The digital Experimental Cancer Medicine Team

Engaging patients, Driving decisions

2022 Report

Digital Experimental Cancer Medicine Team

CANCER RESEARCH UK | MANCHESTER INSTITUTE | CANCER BIOMARKER CENTRE

MANCHESTER 1824
The University of Manchester

NHS
The Christie
NHS Foundation Trust

Contents

World leading scientific research, including pioneering work in precision medicine and cancer treatment is brought together through the Manchester Cancer Research Centre (MCRC) partnership, a unique collaboration that brings together the expertise, vision and resources of its partner organisations: Cancer Research UK, The University of Manchester and The Christie NHS Foundation Trust, all of which have formidable individual reputations in the field of cancer research.

We are excited to join all our Manchester Cancer Research Centre colleagues in the new facility adjoining The Christie during 2023.

Introduction

During 2022 digital ECMT have continued engagement with patient communities and colleagues across Manchester, at The Christie NHS Foundation Trust and Manchester Royal Infirmary as well as national and international collaborators, including Cancer Core Europe, Target National and CRUK UpSMART Accelerator Consortium.

We continue to deliver against our 2021-2025 digital ECMT strategy, with focused leadership from Dr. Donna Graham for our Technology Clinical Trials, Andre Freitas for ethical AI research and Paul Fitzpatrick on Innovative Technology to fulfil our research themes. Further information on each of these areas mentioned above can be found later in the report.

The challenge of managing this portfolio of research, focused on technology clinical trials, algorithms and software, is taken up by The Portfolio Administration and Delivery Team, led by Laura Stephenson. For a summary of our 2022 deliverables and achievements, see (pages 12-13).

The Technology Clinical Trials team has marked many milestones over the last year. Recruitment has continued on the IN-HOME and NOTION studies with completion of patient recruitment on the first phase of the A-EYE study, and progress continued on development of the APACE study. The team discussed the unique challenges faced in developing technology clinical trials in an inclusive manner. Manchester Academic Health Science Centre (MAHSC) funding had been competitively attained to engage with patients and researchers in this area to develop guidelines for inclusivity. Description of the resulting process was selected for oral presentation at the ESMO-EONS conference and awarded the Commitment to Equality Award at the inaugural Greater Manchester Cancer Awards.

Looking ahead to 2023, we aim to continue recruitment to the IN-HOME and NOTION studies with movement into the next phase of the A-EYE study. We look forward to beginning recruitment on the multi-site, multi-national APACE study, using accelerometers to assess activity and sleep in patients on early phase clinical trials. In addition, we continue to work with our collaborators in industry and other academic sites to develop further ideas for technology clinical trials in the year ahead, using inclusive practices to develop these, following publication of our inclusivity guidelines.

Dr Donna Graham. BSc MBBCh MRCUPK PhD

Technology Trials Group Lead

The Artificial Intelligence team progressed on promoting the dialogue between emerging AI methods and their clinical impact. During the last year, the group focused on the development of new methods which can facilitate the integration of distributed, heterogeneous evidence in order to support cancer clinical trials and the discovery of new treatment opportunities. In the context of Horizon 2020 CCE-DART (Cancer Core Europe building DAta Rich clinical Trials) the group explored the impact of generative and explainable AI models to support the integration of multi-omics data for the creation of new complex biomarkers. This is a research avenue which we will continue maturing during 2023. Moreover, the emergence of Large Language Models lowered the barriers to deliver systems capable of interpreting natural language at scale. We are exploring how these models can enable better patient-trial matching and can facilitate oncology experts dialoguing with a growingly complex literature and data landscape. We continue to hold a critical perspective on these emerging technologies, emphasising their ethical and safety alignment within the oncology context.

Dr Andre Freitas

AI Group Lead

Senior Lecturer in Computer Science, University of Manchester, Information Management

It has been another productive year for the Technology Solutions Group and we have achieved the following:

• Provided and maintained Open Source versions of a number of digital health care products. Code has been made available in 14 public repositories of the digital ECMT GitHub.

• Operated a secure and rapid deployment of the Azure platform to support the team's research activity and hosting of live applications. This includes software that enhances Molecular Tumour Boards, augments the matching of patients to Clinical Trials and enables insightful visualisations of clinical trial data.

• We have collaborated with hospitals across Europe and are currently focusing on making digital health care products easier to access, deploy and use.

Paul Fitzpatrick

Technology Solutions Lead

digital ECMT –
strategic ambitions to 2025

In 2022, the digital ECMT continued to enact its new vision to "digitally empower patients and healthcare professionals to innovate and design new cancer care pathways" and implement its mission statement "To provide next generation patient cancer care through comprehensive data-driven evidence to enable the transformation of clinical decision-making, evolve the role of the patient, and improve patient outcomes". This strategy is being achieved by continuously listening to our patients and healthcare professionals, to understand their needs and work proactively with them in our technology clinical trials. These long term goals can be summarised as follows:

1. Develop AI models to support patient care and scientific discovery in oncology.

Our research programme continued to focus on the development of AI models that can support inference clinical decision making in the context of experimental medicine. An emphasis in 2022 was on advancing the mechanisms to scale-up the integration of prior biomedical knowledge within AI models which can support clinical decision making in cancer clinical trials. As priority areas, we investigated biologically-informed deep learning models as a mechanism to develop clinical decision support tools which are better grounded within known biological processes as well as improving

the explainability of the models. Moreover, we developed an explainable meta-analysis informed machine learning model to support the prediction of CRS events, in close dialogue with previous evidence. Expanding on the major developments in language models and generative AI, we critically assessed the ability of these models to support access to large-scale evidence.

2. Build digital solutions to address clinical unmet needs

Key digital solutions delivered in 2022 include: Completion of the iMATCH programme with delivery of a Decision Support System (DSS) for cytokine prediction, continued support of our eTARGET and digital ECMT Cancer Trial Match tools in multi-site clinical trials, an open-source version of the visual analytics system ACUITY. Furthermore, we scoped the development of new tools, based on unmet clinical needs, as part of the Cancer Research UK UpSMART Accelerator Award and repurposing of the dashboard developed for COVID-19, for an oncology use-case, began.

3. Evaluate our technologies under clinical trial conditions (technology clinical trials).

In January 2022, the IN-HOME nephro-oncology study (Home Monitoring of Creatinine in Cancer Patients: Assessing

Acceptability and Clinical Benefit) opened and recruited its first patient to Part B, to assess clinical benefit. The A-EYE ophthalmo-oncology study completed recruitment of 350 patients in August 2022, and the first NOTION (iN-home sampling Of cyTokines in ImmunOtherapy patieNts) study patient was recruited in March. To ensure our research and technology clinical trials processes and practice are more inclusive, inclusivity guidance has been developed following a series of MAHSC funded focus groups with diverse populations. We are proud that this piece of work won Commitment to Equality Award at the Greater Manchester Cancer Awards in October 2022.

Based upon our distinctive research capability, the digital Experimental Cancer Medicine Team (digital ECMT) continued to develop, innovate and deliver 'technology' (software, algorithms, medical devices) clinical trials, which evaluate not only performance characteristics of technology and patient / user acceptability but also clinical benefit showing how the technology enables beneficial changes in the patient care pathway inside and outside of hospitals.

Our research continues to be delivered through our five key research themes, to which we align our research programmes, projects and team resources – as shown below (Figure 1):
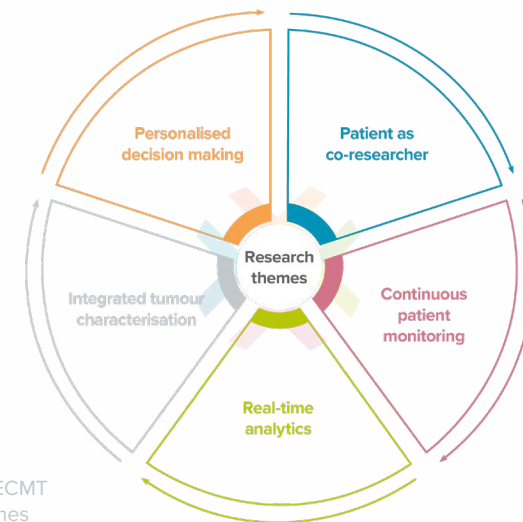
Figure 1: digital ECMT Research themes

The Team

We continue to embrace the COVID legacy of hybrid-working but recognise the value of in-person interactions, increasing the amount of time spent with colleagues in the office, or, for some of us, at the hospital sites closely linked to our Trials.
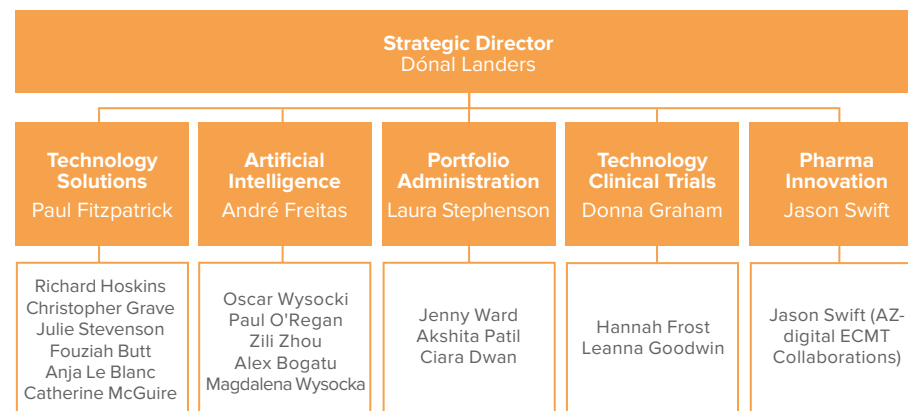
During 2023 we will be co-located within the research space in the new facility being built next to The Christie, something we are all excited about!
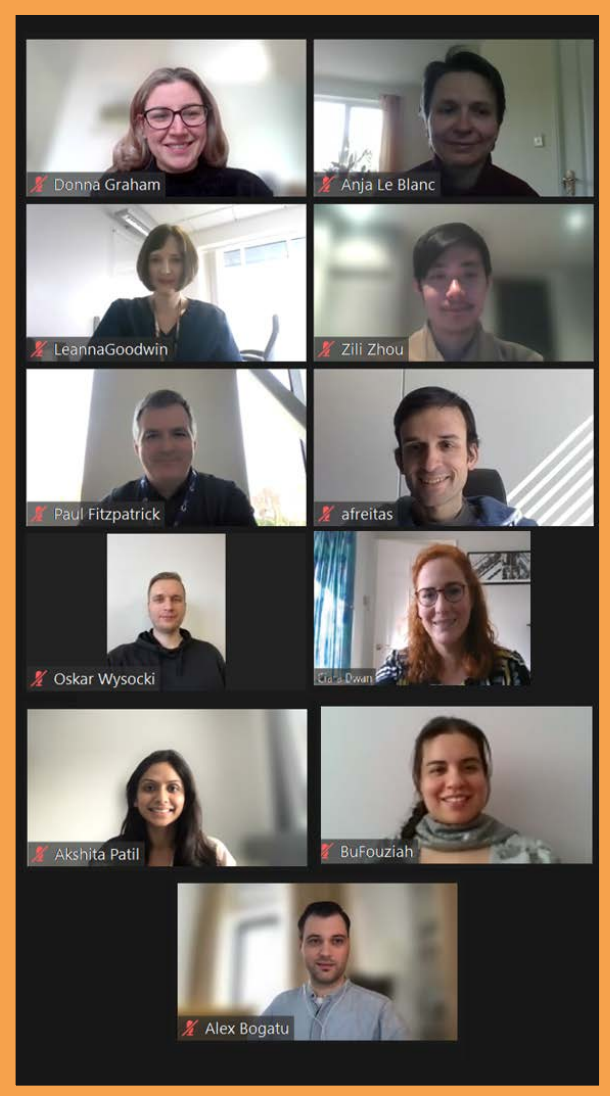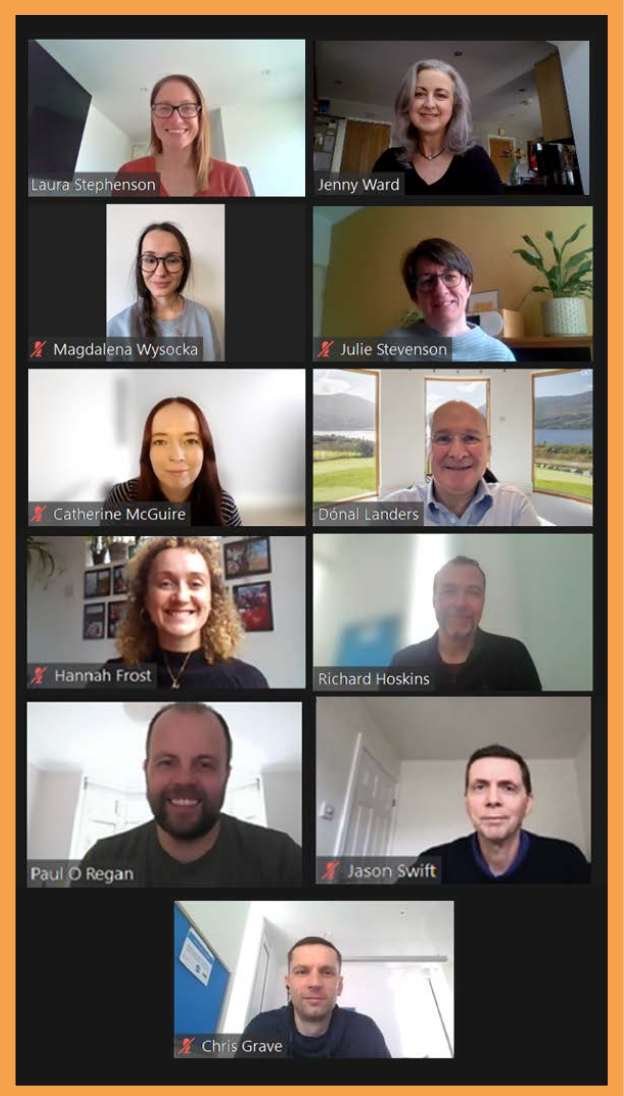
Leavers

During the year, Dónal, our Strategic Director, decided to step down from his role at the digital ECMT for family reasons and also to prioritise his work in oncology early clinical development, his main speciality. The entire team would like to thank Dónal for his valuable input to the team since its inception. His passionate enthusiasm for people – patients, healthcare professionals and team members alike; together with his creative ideas, strategic thinking and clinical and consultancy experience, will be missed by all the team. We wish him luck, success and happiness in all his future endeavours – we know he won't be a stranger!

Skillsets within digital ECMT

Clinical Oncology	Translational Science	Data Science	Artificial Intelligence
Machine Learning	Early Clinical Development	Technology Clinical Trials	Software Development
Project Management	Enterprise Systems Development	Business Analysis	Patient Engagement
Clinical Operations	Nephrology	Mobile Application Development	Care Pathway Development

digital ECMT Organisational Structure 2022

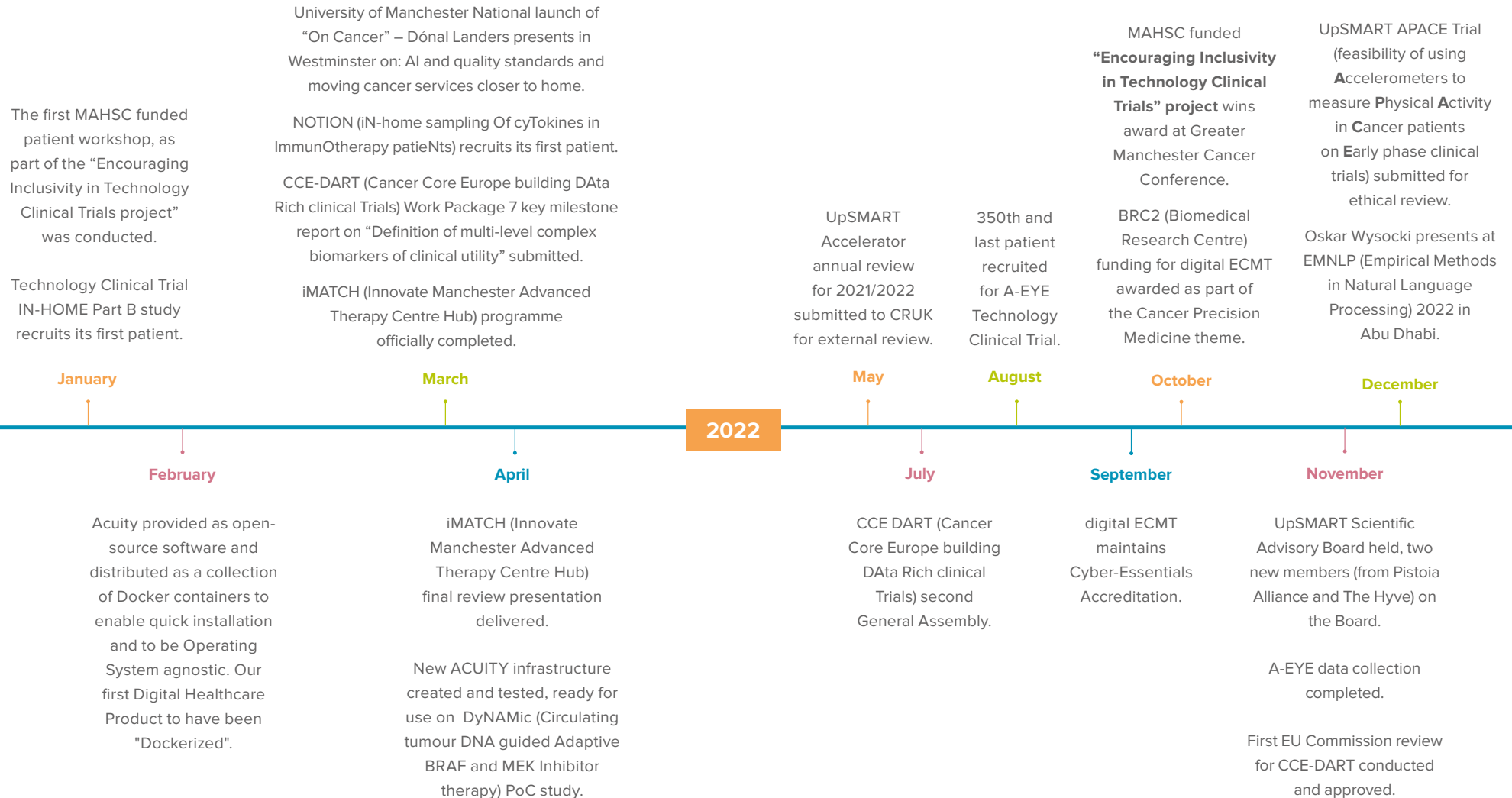| Strategic Director — Dónal Landers				
Technology Solutions Paul Fitzpatrick	**Artificial Intelligence** André Freitas	**Portfolio Administration** Laura Stephenson	**Technology Clinical Trials** Donna Graham	**Pharma Innovation** Jason Swift
Richard Hoskins Christopher Grave Julie Stevenson Fouziah Butt Anja Le Blanc Catherine McGuire	Oscar Wysocki Paul O'Regan Zili Zhou Alex Bogatu Magdalena Wysocka	Jenny Ward Akshita Patil Ciara Dwan	Hannah Frost Leanna Goodwin	Jason Swift (AZ-digital ECMT Collaborations)

Meet the Team

2022 Timeline

2022 was another busy year for the digital ECMT, embedding our 2021-2025 strategy, while still maintaining our momentum and continuing to deliver solid research and innovation. Some highlights of our work over the year are shown below.

January

The first MAHSC funded patient workshop, as part of the "Encouraging Inclusivity in Technology Clinical Trials project" was conducted.

Technology Clinical Trial IN-HOME Part B study recruits its first patient.

February

Acuity provided as open-source software and distributed as a collection of Docker containers to enable quick installation and to be Operating System agnostic. Our first Digital Healthcare Product to have been "Dockerized".

March

University of Manchester National launch of "On Cancer" – Dónal Landers presents in Westminster on: AI and quality standards and moving cancer services closer to home.

NOTION (iN-home sampling Of cyTokines in ImmunOtherapy patieNts) recruits its first patient.

CCE-DART (Cancer Core Europe building DAta Rich clinical Trials) Work Package 7 key milestone report on "Definition of multi-level complex biomarkers of clinical utility" submitted.

iMATCH (Innovate Manchester Advanced Therapy Centre Hub) programme officially completed.

April

iMATCH (Innovate Manchester Advanced Therapy Centre Hub) final review presentation delivered.

New ACUITY infrastructure created and tested, ready for use on DyNAMic (Circulating tumour DNA guided Adaptive BRAF and MEK Inhibitor therapy) PoC study.

2022

May

UpSMART Accelerator annual review for 2021/2022 submitted to CRUK for external review.

July

CCE DART (Cancer Core Europe building DAta Rich clinical Trials) second General Assembly.

August

350th and last patient recruited for A-EYE Technology Clinical Trial.

September

digital ECMT maintains Cyber-Essentials Accreditation.

October

MAHSC funded **"Encouraging Inclusivity in Technology Clinical Trials" project** wins award at Greater Manchester Cancer Conference.

BRC2 (Biomedical Research Centre) funding for digital ECMT awarded as part of the Cancer Precision Medicine theme.

November

UpSMART Scientific Advisory Board held, two new members (from Pistoia Alliance and The Hyve) on the Board.

A-EYE data collection completed.

First EU Commission review for CCE-DART conducted and approved.

December

UpSMART APACE Trial (feasibility of using **A**ccelerometers to measure **P**hysical **A**ctivity in **C**ancer patients on **E**arly phase clinical trials) submitted for ethical review.

Oskar Wysocki presents at EMNLP (Empirical Methods in Natural Language Processing) 2022 in Abu Dhabi.

The Technology Clinical Trial
Delivering tomorrow's clinical trials today

2022 has been filled with challenges, successes, valuable contributions from patients and others contributing to workshops and focus groups. We are incredibly proud of the achievement of the team involved in the MAHSC funded Encouraging inclusivity in technology clinical trials project, presented at The Great er Manchester Cancer Awards – and covered in the **Manchester Evening News**. We continue to recruit to our open Technology Clinical Trials.

IN-HOME

Some anticancer therapies cause damage to kidneys. Such nephrotoxicity of anticancer agents may limit dosing and impact effectiveness. Improved monitoring of renal function could potentially lead to earlier detection of adverse renal events and improve outcomes for patients with malignancy.

The IN-HOME study assesses the feasibility and acceptability of using a whole blood creatinine Point-of-care testing (POCT) device (NOVA Biomedical StatSensor® Xpress) to monitor patients kidney function whilst receiving potentially nephrotoxic anti-cancer treatments. digital ECMT have been working on this project for 5 years now, developing and implementing the end to end process by which creatinine can be monitored by patients in the home and an AKI assessment made and reported to an appropriate clinician.

Part A of the trial opened late in 2019, but due to COVID-19 had delays to recruitment when research trials were paused. In Q1 of 2021, we completed Part A of the study having enrolled 13 Head and Neck cancer patients and 1 Experimental Cancer Medicine Team Breast cancer patient.

Based on the successful results from the Part A feasibility assessment, which showed that intensive home monitoring of creatinine with a POCT device is acceptable for patients receiving cancer treatments, with a high degree of patient compliance, Part B of the trial recruited its first patient in January 2022. This part of the trial aims to assess the clinical benefit of home based creatinine monitoring by evaluating the potential for earlier diagnosis of AKI / change in renal function in cancer patients with intensive home monitoring. The recruitment target is 60 patients for Part B, with 30 being recruited to the standard of care arm and 30 to the monitoring arm, who will use the POCT device. To date we have recruited 12 patients to Part B.

A-EYE

This ophthalmo-oncology project was initiated to try and address resourcing issues which can leave cancer patients, particularly those on early phase cancer clinical trials, requiring specialist eye treatment and support. Novel cancer therapies often have unknown toxicity profiles that can include changes to the eye. Many clinical trials now require regular ophthalmology assessments with ongoing expert opinion, which may extend beyond the trial and place an increased burden on the ophthalmology service. As these novel agents progress into later phase trials and approved usage the burden on ophthalmology services will further increase.

The University of Manchester sponsored A-EYE study, aims to develop new AI methods to detect adverse retinal abnormalities associated with cancer treatment and assess against ophthalmologists' decisions. This study opened to recruitment at the Manchester Royal Eye Hospital in June 2021 (our collaborators on this study). By November 2022, data collection from all 350 patients recruited to the study had been completed. The data collected from the patients includes their anonymised eye scan alongside relevant clinical data. Our AI team are using these to develop and test an ethical and explainable algorithm to detect eye toxicities from eye scans. We have extended the study to a further 20 consultant specialist ophthalmologists, who will be interviewed to discuss the acceptability of the AI algorithm in clinical practice and a further 100 patients will complete a questionnaire on the use of AI in their care.
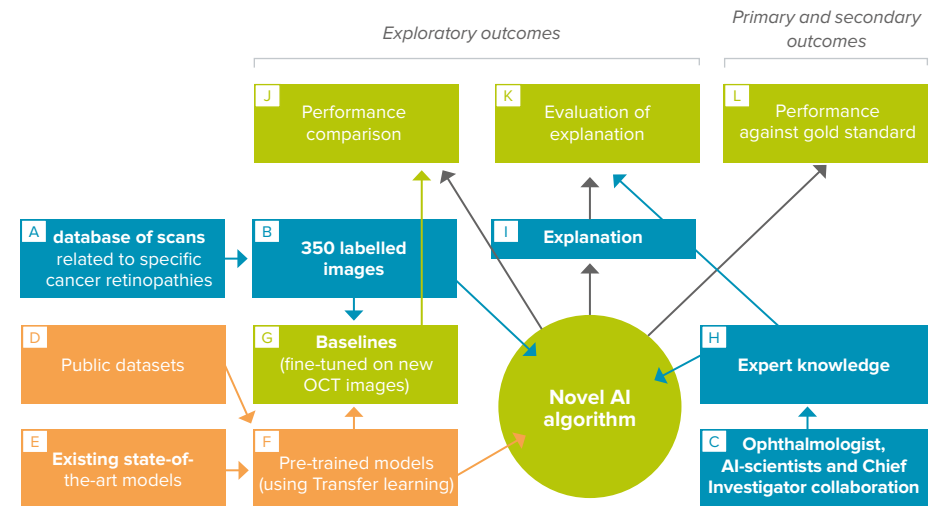

Figure 2: AI algorithm development diagram

NOTION

Use of immunotherapy for treatment of cancer is increasing in both routine management and clinical trials. Side effects related to the mechanism of action of these treatments are termed immune-related adverse events. These adverse events are very common with up to 90% of patients experiencing side effects on combination immunotherapies. Early evidence suggests that changes in cytokines may correlate with the development of immune related adverse events. Therefore, monitoring of cytokines may help detect the onset of side effects and help manage them better for patients. The NOTION study (iN-hOme sampling of cyTokines in Immunotherapy patieNts) is a feasibility study to assess whether patients will take blood samples at home. The blood samples will be analysed retrospectively to assess whether changes in patients' cytokines correlate to the development of immune-related adverse events. The NOTION study is a great example of collaborative working. We have partnered with the Immuno-Oncology group at

The Christie to develop the study protocol and research package. Additionally, we have worked closely with the CRUK MI CBC Cells and Protein Team, Tumour Immunology & Inflammation Monitoring Lab to validate the lab method for detection of cytokines from a dry-blood spot sample.

The NOTION study recruited its first patient in March 2022 and participants include patients with Head & Neck, Renal and Urology malignancies. This feasibility study gives the opportunity to explore the end-to-end process of patients collecting their own samples in the home and postage of them to a lab for analysis prior to review by the research team. To date 11 out of 30 patients have been recruited to the study and 377 samples have been collected by patients in their homes, posted and received by the CRUK MI labs and successfully analysed. End of study patient interviews are being conducted and will give a unique insight into the challenges and practicalities of home sampling and the logistics around it.

Images provided by Neoteryx, LLC

MAHSC funded "Encouraging Inclusivity in Technology Clinical Trials" project

There is a growing appreciation of the impact of a "digital divide" in healthcare technology which should be addressed during study design to ensure modified care pathways are inclusive to all. In 2021, we were successful in a Manchester Academic Health Science Centre funding proposal, and in February we completed a 7-month collaboration with specialist organisations including Vocal (a Manchester-based not-for-profit organisation which brings people and health research together) to create agreed inclusivity guidance for future development of technology clinical trials across Greater Manchester and beyond. We hope to ensure that our future healthcare pathway development is designed to include all patients, regardless of access and skill with technology.   See the Collaborations and Grants/Awards in 2022 section for more information.

Figure 3: Leanna Goodwin – Diversity in Technology Clinical Trials at ESMO congress, Paris 2022

Decision Science
Supporting the way we interpret clinical trials and make decisions
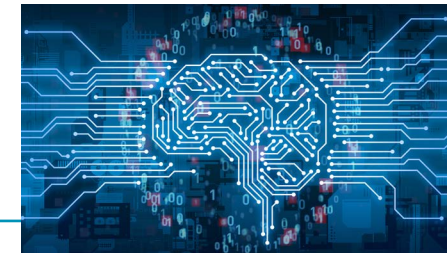
The activities of the AI Team at the digital ECMT concentrated on the development of new AI methods which can support the interpretation of increasingly complex patient data to improve disease understanding and to support the design of new treatments in oncology.

The recent evolution of generative AI methods brings the opportunity to address the challenge of integrating and interpreting fragmented and heterogenous evidence, which can be used to inform the development of new predictive multi-layered biomarkers, better understanding between responders and non-responders and patient-treatment matching.

Strategic research areas currently emphasised at the digital ECMT include:

- Biologically-informed deep-learning models: supports the integration of existing prior mechanistic knowledge (e.g. signalling pathways) into predictive models, providing models with better biological consistency, explainability and data efficiency.

- Generative models for the integration of multi-omics data: development of generative models (such as Variational Autoencoders – VAEs) specialised for integrating multi-omics data, across different studies. Particular emphasis is given to delivering robust inference

controls in order to find most similar cases, which can be used as anchor points for clinical reasoning.

- Natural language inference: Using the recent advances in generative Natural Language Processing (NLP), we are systematically assessing their ability to support scale-up text understanding, for example using the semantic flexibility introduced by these methods to find best matching candidate trials.

- Pragmatic evaluation of safe, explainable and ethical AI in oncology: Developing AI models suitable for Healthcare with a particular emphasis on safety, explainability, ethical awareness and on their pragmatic assessment to support clinical reasoning.

Moreover, we continued the engagement with Cancer Core Europe (CCE), in the context of the HORIZON 2020 DART consortium (Developing DAta Rich Clinical Trials), focusing on the translation of contemporary AI methods into a clinical trials setting.

These strategic areas have delivered the following outcomes:

- Bogatu, M. Wysocka, O. Wysocki, H. Butterworth, M. Pillai, J. Allison, D. Landers, E. Kilgour, F. Thistlethwaite, and A. Freitas. Meta-analysis Informed Machine Learning: Supporting Cytokine

Storm Detection during CAR–T cell therapy. Journal of Biomedical Informatics, 2023.

The paper addresses a problem introduced by the variability of general symptoms associated with Cytokine release syndrome (CRS), its low prevalence and the sub-optimal standardisation of cytokine biomarkers preventing accurate and explainable statistical analysis. Several CRS clinical studies have suggested that, when patient data is available, statistical and analytical investigations of carefully selected cytokines can support CRS prediction. However, existing studies do not include correlations with previous work and they also employ statistical methods with low adoption among clinicians due to their lack of explainability. This paper proposes a general meta-analysis informed machine learning framework that is applied to CRS detection, built on evidence from current data and previous studies and explainable with respect to existing CRS knowledge. This was a key final output from our works as part of the iMATCH consortium.

- M. Wysocka, O. Wysocki, M. Zufferey, D. Landers, A. Freitas. A systematic review of biologically-informed deep learning models for cancer: fundamental trends for encoding and interpreting oncology data. Bioinformatics, 2023.

There is an increasing interest in the use of Deep Learning (DL) based methods as a

supporting analytical framework in oncology. However, most direct applications of DL will deliver models with limited transparency and explainability, which constrain their deployment in biomedical settings. The paper provides a critical outlook into contemporary methods for explainability and interpretability used in DL for cancer with a particular emphasis on multi-omics analysis. It focuses on how existing models address the need for better dialogue with prior knowledge, biological plausibility and interpretability, fundamental properties in the biomedical domain. The analysis points in the direction of a convergence between encoding prior knowledge and improved interpretability. We introduce bio-centric interpretability which is an important step towards formalisation of biological interpretability of DL models and developing methods that are less problem – or application-specific.

- Mael Jullien, Marco Valentino, Hannah Frost, Paul O'Regan, Donal Landers, and André Freitas. 2023. Semeval-2023 task 7: Multi-evidence natural language inference for clinical trial data. In Proceedings of the 17th International Workshop on Semantic Evaluation.

We organised 2 SemEval tasks, a Natural Language Inference task, and an evidence selection task on clinical trial data, annotated by our team of domain experts. The proposed challenges require multi-hop biomedical and

UpSMART Accelerator update

numerical reasoning, which are of significant importance to the development of systems capable of large-scale interpretation and retrieval of medical evidence, to provide personalised evidence-based care. The combined tasks received over 1000 submissions from 23 participants. The tasks are challenging, with the majority of submitted systems failing to significantly outperform the majority class baseline on the entailment task, and we find that increasing the number of model parameters leads to the most significant and direct increase in performance.

Empirical Methods in Natural Language Processing, Abu Dhabi, December 7-11 2022

Oskar Wysocki attended the 2022 Conference on Empirical Methods in Natural Language Processing, Abu Dhabi, December 7-11 2022, where he gave a talk presenting the recent work on 'Transformers and the Representation of Biomedical Background Knowledge' (in collaboration with other members of the team: Zili Zhou, Paul O'Regan, Magdalena Wysocka). During the talk, he discussed the potential utility of language models to support inference in cancer precision medicine—namely, the interpretation of the clinical significance of genomic alterations. The paper is published in *Computational Linguistics* (2023) 49 (1): 73–115.

The digital ECMT, along with our EU colleagues, including those from Fondazione IRCCS Istituto Nazionale dei Tumori Milano and Instituto de investigación Oncologica de Vall d'Hebron, Barcelona continued to work collaboratively on the 5-year CRUK Accelerator Award, UpSMART, to enable SMART Experimental Cancer Medicine Trials.

Year 3 of the Accelerator award (2022) has been another busy year for the UpSMART team, who continue to support the uptake and adoption of digital healthcare products (DHPs) that have been made available to the network and progress development of several prioritised DHPs in the network's portfolio. The DHPs that have been made available to date are described below:

Cancer trial finder template - Displays all recruiting clinical trial options to members of the local clinical research team thus improving awareness to clinical research staff as to open clinical studies, thereby improving opportunities for patients' access to clinical trials (Oct 2021)

dECMT Cancer Trial Matching tool - System to help clinicians identify the right clinical trials for patients. It integrates a patient's cancer type and tumour genotype with ClinicalTrials.gov and other online data sources and returns a list of potential matching trials (Jan 2021)

eTARGET - Decision-support system integrating the patient's genomic profile with their clinical characteristics. Used as part of a monthly Molecular Tumour Board (July 2021)

CORONET, COVID-19 Risk in ONcology Evaluation Tool - A web-based decision support DHP which allows clinicians to enter 10 physiological criteria and based on a machine learning algorithm provides a likelihood of whether a cancer patient presenting with COVID-19 symptoms will require hospital admission (v2 May 2021)

ACUITY - Interactive set of visualisations for clinical trial data which has been entered into the clinical trial database; for data interpretation at both the population and patient level to enable an earlier understanding of patient benefit-risk profile). The code base for ACUITY was made open-source early in 2022. The open-source license ensures that the ACUITY Tool is freely available and can be enhanced by users should they wish. Distributing ACUITY as Docker containers enables it to be installed quickly and allows it to run on most computers regardless of Operating System. (Jan 2022)

PIPO, Phase I prognostic online - An online tool that can be used as an objective way for predicting overall survival outcomes in patients prior to enrolment on early phase clinical trials (March 2021)

PROACT 2.0, Patient Reported Opinions About Clinical Tolerability - A patient application for secure, direct communication between clinical trial participants and their medical team. PROACT 2.0 has been developed by the team at INT Milan in conjunction with Work Package 2 over 2022 (WP2) (Jan 2023).

UpSMART Accelerator Work Packages

1	2	3	4
DHPs for Data acquisition	DHPs for Data interpretation	Training on setup and conduct of Clinical Trials for DHPs	Technical Hub for deployment & adoption of DHPs

Figure 4: UpSMART Accelerator Work Packages

DHP = Digital Healthcare Product

Following the onboarding of Centre Léon Bérard (CLB) as an UpSMART collaborating centre, WP2 are embarking on an exciting multidisciplinary collaboration to develop a DHP focussed on screening eligibility for patients enrolled on early phase clinical trials. The initial scope of the collaboration will be to develop a new AI model to understand the likelihood that a patient will pass screening procedures and the first cycle of treatment for a generic Phase I trial. This would reduce burden to the patient as well as maximizing use of resources on the trial.

UpSMART clinical trials with Digital Healthcare Products – efforts across the network have been directed towards setting up clinical trials with DHPs. Three trials are currently being conducted and are described below:

1. VHIO have gained ethical approval for a validation study of the Phase I prognostic online (PIPO) tool. It will assess PIPO's prognostic capacity to be used as a decision support system in clinical practice of drug development units for objectively estimating life expectancy criterion in phase 1 trials. The study aims to recruit 586 participants and will open across Spain sites imminently, we aim to explore the potential for the study to expand across UK, Italy and France sites next year.

2. Working with the NIHR Biomedical Research Centre (BRC) in Leicester, a research package for a feasibility study evaluating the use of accelerometers to capture physical activity levels in cancer patients on early phase clinical trials (APACE) has been submitted for approval. The study aims to evaluate the feasibility of collecting accelerometer assessed physical activity and sleep data from patients with advanced cancer on early phase clinical trials in 8 sites across UK, Spain and Italy. An optional module has been incorporated to enable the eNUTRI nutritional tool to be used at the UK sites to evaluate its usability in an early phase cancer setting. To increase inclusivity and accessibility within the APACE trial, Read-it-to-me (RITM) will be used, allowing participants secure access to trial specific information in their chosen language.

As part of patient and public involvement, three focus groups were conducted (in UK and Italy), to gain feedback on the overall study design, the inclusion of the applications (eNutri and RITM) and the patient information.

Accelerometer devices and training will be provided for free by the NIHR BRC in Leicester. They will also provide expert support in the charging, use and interpretation of data collected from the devices.

3. INT Milan conducted a usability study for the PROACT 2.0 application with a cohort of 15 patients, ahead of the open source release of the DHP.

The manuscript developed during 2020 outlining the UpSMART programme, vision and overall ambition, was published in Digital Medicine (a publication of International Society of Digital Medicine) in January 2022.

We conducted our second Scientific Advisory Board (SAB) towards the end of Year 3 which gave an opportunity for industry specialists to independently review, provide challenge and offer advice to our programme.

The UpSMART website (https://upsmart. digitalecmt.com) is the one-stop-shop for all information related to UpSMART including DHP-specific information such as training materials and installation guides.

> " In an era of more patient-centered care pathway and rising complexity, improving effective communication between patients and their medical team and collecting PROs is more important than ever. It's exciting to work in a multidisciplinary team of software developers and clinicians in developing PROACT 2.0, a platform which helps researchers to reach this goal. "
>
> **Dr. Silvia Damian MD**
> *Medical Oncologist Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

Cancer Core Europe building DAta Rich clinical Trials (CCE-DART)

As a member of the CCE-DART consortium (a 4 year programme of work funded by Horizon 2020 European Union Funding for Research & Innovation program, digital ECMT leads on two of the 18 work packages (WP), firstly, WP7 on the discovery of multi-layer complex biomarkers and secondly, WP12 on the development of online tools for Patient Reported outcome (PRO) measurements (in conjunction with the National Cancer Institute – NKI Amsterdam).

WP7 - Discovery of multi-layer complex biomarkers

WP7 targets the development of novel, multi-layered, AI-based biomarkers. As part of EU Horizon CCE DART we are systematically and critically assessing the impact of emerging AI models to support the development of new multi-layered/multi-modal biomarkers. In close collaboration with consortium partners from Cancer Core Europe, we are developing novel models which can support the integration of heterogeneous multi-omics data, which can lead to new biomarker hypotheses. Particular methodological focus is given to Generative and Explainable AI methods. The following publications are some of the outcomes of this project.

Wysocki O, Zhou Z, O'Regan P, Ferreira D, Wysocka M, Landers D, Freitas A, Transformers and the Representation of Biomedical Background Knowledge. Computational Linguistics 2022 DOI: **https://doi.org/10.1162/coli_a_00462**

Wysocki O, Davies JK, Vigo M, Armstrong AC, Landers D, Lee R, Freitas A, Assessing the communication gap between AI models and healthcare professionals: Explainability, utility and trust in AI-driven clinical decision-making, Artificial Intelligence, 2022 **DOI: 10.1016/j.artint.2022.103839**

M. Wysocka, O. Wysocki, M. Zufferey, D. Landers, A. Freitas. A systematic review of biologically-informed deep learning models for cancer: fundamental trends for encoding and interpreting oncology data. Bioinformatics, pending publication in 2023.

Bogatu, M. Wysocka, O. Wysocki, H. Butterworth, M. Pillai, J. Allison, D. Landers, E. Kilgour, F. Thistlethwaite, and A. Freitas. Meta-analysis Informed Machine Learning: Supporting Cytokine Storm Detection during CAR–T cell therapy. Journal of Biomedical Informatics, pending publication in 2023.

WP12 - Development of online tools for Patient Reported outcome (PRO) measurement

WP12 involves the development of online tools for patient reported outcome (PRO) measurement. We are aiming to improve the quality of clinical trials by using patient derived data collected by online tools by the patients themselves during a trial. The Cancer Research UK UpSMART Accelerator Award developed PROACT 2.0 app will be used. PROACT 2.0 allows the patient to recorded their experience with medication using Video, text, voice mail and digital questionnaire and could help to better understand the patients' experience with experimental anticancer medication.

WP12 aims to perform a feasibility study within Phase 1 and 2 anticancer drug trials in CCE centres, to collect data on the experience of patients and health care workers (medical doctors) with different functionalities of this tool (Video and digital questionnaire). Patients will be allocated to use one of the functionalities or to the standard patient reported outcome measurements (on paper) during the trial.

We delivered the assessment of PROM (Patient Recorded Outcome Measures) requirements for the CCE Basket of Baskets (BOB) trial on time. It was decided by the BOB team to implement PROMS questionnaire in the new amendment for the BOB trial. In the last year we wrote the scientific protocol and patient leaflet for the feasibility study. We have adapted and evolved the study to overcome several challenges and changes of direction. This has put us in a strong position coming into 2023, where we aim to start to recruit to this study from April.

We submitted our progress report as part of the CCE DART Period Technical Report - RP1 submission to the EU Commission and received approval.

Cancer Core Europe building DAta Rich clinical Trials

Collaborations and Grants / Awards in 2022

MAHSC funded "Encouraging Inclusivity in Technology Clinical Trials" Project and Greater Manchester Cancer Conference – Commitment to Equality Award

Clinical trials exist to determine safety and efficacy of emerging therapies or interventions; participants should therefore be representative of all patients. Despite a global increase in trial participation, trial population diversity remains an issue, within the UK and globally. Our technology clinical trials are designed to use digital technology (e.g., devices or mobile applications) to develop new technologically enabled healthcare pathways through empowerment of patients to become co-researchers. It is hoped this will ultimately increase accessibility of healthcare for patients, with reduced intensity of hospital attendance. However, it is acknowledged that using technology may inadvertently exclude certain groups.

Vocal (a Manchester-based not-for-profit organisation which brings people and health research together) and digital ECMT facilitated 3 half-day online workshops over a 6-month period. These involved patients from diverse backgrounds and their representatives, healthcare workers and researchers with an interest in digital healthcare and inclusion. The aim of the workshops was to create inclusivity guidance for development of Technology Clinical Trials across the Greater Manchester Region, ensuring that future healthcare pathway

development is designed for all. During the workshops, the processes of developing, establishing and running a Technology Clinical Trial were discussed and evaluated.

This process helped digital ECMT to reflect on our Technology Clinical Trial design from different perspectives, and conducting workshops highlighted immediate changes that we could make in addition to changes to trial management processes and communication that we will be building into our trial processes. More broadly it highlighted the value of collaborating with others to both question practice and identify solutions. The legacy of this project will be to make our processes and practice more inclusive in all future Technology Clinical Trials, and to contribute to the wider discussion of addressing the digital divide in clinical research.

We are proud that this piece of work won Commitment to Equality Award at the Greater Manchester Cancer Awards in October 2022.

NIHR BRC (National Institute for Health and Care Research, Biomedical Research Centre)

Manchester BRC, which brings together world-leading researchers based at The University of Manchester and six of the country's foremost NHS Trusts, was awarded £59.1 million (2022-2027) to drive health improvements and lasting change for all through creative, inclusive and proactive research that identifies and bridges gaps between new discoveries and

individualised care via pioneering research in several areas, including Cancer prevention and early detection, advanced radiotherapy and precision medicine.

The digital ECMT was delighted to receive funding to deliver Programme 4 (Digital Clinical Trials with patients as co-researchers) of the Cancer Precision Medicine theme over the next 5 years. The aim is to revolutionise patient care via community/in home-based clinical trials and support near real-time interrogation of holistic clinical and complex laboratory biomarker data. Also, expansion of digital approaches (devices, software, clinical algorithms) into patient-centred, EDI (Equality, Diversity and Inclusion)-embedded and PPIEP (Patient and Public Involvement, Engagement and Participation)-informed care pathways.

The Christie NHS Foundation Trust

In addition to the NOTION, IN-HOME and A-EYE clinical trials, digital ECMT have continued their collaborative work with The Christie on various projects in 2022.

The code base for the **eTARGET** decision-support system, which integrates the patient's genomic profile with their clinical characteristics, and the digital ECMT Cancer Trial Matching Tool, which helps clinicians identify the right clinical trials for patients based upon their cancer type, genetic alterations and/or trial drug mechanism. Since being made open-source in 2021, digital ECMT have continued to host and

support instances of these tools which are being actively used at the Molecular Tumour Board (MTB) meetings for two multi-site clinical trials led by Manchester ECMC and sponsored by The Christie - TARGET National and CUP-COMP.

Professor Paul Lorigan and Dr Rebecca Lee at The Christie were successful in their bids to Pierre Fabre and The Jon Moulton Charity Trust (a registered charitable organisation) to run a non-commercial investigator led clinical trial investigating Circulating tumour DNA guided Adaptive BRAF and MEK Inhibitor therapy (DyNAMiC) for the treatment of stage III un-resectable or stage IV BRAF mutant metastatic melanoma. When the study opens to recruitment, digital ECMT will host and maintain an instance of the ACUITY visualisation tool for the DyNAMiC study team to use. This will facilitate real time ctDNA monitoring alongside the clinical data to support the clinician's decisions regarding adaptive therapy.

An independent pilot study at The Christie to evaluate the practicalities of using an eSOURCE solution in a Phase 1 setting is nearing completion. This would support the longer term vision for The Christie NHS Foundation Trust in becoming paperless. digital ECMT, as part of UpSMART, have supported the technical aspects of this evaluation as well as demonstrating feasibility in connecting wearble devices to the platform. Once The Christie have analysed and reported on this eSOURCE pilot, key learnings will be shared with our UpSMART collaborators.
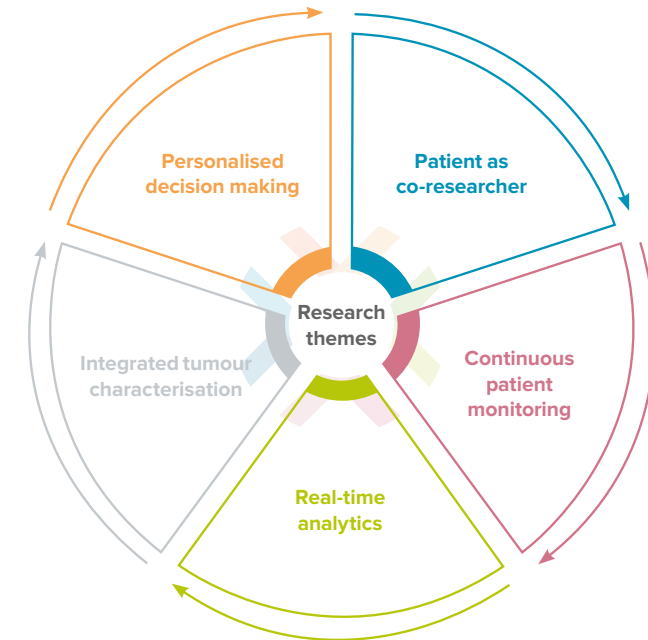
2022 news and research activities

Title/Event	Type	Location	Date
Publications			
Rules of the Road: The need for new quality standards for AI technology in healthcare	Publication	ON CANCER – University of Manchester	January
Access and inclusion: Can we move cancer services closer to home?	Publication	ON CANCER – University of Manchester	January
The UpSMART Accelerator: Driving Digital Innovation to Change the Conduct of Early Phase Cancer Medicine Trials	Publication	Digital Medicine	January
Biomarker identification using dynamic time warping analysis: a longitudinal cohort study of patients with COVID-19 in a UK tertiary hospital	Publication	BMJ Open	February
Establishment of CORONET; COVID-19 Risk in Oncology Evaluation Tool to identify cancer patients at low versus high risk of severe complications of COVID-19 infection upon presentation to hospital	Publication	JCO Clinical Cancer Informatics	May
An International Comparison of Presentation, Outcomes and CORONET Predictive Score Performance in Patients with Cancer Presenting with COVID-19 across Different Pandemic Waves	Publication	Cancers	August
Patient attrition in Molecular Tumour Boards: a systematic review	Publication	Nature – British Journal of Cancer	August
Transformers and the representation of biomedical background knowledge	Publication	Computational Linguistics	September

Title/Event	Type	Location	Date
Publications			
Meta-analysis Informed Machine Learning: Supporting Cytokine Storm Detection during CAR–T cell therapy.	Pending publication	Journal of Biomedical Informatics	
A systematic review of biologically-informed deep l earning models for cancer: fundamental trends for encoding and interpreting oncology data.	Pending publication	BMC Bioinformatics	
Multi-evidence natural language inference for clinical trial data.	Pending publication	17th International Workshop on Semantic Evaluation	
Conferences/Workshops/Presentations			
University of Manchester ON Cancer Launch – Nationwide	Panel	Westminster	March
MRes Lecture - Bringing decision science innovation to our clinical trials (at The Christie)	Lecture	The Christie	March
Attempting to Navigate the Hyperbole: AI in Experimental Cancer Medicine	Presentation	PwC EMEA Partner Event	May
The Use of digital technology in trials and inclusivity in digital research	Presentation	ECMC Network/JING	May
Artificial intelligence for RWD: understanding the benefits and limits	Presentation	European Organisation for Research and Treatment of Cancer (EORTC) Forum	June
Encouraging Inclusivity in Technology Clinical Trials	Presentation	ESMO	September

2022 news and research activities

Title/Event	Type	Location	Date
Addressing Equity, Diversity, and Inclusion (EDI) in Clinical Cancer Research and Assessment of Technology	Presentation	Clinical Trials Europe	November
Focus group			
UpSMART Accelerator APACE Technology Trial – Feedback on Patient Information Sheet.	Online Focus Group	Zoom call	22 March 2022
Assess data provision to patients in Clinical Trials to support their roles as co-investigators	Online Focus Group	Zoom call	15 December 2022

LINKS – group Websites and Tools

1. UpSMART ACUITY- More information on the ACUITY clinical trial visualisation and analytics tool on the UpSMART website (this has been developed to an open-sourced version).- **UpSMART ACUITY**

2. UpSMART website Primary source of information for the UpSMART consortia providing details of the Accelerator Award and information on the Digital Healthcare Products (DHPs). Updated as and when new products become available.- **UpSMART Accelerator**

3. CORONET- COVID-19 risk in Oncology Evaluation Tool - **CORONET**

4. Digital ECMT Cancer Trial Matching Tool- digital ECMT Cancer Trial Matching Tool Trial Matching software to support clinical decision making – matching a cancer patient's tumour genetic profile to optimal clinical trials, supporting our precision medicine research.- **https://trialmatch.digitalecmt.com**

5. CCE-DART - **CCE_DART (cce-dart.com)**

6. PROACT - **PROACT 2.0 – UpSMART (digitalecmt.com)**

7. eTARGET - **eTARGET**

8. P1PO - **https://upsmart.digitalecmt.com/?page_id=852**

9. GitHub repository for digital ECMT code - **Github.com/digital-ECMT**

Research themes

Research themes

- Personalised decision making
- Patient as co-researcher
- Continuous patient monitoring
- Real-time analytics
- Integrated tumour characterisation

" The digital ECMT continue to push the boundaries regarding the conduct of clinical trials, bringing new digital tools to support patient treatment decisions, and critically, involving the patient as a researcher in their own trial. "

Prof Caroline Dive CBE, FMedSci
Interim Director CRUK Manchester Institute (MI) and Director CRUK MI Cancer Biomarker Centre and PI on the UpSMART Accelerator Award

Contact us

We work together in partnership to transform decision-making and the patient's role.

If you are interested in collaborating with us in research under any of the themes on the left, please contact us.

Lets work together!

To get in touch
please contact us at info@digitalECMT.org

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