observational study, the largest of its kind, which is recognised as an exemplar of the type of multi-disciplinary, multi-national work that can and should be carried out in the radiotherapy-related research field.

2. REQUITE Objectives

(1) Perform a multi-centre, observational cohort study

The first objective of REQUITE was to perform a multicentre observational study to collect standardised radiotherapy toxicity data, non-genetic risk factor data (e.g. dosimetry, chemotherapy use, age, diabetes, smoking history, gender) and samples for biomarker assays with centralised prospective data collection and biobanking. A key priority for the consortium was the collection of the same data (according to SOPs) in multiple centres. Also to minimise the amount of missing data that has traditionally hampered the research community's ability to validate models that predict a cancer patient's risk of side effects following radiotherapy. Finally to provide an accessible centralised database for future radiotherapy related studies. The database was customised specifically to meet the needs of REQUITE, to allow for the collection of dose volume histograms, the centralised storage of digital photographs of breast cancer patients and for electronic data capture of patient reported outcomes. Although there are numerous cancers for which radiotherapy is an important part of potentially curative treatment, REQUITE focussed on the three most prevalent cancer sites for both gender: breast, prostate and lung.

(2) Produce a centralised biobank

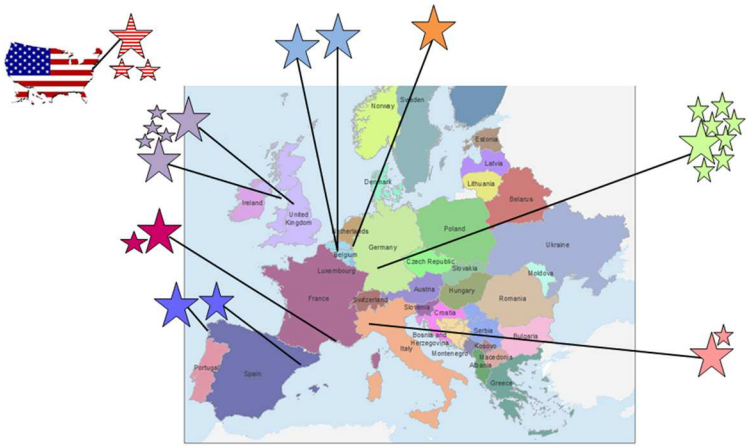
The second objective of REQUITE was to produce a centralised biobank of DNA from the patients enrolled in the observational study. This biobank would be linked to the clinical database. Biobanking is critically important for future developments in health research and there is a demand for high quality samples linked to accurate, reliable, and standardised clinical and laboratory data. Sample collection, processing, storage, tracking, and shipment of biospecimens would be optimised and ISO standards applied. REQUITE worked to produce a centralised, easily accessible, high quality resource linked to the clinical database with centralised DNA extraction for use in biomarker studies not only those in REQUITE but also future studies.

3. REQUITE Recruitment

REQUITE set an ambitious two year target from 1st April 2014 to 31st March 2016 to recruit 2,100 breast cancer patients, 2,100 prostate cancer patients and 1,100 lung cancer patients. However, due to delays receiving some regulatory approvals recruitment was extended by six months for breast and prostate patients to 30th September 2016 allowing time for collection of the primary end point at two years following radiotherapy, and by 12 months for lung patients to 31st March 2017 for collection of follow-up data one year following radiotherapy.

The radiotherapy schedule was prescribed by the local physician according to local standard-of-care, and patients were followed up by their local cancer care team. The primary endpoints were change in breast appearance at two years (breast), rectal bleeding at two years (prostate) and breathlessness at 12 months (lung). The study was registered with International Standard Randomised Controlled Trial Number Register (ref: ISRCTN98496463) http://www.controlled-trials.com/ISRCTN98496463

Patients were recruited at 26 hospitals in eight countries. The main centres were in Gent & Leuven (Belgium), Montpellier (France), Heidelberg area & Mannheim (Germany), Milan (Italy), Maastricht (Netherlands), Santiago de Compostela & Barcelona (Spain), Manchester & Leicester (UK), and New York (USA).



In total, 4,438 patients with breast, prostate or lung cancer were recruited prospectively (see table).

Country	**Belgium**		**France**	**GER**	**Italy**	**NL**	**Spain**		**UK**		**USA**	
Main site	Gent	Leuven	Montpellier	Heidelberg/ Mannheim area	Milan	Maastricht	Barcelona	Santiago	Leicester	Manchester	New York	**TOTAL**
Breast	298	253	458	216	102	--	215	101	350	--	76	**2,069**
Prostate	199	127	264	82	206	74	--	294	250	263	49	**1,808**
Lung	53	90	53	--	55	61	36	88	42	51	32	**561**
												4,438

Thanks to the patients who agreed to take part in the REQUITE study, the consortium achieved:

- 99% of target for breast (n=2,069)
- 86% of target for prostate (n=1,808)
- 51% of target for lung (n=561)

Furthermore ‘additional lung cohorts’ were identified at two centres across the consortium such that samples from 383 additional lung cancer patients were genotyped alongside the REQUITE cohorts. The associated phenotype data is also available and will be included in the lung GWAS (n= 944). Although the datasets associated with these additional cohorts are not as comprehensive as in REQUITE, 12 month follow up data was collected that included REQUITE’s primary endpoint for lung namely breathlessness.

4. REQUITE Data

REQUITE produced standardised case report forms to collect epidemiological, treatment, side-effect and quality-of-life data from patients recruited across the 26 hospitals. Questionnaires for collecting patient reported side effects (developed from the Common Toxicity Criteria for Adverse Events v4) were translated into multiple languages (German, Spanish, French, Italian & Dutch), and validated by testing the specific wording and overall acceptability in multiple, small patient cohorts. These forms are being shared worldwide to improve the standardisation of data collection.

REQUITE collected (and continues to collect) a lot of information including patient reported outcome data (PRO) and evaluations from the health professional team (MD) (see table).

Uploaded data forms on side effects in the REQUITE database by time points (as of November 2018)												
Time Point	**Baseline**		**RT end/ 3 months**		**6 months**		**12 months**		**24 months**		**36 months**	
	PRO	**MD**	**PRO**	**MD**	**PRO**	**MD**	**PRO**	**MD**	**PRO**	**MD**	**PRO**	**MD**
Breast: 2,069	2000 (97%)	2057 (99%)	1865 (90%)	2057 (99%)	--	--	1732 (84%)	1870 (90%)	1529 (74%)	1707 (83%)	353 (17%)	336 (16%)
Prostate: 1,808	1711 (95%)	1760 (97%)	1647 (91%)	1760 (97%)	--	--	1505 (83%)	1627 (90%)	1378 (76%)	1463 (81%)	338 (19%)	227 (13%)
Lung: 561	487 (87%)	530 (95%)	394 (70%)	495 (88%)	339 (60%)	419 (75%)	268 (48%)	332 (59%)	93 (17%)	95 (17%)	*n/a*	*n/a*

RT=radiotherapy, PRO=patient reported outcome; MD=medical doctor evaluation based on standardized classification of side effects

Anonymised patient data are held in a bespoke central database at The University of Leicester in the UK. A comprehensive data validation and QC process was completed. The database contains:

- >100,000 completed case record forms (completed by patients & health professionals)
- 11,563 breast photos (photographs taken from three angles at two time points per patient)
- 17,107 DICOM files (radiotherapy treatment plans)
- 12,684 DVH files (radiation dosimetry files)
- 2.04 billion directly typed genotypes from 4,634 patients
- 55.2 billion imputed genotypes from 4,304 patients

5. REQUITE Samples

All patients donated at least two blood samples prior to the start of radiotherapy: an EDTA sample for SNP genotyping and a PAXgene and/or a Lithium Heparin sample. DNA was extracted from the EDTA blood sample for genotyping common genetic variants (single nucleotide polymorphisms), which took place at The University of Cambridge, UK; and PAXgene samples are stored in the centralised biobank for RNA extraction. These samples are held in the CIGMR Biobank at The University of Manchester, UK. Therefore REQUITE succeeded in establishing a centralised biorepository linked to the database.

In addition, a subset of patients from France, Germany and the UK gave a blood sample in a Lithium Heparin tube for prospective radiation induced lymphocyte apoptosis (RILA) assays using an established method developed by Prof David Azria at the Institute of Cancer in Montpellier

France. All three recruitment centres followed the same SOP to ensure standardisation across the laboratories. Data from the RILA assay were generated on 1,319 patients, which is also stored in the central database.

The DNA extracted from patient blood samples was of high quality and was fit for purpose. Sufficient DNA was extracted for use within REQUITE for genotyping as planned but also – where explicit permission was given by the patient in the consent form - for DNA to be shared for related research studies carried out by members of the REQUITE consortium and for sample sharing with the wider radiotherapy research community.

6. REQUITE for the future

Recognising the enormous contribution made by the REQUITE patients, the consortium has created a comprehensive centralised database and linked biobank that will serve as a valuable resource for the international radiotherapy community. It will provide data to validate models and biomarkers, and their use in future interventional trials will have a long-term impact on the health-related quality-of-life of cancer survivors.

Two video shorts were produced to explain the work of REQUITE. One is aimed at current/ recently diagnosed patients https://www.requite.eu/node/189 and the second is for health professionals and researchers https://www.requite.eu/node/190.

The videos summarise i) the core aims of the project, explaining the importance and motivations of the REQUITE consortium, the success of the observational study and what impact it will have on future treatments and research and ii) highlighting the REQUITE resource to increase visibility and promote data discoverability.

The REQUITE patient video highlights the goals of this multi-centre international study and the progress so far. The audio of the patient video is in English but is subtitled in Spanish, French, German, Italian, Dutch and also English.

- Erik Briers, member REQUITE patient advisory group: "For the REQUITE project, the optimal outcome would be that it could find a marker that could be analysed in future patients".
- Chris Talbot, deputy lead of REQUITE: "A big thank you has to go to every patient, because their involvement will help patients in the future who are undergoing cancer treatment."

A patient focussed animation is also available to try and address the concerns and questions of patients who have recently been diagnosed with cancer and expect to receive radiotherapy as part of their care: https://www.requite.eu/node/193. It highlights the work of REQUITE, progress to date and describes the breadth of the resource for future research that aims to help more patients survive and improve their quality of life.