The Efficacy and Mechanism Evaluation (EME) Programme: A 10-year Impact Assessment

Supplementary material – Extended case studies

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1 Molecular selection of therapy in metastatic colorectal cancer: a molecularly stratified randomised controlled trial programme (FOCUS4)

Funding period:	April 2013 – December 2021
Funding amount:	£3,920,117
Lead CI:	Professor Timothy Maughan
Lead institution:	University of Oxford
Reference:	11/100/50; commissioned call 11/100 Initial Commissioning Brief

Summary

The FOCUS4 trial aimed to evaluate different cancer drugs in different subtypes of colorectal cancer using a novel methodology termed Multi-Arm, Multi-Stage (MAMS) design. MAMS trials compare different treatment options simultaneously, using multiple tests (so-called 'arms') that run in parallel. Individual trial arms can be stopped early if interim analyses show a lack of benefit, and new arms can be added over the course of a trial. This flexibility accelerates progress, lowers costs, and reduces the number of patients given ineffective treatment.

The FOCUS4 trial incorporated this new approach to trial design by linking evaluation of novel treatments with the concurrent evaluation of a biomarker. A total of 1349 patients with advanced or metastatic colorectal cancer were recruited to the trial between January 2014 and November 2019. Patients were assigned to one of four cohorts, depending on the presence (or absence) of specific genetic mutations that had been associated with subtypes of colorectal cancer. These formed the four arms of FOCUS4, each of which tested a different novel treatment regimen tailored to 'its' cancer subtype.

In 2016, one of the arms was closed early due to failure to recruit enough participants to a randomisation to aspirin. The closure of this trial arm demonstrated that the MAMS trial design can inform the decision to proceed or stop clinical evaluation of a targeted treatment within a molecularly defined cohort of patients, avoiding unnecessary cost. FOCUS4 closed in October 2020 and publications are under review with journals.

FOCUS4 had methodological impact internationally: Learnings from the trial's statistical and operational aspects have been published and team members have contributed to national and international guidelines and recommendations on the implementation of complex innovative trials including the MAMS design.

Background

Colorectal or bowel cancer is the fourth most common cancer in the UK with around 42,300 people diagnosed with this condition each year.[1] Treatment depends on the stage of cancer (size and number of tumours, spread to distant sites) and location (colon or rectum), and may include surgery, radiotherapy, chemotherapy, or a combination of these.[2] Several new cancer drugs have emerged which may benefit colorectal cancer patients. However, their efficacy may depend on the subtype or associated mutations present in individual patients. Different patient populations can be defined using biomarkers, such as the presence of specific mutations.

Trials based on biomarkers can help to identify which drug works best for which patients. These can be conducted in one of two ways: (1) retrospective analysis of existing trial data and (2) prospective designs where a drug or treatment is tested in trial participants who have a specific biomarker.[3] However, these trial designs are often inefficient: They require a large trial size, can only evaluate a single treatment or biomarker, and the trial may 'fail', i.e. the biomarker used to identify trial participants may not be predictive of the outcome of treatment.[3]

Clinical trials are usually classified according to 'phases': phase I (dose finding and safety), phase II (activity or early efficacy), phase III (efficacy compared with current standard of care) and sometimes phase IV (post-marketing studies). A new treatment such as a cancer drug is usually tested sequentially through these phases, encountering substantial financial and regulatory hurdles along the way.[4] It is estimated that only 13.8% of compounds tested will be successful in advancing along this pathway to achieve a marketing license.[5] Thus, novel trial methodologies have been developed to streamline the pipeline of drugs from preclinical work to proven treatments.

One such design is the Multi-Arm, Multi-Stage (MAMS) trial design. Rather than having to conduct a series of separate studies, the MAMS design allows for movement from phase 2 to phase 3 in a single protocol. MAMS trials also compare different treatment options simultaneously, in multiple tests (so-called 'arms') that run in parallel under the same overarching protocol. Individual arms can be stopped early if interim analyses show a lack of benefit, and new arms can be added during the course of a trial. This flexibility accelerates progress and lowers costs.[4]

The EME award

The FOCUS4 trial aimed to evaluate different cancer drugs in different subtypes of colorectal cancer using a MAMS trial design.[6] The FOCUS4 team led by Professor Timothy Maughan brought together investigators from the University of Oxford, Queen's University Hospital

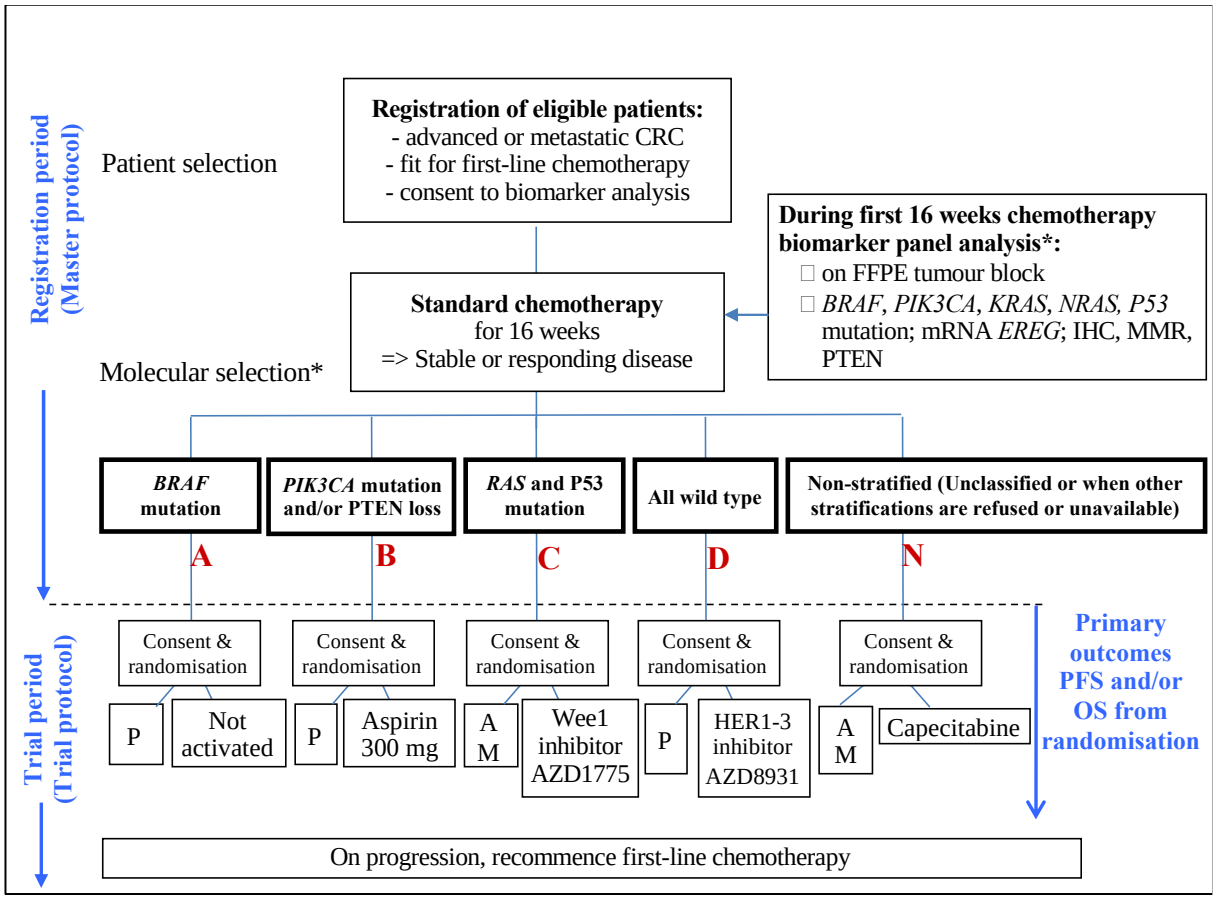
(Belfast), University of Birmingham, University of Leeds, Velindre Cancer Centre (Cardiff), Aberdeen Royal Infirmary and the University of Glasgow.[6] The trial was coordinated by the MRC Clinical Trials Unit at University College London (UCL) and sites included hospitals in England, Scotland and Northern Ireland.[4] It was jointly funded by Cancer Research UK and the Medical Research Council/National Institute of Health Research Efficacy and Mechanism Evaluation Programme (EME).[3]

The trial incorporated a new approach to trial design by linking evaluation of novel treatments with the concurrent evaluation of a biomarker.[3] Patients with newly diagnosed advanced or metastatic colorectal cancer who were not eligible for curative surgery were recruited to participate in FOCUS4 – a total of 1349 patients between January 2014 and November 2019.[6] The trial protocol involved 16 weeks of treatment with any standard first line colorectal cancer treatment followed by a programmed treatment break.[6,7] If the cancer had shrunk or at least not grown, patients were allocated to one of four cohorts depending on the presence (or absence) of specific genetic mutations that were thought to be associated with subtypes of colorectal cancer. These made up the four arms of FOCUS4:

- The PIK3CA subtype: an abnormal (mutated) version of the PIK3CA gene or loss of a protein (PTEN) in the cancer (B)
- The RAS subtype: an abnormal (mutated) version of the KRAS or NRAS genes in the cancer, plus a mutation in the TP53 gene (C)
- The 'no mutation' subtype: no change (mutation) in the BRAF, PIK3CA, KRAS and NRAS genes in the cancer (D)
- Non-classified patients: the tests fail to work so it is not possible to classify the tumour as any one of the specific subtypes above (N)

Participants in each of these cohorts were then given a novel treatment regimen (aspirin, AZD1775, AZD8931 or capecitabine, respectively) or placebo in an adaptive double-blind randomised trial design. To allow arms to be terminated early if there is no strong evidence of a treatment benefit, multiple interim analyses were performed. The primary outcome measure was progression-free survival (time to death or progression requiring resumption of chemotherapy).[6,7] The trial schema is shown in the diagram below.

FOCUS4 trial schema



Source: Reproduced with permission from Professor Tim Maughan, 2021 (personal communication) (*) *The molecular cohorts are arranged in a hierarchy from left to right. For example, a patient with both a BRAF and a PIK3CA mutation is classified into the BRAF mutation cohort. P=Placebo; AM=Active Monitoring; PFS=Progression-Free-Survival; OS=Overall Survival.*

Findings

FOCUS4 closed in October 2020, and data from two of the four trial arms (N and C) have been presented[8] or are due to be presented at international conferences (American Society of Clinical Oncology Annual Meeting 2021 and European Society for Medical Oncology Congress 2021, respectively). Three publications are currently under review with journals. The fourth arm, arm D (participants of the 'no mutation' subtype), closed early: At the first interim analysis in March 2016, the independent data monitoring committee recommended closure because there was no evidence of benefit of the treatment.[9] The final analysis confirmed that no effect on the primary outcome was observed for the therapy, AZD8931 (HER1,2,3 inhibitor), compared with placebo for this patient group. The 'failure' of this trial arm demonstrated that the MAMS trial design can inform the decision to proceed or stop clinical evaluation of a targeted treatment within a molecularly defined cohort of patients, avoiding unnecessary cost.[9]

In recent years, the understanding of colorectal cancer has changed, which would impact the design if FOCUS4 were being initiated now. The trial was predicated on the fact that single gene alterations could identify subtypes of the disease with fundamentally different biologies. However, recent work done within research consortia, which Professor Maughan and some of the trial members participate in, has shown that this paradigm only applies for some genetic markers (S:CORT, Stratification in Colorectal Cancer, an MRC and Cancer Research UK funded UK-wide multi-disciplinary stratified medicine consortium and ACRCelerate, Colorectal Cancer Stratified Medicine Network, a Cancer Research UK funded EU-wide consortium). This has led to a more integrated understanding of colorectal cancer and revealed that gene expression biomarkers, and possibly protein biomarkers, play more important roles than simple DNA mutations.

The interaction between investigators, the EME Programme Team and Cancer Research UK for review of progress and the addition of new arms was novel but also vital to the trial which could easily have been closed early due to substantial difficulties working with industry. There were difficulties procuring some novel drug agents from companies, which impacted one proposed trial arm in particular – the BRAF mutation arm (arm A) – which had to be abandoned.

Other learnings have included the set-up and running of diagnostics for the trial platform. In response to delays and inconsistencies in the submission of samples from NHS pathologists for genetic testing, the team developed and implemented facilitation strategies to help reduce the delays.

Impact

FOCUS4 has introduced a new paradigm in clinical research of solid tumours in the form of the MAMS design, allowing the evaluation of multiple treatments and biomarkers rapidly and in an adaptive way.[3,10] Its umbrella protocol offers a structure in which patient groups are characterised based on the presence of specific mutations or expression markers to define biological cohorts. As part of FOCUS4, seven key principles underpinning its MAMS trial design were developed which can be transferred to other diseases and contexts.[3] Furthermore, a large national study with this design could allow recruitment of practically all patients and thus rapid and efficient comparison of several biomarkers and treatments in parallel, including of rare subtypes.

FOCUS4 has had methodological impact internationally. The MRC Clinical Trials Unit at UCL has published the lessons learned from the implementation of the FOCUS4 trial platform, particularly the data and trial management aspects,[10–14] and has contributed to the writing of recommendations on the implementation of complex innovative trials.[15] The UCL Institute of

Clinical Trials and Methodology, which includes the MRC Clinical Trials Unit, also offers training courses in MAMS trial methodology.[16]

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2 A randomised double-blind placebo-controlled Phase 2B clinical trial of repeated application of gene therapy in patients with Cystic Fibrosis

Funding period:	March 2012-July 2014
Funding amount:	£3,228,384
Lead CI:	Professor Eric Alton
Lead institution:	Imperial College London
Reference:	11/14/25; researcher-led call

Summary

Gene therapy is a novel therapeutic technique based on introducing normal 'working' copies of a gene into the appropriate cells within the patient's body to replace or override faulty copies present in the genome.[1] While gene therapies have been in development for more than 30 years, it is still a novel technology with only a small number approved for treatment of patients.[2]

Cystic fibrosis (CF) is an inherited disease caused by mutations in a single gene, the CF transmembrane conductance regulator (CFTR). The lack of normal CFTR protein leads to a build-up of thick mucus in the lungs and results in severe lung disease and a shortened lifespan due to eventual respiratory failure.[3]

The EME study 'A randomised double-blind placebo-controlled Phase 2B clinical trial of repeated application of gene therapy in patients with Cystic Fibrosis' tested whether monthly delivery of optimised CFTR gene therapy formulations to the airways for 1 year can improve the lung function of CF patients. Globally, the trial was the first that tested repeated application of a non-viral vector looking for clinical benefit in CF patients.

The trial found that monthly treatment with the CFTR gene therapy significantly improved lung function.[3,4] The study confirmed that a CFTR gene therapy can correct human CF lung disease, is likely to be safe, and can be provided through repeated dosing. However, the improvement in lung function was modest and did not lead to detectable improvement in patients' quality of life. Thus, the formulation tested was not pursued further.

Evidence and experience gained from the trial is however underpinning further research on CF gene therapy. The data provide an important benchmark for a novel viral vector the research team developed and contributed to the establishment of a tripartite partnership with Boehringer Ingelheim and Oxford Biomedica. This partnership has progressed the manufacturing of the viral platform, developed a protocol for a clinical trial, and is carrying out toxicology studies.[5] The team also received support for a total of £9.1m from the Wellcome Trust for further development of gene therapies.

Background

Cystic fibrosis (CF) is an inherited disease caused by mutations in a single gene, the CF transmembrane conductance regulator (CFTR). The lack of normal CFTR protein leads to a build-up of thick mucus in the lungs and digestive system and results in severe lung disease due to chronic lung infections, inflammation and a shortened life span due to eventual respiratory failure.[3] CF affects around 10,000 people in the UK.[6] The vast majority of CF patients used to receive treatments targeting downstream effects of the disease rather than the cause. While these early treatments could delay the decline in lung function, they were not able to prevent it.

Gene therapy is a novel therapeutic technique based on introducing normal 'working' copies of a gene into cells within the patient's body to replace or override faulty copies present in the genome.[1] While gene therapies have been in development for more than 30 years, only a small number are approved to treat patients.[2] Given that CF is caused by a single mutation, a gene therapy approach - delivery of normal copies of the CFTR gene into the lung - can enable cells to produce functioning CFTR protein and thus prevent the build-up of mucus and associated lung problems. CFTR modulator therapies have more recently been developed to correct specific mutations.

In the lab, researchers had shown that introducing a functioning copy of CFTR into cells isolated from CF patients corrects the primary problem of CF at the molecular level.[7,8] However, for the therapy to work in patients, the DNA encoding the healthy gene has to reach and be taken up by lung cells inside the human body, at sufficient levels and intervals without triggering substantial negative side-effects.

Early studies had shown that lipid droplets, so-called liposomes, containing a CFTR vector worked in principle and were safe when inhaled by CF patients. However, the observed effects were too small and short-lived to have a therapeutic benefit in a single dose study.[3] To address this issue, the UK Cystic Fibrosis Gene Therapy Consortium, a collaboration of scientists, clinicians and allied health professionals from the University of Edinburgh, Imperial College London and University of Oxford, developed and patented an improved non-viral CFTR vector and optimised the lipid formulation and delivery protocol for CFTR gene therapy in animal and early clinical studies. Evidence gathered in these multi dose studies was promising. The next step was to assess whether repeat treatments with this novel gene therapy would result in clinical benefits for CF patients.

The EME award

The EME award 'A randomised double-blind placebo-controlled Phase 2B clinical trial of repeated application of gene therapy in patients with Cystic Fibrosis' tested whether monthly delivery of the CFTR gene therapy formulations to airways for 1 year can improve the lung

function of CF patients. The trial was the first trial globally that tested repeated application of a non-viral vector looking for clinical benefit.

Patients who participated in the trial received either the CFTR formulation or a placebo (saline solution) in nebulised form at the Royal Brompton Hospital, London or Western General Hospital, Edinburgh. The trial was led by Professor Eric Alton, Imperial College London/Royal Brompton Hospital with collaborators from the UK Cystic Fibrosis Gene Therapy Consortium from London, Edinburgh, and Oxford.[3] Genzyme Inc. (Cambridge, MA, USA) provided the liposome formulation free of charge and provided advice throughout the study.

Administration of the treatment required specialised infrastructure such as containment cubicles for nebulisation. The trial thus benefitted from infrastructure of a) the NIHR Respiratory Biomedical Research Unit at the Royal Brompton Hospital, which had been built just before the trial started to include six cubicles appropriate for delivering gene and cell therapy and b) the Edinburgh NIHR Clinical Research Facility at the Western General Hospital. This need for specialised infrastructure posed a challenge to patient recruitment: not only did participants have to undergo monthly visits, but many also had to travel long distances to either London or Edinburgh for treatment.

The study was supported by strong patient and public involvement (PPI), particularly parents of children with CF (E. Alton, personal communication, 10 March 2020).[9] As well as having a formal patient representative on the trial steering committee and input from the NIHR Respiratory Biomedical Research Unit patient group, the researchers attended patient and family meetings to discuss the trial programme. PPI input resulted in adjustments to the trial design, including a reduction in the length of time of the nebuliser treatment (as the originally planned duration of 6 hours was flagged as intolerable). PPI representatives also joined a meeting between the research team and the regulators. For example, when the planned study was questioned as too risky in a meeting with the Gene Therapy Advisory Committee, a parent highlighted the urgent need for CF treatments to extend their children's lifespan and improve their quality of life.

Findings

The trial found that monthly treatment with the tested CFTR gene therapy formulation significantly improved lung function, as measured by the volume of air participants receiving the treatment were able to force from their lungs in one second (FEV_1), and other clinically relevant outcomes.[3,4] The study thus confirmed that a CFTR gene therapy can improve human CF lung disease, is likely to be safe, and can be provided through repeated dosing. However, the overall improvement in FEV_1 was modest, at less than 4%, and did not lead to detectable improvement in patients' quality of life.

The data indicated that patients with more severe CF symptoms benefitted more from the therapy, potentially due to a higher deposition of the drug along the proximal airways (airways leading into the lungs). This finding indicates that outcomes may be further improved if higher doses of the gene can be delivered to cells.

The study also collected a range of samples (sputum, blood and urine) from patients at each of the monthly check-ins. The samples were made available for other researchers and have been shared widely.

Impact

Viral vectors tend to be more efficient at delivering transgenes into the patient's cells compared to non-viral vectors. However, at the time of the EME award, viral vectors available that could be repeatedly administered had not yet been developed. Thus, after a small number of treatments, these vectors 'stopped working' due to the body's immune response.

In parallel to the work on liposome-based therapy, the UK CF Gene Therapy Consortium was developing a novel viral vector that could be re-administered.[10] Data from the EME trial on the non-viral vector-based therapy is providing a critical benchmark against which to assess the efficacy and toxicity of the new lentiviral vector.[11] This vector has performed more strongly in preclinical studies than the liposome non-viral vector, a positive signal for the potential of the technology in human trials. Implementation of the EME-funded phase 2b trial has also generated trust in the CF Gene Therapy Consortium's ability to deliver later phase clinical studies.

As a result, the UK CF Gene Therapy Consortium was able to secure follow-on funding and secure a partnership with industry to continue development of the vector technology:

In 2017, the research team received two grants from the Wellcome Trust. One grant provides £2.7m for a Phase 1/2a trial of the lentiviral vector in CF patients, the other supports the team with £6.4m to apply the underpinning viral vector platform to five non-CF projects (funded through Wellcome's Innovation funding stream).[5]

In 2018, the UK CF Gene Therapy Consortium established a funded collaboration with Boehringer Ingelheim and Oxford Biomedica.[12][13] This partnership has made progress with manufacturing the novel lentiviral platform, developed a protocol for a clinical trial, and is carrying out toxicology studies.[5]

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3 Clinical Efficacy and Mechanistic Evaluation of Aflibercept for Proliferative Diabetic Retinopathy (CLARITY)

Funding period:	July 2014-July 2017
Funding amount:	£1,083,613
Lead CI:	Professor Sobha Sivaprasad
Lead institution:	Moorfields Eye Hospital NHS Foundation Trust
Reference:	12/66/15; commissioned call 12/66 Retinal Disease

Summary

Diabetic retinopathy is a complication of diabetes which causes damage to the retina. If left untreated, the most severe form of the disease, proliferative diabetic retinopathy (PDR), can lead to severe vision problems. The standard of care for PDR is pan-retinal laser photocoagulation (PRP) which uses laser to destroy blood vessels growing on top of the retina. PRP lowers the risk of severe visual loss but is associated with several side effects.

The CLARITY trial set out to investigate a novel treatment for PDR, injection of the anti-vascular endothelial growth factor (anti-VEGF) aflibercept (commercially available as Eylea®). Aflibercept is known to inhibit the action of VEGF, a key stimulus in PDR. The trial compared the efficacy and cost-effectiveness of PDR treatment by injection of aflibercept with standard PRP treatment. It was implemented in 22 NHS trusts and was led by Professor Sobha Sivaprasad, Moorfields Eye Hospital NHS Foundation Trust/University College London (UCL) with co-investigators from UCL, Imperial College, King's College London, and Bangor University.

CLARITY demonstrated that aflibercept treatment was superior to PRP in terms of clinical outcomes at 1 year, and was associated with fewer adverse effects and higher patient satisfaction. However, the study's economic evaluation highlighted significant cost implications, with a total additional cost of £5475 per patient compared to PRP.

While the high cost of aflibercept treatment precludes adoption by the NHS, evidence from CLARITY has informed regulatory decisions and clinical practice abroad. For example, data from CLARITY was included in an application for regulatory approval of aflibercept to the US Food and Drug Administration, which was successful in 2019. The trial continues to inform the debate on which treatment to recommend for patients with PDR in other countries. Prof Sivaprasad has presented at more than 40 international meetings and CLARITY continues to be mentioned in reviews, conference panel discussions, and professional magazines from across the globe. CLARITY has also helped to place the UK on the map for ophthalmology research by demonstrating the UK's capabilities in successfully implementing multi-centre ophthalmology studies to a high level of quality.

Since CLARITY, Prof Sivaprasad has led a further fifteen trials and has won numerous awards and nominations. For example, she was named 'Researcher of the Year 2017' by the NIHR and the Royal College of Ophthalmologists (RCOphth), received the RCOphth's Nettleship Medal for CLARITY as "the best piece of published original work by a British ophthalmologist", and was appointed to the HTA board for NIHR commissioned calls and chair for a Clinical Study Group of the UK-wide Ophthalmology Clinical Research Strategy.

Background

Diabetic retinopathy (DR) is a complication of diabetes, caused by high blood sugar levels which block the small blood vessels causing damage to the retina. In the most severe form of the disease, proliferative diabetic retinopathy (PDR), new abnormal vessels grow over the retina or optic disc. If left undiagnosed and untreated, this leads to severe vision problems and even blindness in almost half of cases.[1]

DR is common among individuals with diabetes, and increases in prevalence with duration of disease — from 20% in those with a diabetes duration of fewer than 10 years, to 76% in those with two decades or more disease duration.[2] A UK cohort study for the 2004 to 2014 period showed that DR affected nearly 50% of individuals with type 1 diabetes and 28% with type 2 diabetes.[3] Severe DR was present in 7.0% of the population with type 1 diabetes and 1.4% of the population with type 2 diabetes. An analysis of prevalence across the globe arrived at higher figures, with overall PDR prevalence at 7.2% (32% in individuals with type 1 diabetes and 3% in those with type 2 diabetes).[2] This has to be considered in the context of the high – and rising – number of people living with diabetes, estimated at 463m adults in 2019 and expected to rise to 700m by 2045.[4] Applying the estimated PDR prevalence rate of 3%, this indicates an expected increase of individuals suffering from PDR from approx. 14m to 21m.

The standard of care for patients with proliferative diabetic retinopathy is a procedure called pan-retinal laser photocoagulation (PRP). This treatment uses laser to apply burns to the peripheral retina, destroying some of the proliferating retinal tissue. This preserves the retina's central vision, important for visual acuity, and reduces further growth of blood vessels. PRP is effective, lowering the risk of severe visual loss by 50%.[1] It is however a destructive procedure with well-documented side effects, including pain during treatment, temporary disturbance of visual acuity, as well as loss of the peripheral visual field and impairment of night vision which worsen over the course of repeated PRP treatments ([5,6] and references within). In addition, approximately 13% of those treated develop visual loss due to the development of diabetic macular oedema (DMO), and nearly 5% of individuals experience progression of visual loss despite PRP treatment.[6]

The CLARITY trial set out to investigate a novel treatment for PDR: repeated injections of the anti-vascular endothelial growth factor (anti-VEGF) aflibercept. Aflibercept is commercially available under the name Eylea® from Bayer Healthcare, Germany and Regeneron, USA.[7] It inhibits the action of vascular endothelial growth factor (VEGF), a small molecule which causes blood vessels to proliferate. VEGF is produced by the retina in response to the blockage of retinal blood vessels, a result of diabetes, and is a key stimulus for the growth of new blood vessels in PDR.

At the time when the idea for CLARITY was conceived, a range of anti-VEGF therapies, including aflibercept, had already been tested and licensed for use to treat other diseases of the eye such as some forms of age-related macular degeneration and diabetic macular oedema (e.g.[8–10]). In addition, studies had shown promising short-term results for anti-VEGF agents in PDR, but these were limited to a few patients.[11] Hence, aflibercept was known to block a broad range of VEGFs, and there were indications that it could be a treatment for PDR, but it had not yet been fully evaluated.[6]

The EME award

The CLARITY trial was a phase 2b, single-blind, non-inferiority trial to test the clinical efficacy and cost-effectiveness of treatment of PDR by injection of aflibercept compared with PRP. Treatments were provided for one year, at which point the primary endpoint of the study - change in visual acuity, or 'sharpness' of vision - was assessed. The trial also compared other outcomes such as the ability to distinguish contrast, the field of peripheral vision, regression ('trimming back') of new blood vessels and safety profiles. The study included an economic evaluation assessed the costs associated with aflibercept and PRP treatments. In addition, CLARITY conducted a mechanistic sub-study investigating the effect of aflibercept and PRP on the blood supply and oxygen levels in the retina over the course of the trial to provide evidence of the mechanisms of action of the two treatments.

The CLARITY trial was implemented in ophthalmology departments of 22 NHS trusts and recruited 232 patients, achieving its full target. It was led by Professor Sobha Sivaprasad, Moorfields Eye Hospital NHS Foundation Trust ('Moorfields') and University College London (UCL) and Dr Philip Hykin (UCL), with co-investigators from Imperial College and King's College London, and team members from the Bangor University. The accompanying mechanistic study was implemented at a single centre with 40 patients, managed by Dr Luke Nicholson, a research fellow at Moorfields.

In addition to the EME award, CLARITY was supported by the NIHR Biomedical Research Centre (BRC) at Moorfields Eye Hospital NHS Foundation Trust and UCL's Institute of Ophthalmology,

the NIHR Moorfields Clinical Research Facility (CRF) and the UK Clinical Research Collaboration-registered King's Clinical Trials Unit at King's Health Partners. The anti-VEGF therapy, aflibercept, was supplied by Bayer Healthcare free of charge.

During the proposal development phase for the trial, the research team consulted with patients which it had identified with the help of two charities, the Macular Society and the Royal National Institute of Blind People (RNIB), as well as with the NIHR diabetes research network, a network of primary and secondary care centres. This helped to shape the trial design and put in place arrangements for patient recruitment. The trial was further supported by two patient representatives on the trial steering committee.

While CLARITY met its recruitment target and was successfully implemented, the research team encountered a range of the challenges:

- Site set-up: The trial recruited at a large number of sites, 22 across the UK, of which only four or five were already set up for research. As a result, a considerable amount of ad-hoc training was required including on Good Clinical Practice and protocol implementation, with time and resource implications for the study team. While trials involving a large number of sites reduces the burden on each individual site, it increases the complexity of and demands on trial management.
- Recruitment: Time and resources pressures at trial sites impacted their ability to focus on recruitment and retention. The CI overcame this issue by initiating frequent active communication to steer continued activity.
- Lack of experience in implementing ophthalmology trials in the UK: CLARITY was among the first large-scale multi-centre clinical trials in the UK in the field of ophthalmology. The lack of experience in implementing large trials meant that the study team had to master a steep learning curve themselves as well as provide training in research methodology for 'research-naïve' trial sites (see above).
- Non-standard trial methodology: CLARITY followed a non-standard methodology - a non-inferiority study - which requires trial implementation and data collection to a particularly high level of rigour for robust conclusions to be drawn. This represented a challenge - and learning opportunity – for the senior statistician on the trial, Prof Toby Prevost, who had not previously been involved with this methodology, and the CI, who had to ensure engagement and compliance of each of the 22 sites throughout the trial.
- Administrative requirements inherent in an NHS sponsor–university collaborator model: When trials are solely sponsored by an NHS Trust - as was the case for CLARITY -, oversight processes for collaborators tend to follow the same 'vendor oversight' approach for Clinical Trial Units in academic institutions as used in commercial trials. While suited for Contract

Research Organisations, this approach does not take account of the different mode of working of academic CTUs: flexible and collaborative, rather than 'fee-for-service'. The additional administrative efforts required are not costed into the collaboration agreement, and are a disincentive for academic CTUs to support trials solely sponsored by NHS Trusts.

A contributing factor to successful trial implementation was the stability of the study team, with all individuals remaining in post for the duration of the trial, and a team atmosphere that was described as 'collegiate and fun'. These positive interactions enabled issues to be effectively solved to progress the trial.

Findings

The CLARITY trial demonstrated that aflibercept injected into the eye improves visual acuity and is an effective treatment for active PDR.[6,12] The therapy was superior to PRP in terms of clinical outcomes at 1 year – a finding that was unexpected, as the trial had only set out to show that it was 'as good' as PRP (non-inferiority). CLARITY also showed that aflibercept treatment was associated with a lower incidence of other conditions such as DMO, fewer adverse effects, and higher patient satisfaction scores.

While the trial's results indicated that aflibercept therapy could be adopted as an alternative to PRP, the economic evaluation conducted as part of the study highlighted significant cost implications: Compared with PRP, treatment with aflibercept carried a total additional cost of £5475 per patient over a 12-month follow-up period, primarily due to the higher cost of purchase of aflibercept and the need for repeated administration of aflibercept and associated hospital costs[6]. CLARITY's findings were published in The Lancet in 2017,[12] with more extensive data made available in a publication in the EME Journal in 2018.[6]

The mechanistic sub-study conducted within CLARITY supported the trials' clinical findings: Aflibercept was shown to achieve an earlier and complete regression of new blood vessel growth compared with PRP. However, unexpectedly, the therapy did not result in an overall increase in retinal oxygen levels - a change that was triggered by PRP and is thought to be central to the treatment's mechanism of action.[13] This finding highlighted areas for further investigation to better understand the effect of aflibercept treatment, e.g. whether the changes in oxygen levels are extremely slow and require timeframes beyond the 1 year duration of CLARITY, or whether a different mechanism underlies aflibercept's effect on the retina. It also indicates that aflibercept and PRP may have different mechanisms of action and could hence have synergistic effects in the management of PDR. The results of the mechanistic sub-study were published in the journal Retina.[13]

Impact

CLARITY showed that aflibercept therapy could be adopted as an alternative to PRP, but at a considerably higher cost than PRP. While latter precludes adoption by the NHS, evidence from the trial has informed regulatory decisions and clinical practice abroad. For example, published data from CLARITY, alongside evidence from other trials, was included in an application for regulatory approval of aflibercept for treatment of DR to the US Food and Drug Administration (FDA), which was successful in 2019.[14] The study is also cited in UK guidelines: a recent statement of the UK Consensus Working Group on DR and DMO pathways and management reports on CLARITY's findings ("Anti-VEGF therapies have been shown to be efficacious in treating PDR.").[15] However, the statement recommends that "PRP remains the standard treatment for PDR" based on concerns about patients failing to seek the necessary follow up anti-VEGF treatments.

Interest in CLARITY has been considerable - Prof Sivaprasad has presented at more than 40 international meetings – a clear signal that the trial filled a clear need in research evidence. The trial informed the ongoing debate on which treatment, or combination thereof, to recommend for patients with PDR, as evident in numerous citations and mentions of CLARITY in reviews, conference panel discussions, and professional magazines from across the globe.[16–20] By 2020, the 2017 Lancet paper had been cited more than 80 times in the scientific literature (Scopus search on 16 Feb 2021).

CLARITY has also helped to place the UK on the map for ophthalmology research globally. The trial demonstrated the UK's capabilities in successfully implementing multi-centre ophthalmology studies to a high level of quality, employing a trial design (non-inferiority study) that was novel to this area of research. CLARITY is thus likely to have contributed to the UK becoming a recognised player in ophthalmology research – the share of phase 2 and 3 clinical trials registered with clinicaltrials.gov which involved at least one UK recruitment site increased from 4% over the 2000-2009 period (39 of 905) to 8% for 2010-2014 (70 of 870) and to 13% for 2015-2020 (108 of 933). (It should be noted that this is only a subset of global clinical trials; trials may be registered only in other registries such as the European Clinical Trials Register or the ISRCTN Registry, or not registered at all.[21])

CLARITY has also helped to avoid "research waste": While the high cost of aflibercept treatment limits the therapy's use to treat PDR in the UK, conducting an economic assessment within the EME-funded Phase 2b study has avoided unnecessary research spend, as a larger HTA trial is clearly not warranted at this point.

Career development

The experience of leading CLARITY has had a lasting impact on Prof Sivaprasad's research career, and she has since been the CI for a further fifteen trials. As result of her increased profile, she was approached by research groups to be co-applicant on grant proposals. She also won numerous awards and nominations: In 2017, Prof Sivaprasad was named 'Researcher of the Year' by the NIHR and the Royal College of Ophthalmologists (RCOphth)[22] and received the Macula Society's 'Rising Star' award.[23] In 2018, she took on the role of Editor-in-Chief of the journal Eye,[24] and became a member of the HTA board for NIHR commissioned calls. In addition, the CLARITY paper was named runner up for the "UK Research Paper of the Year" award by the British Medical Journal.[25] In 2019, Prof Sivaprasad was awarded the RCOphth's Nettleship Medal for CLARITY as "the best piece of published original work by a British ophthalmologist".[26] She was also appointed chair for one of the Clinical Study Groups of the UK-wide Ophthalmology Clinical Research Strategy.[27]

The EME award also supported the career of Dr Luke Nicholson, at the time a Research Fellow at Moorfields, who managed the mechanistic sub-study to CLARITY. Dr Nicholson has since been appointed as a consultant at Moorfields, where he continues research on retinal non-perfusion.

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4 Evaluation of Image Guided Radiotherapy (IGRT) for more accurate Partial Breast Intensity-Modulated Radiotherapy: comparison with standard imaging technique

Funding period:	March 2011 – September 2013
Funding amount:	£298,175.20
Lead CIs:	Professor Philip Evans / Professor Charlotte Coles
Lead institution:	Institute of Cancer Research
Reference:	09/150/16; researcher-led call

Summary

Radiotherapy is used to destroy possible cancer cells remaining after breast-conserving cancer surgery. An additional radiotherapy dose (a "boost") reduces the risk of cancer recurrence in the breast. However, irradiation of surrounding healthy tissue needs to be kept to an acceptable level to minimise tissue damage and long-term side effects. This depends on the ability to precisely locate the site from which the tumour was removed (the "tumour bed") and to guide radiotherapy treatment accordingly.

The EME-funded IMPORT IGRT study was a sub-study of the IMPORT HIGH trial, a phase 3 trial aiming to optimise radiotherapy treatment after breast-conserving cancer surgery. IMPORT IGRT compared standard techniques for guiding radiotherapy to a novel image-guided radiotherapy technique (IGRT). IGRT relies on titanium clips inserted by the surgeon after removal of the cancer.

IMPORT IGRT provided robust evidence of the benefits of clip-based IGRT compared to standard techniques. The study demonstrated that clip-based IGRT improves radiotherapy targeting and quantified the reduction in the amount of healthy breast tissue irradiated. This benefits patients by reducing adverse effects of radiotherapy and contributed to a change in clinical guidelines and a shift in routine practice. The ability to target radiotherapy more precisely has opened the door for treatments tailored to the individual patient.

The IMPORT IGRT sub-study also provided a model for the research team of how to derive full value from data collected in clinical trials. Nesting a study within a trial takes advantage of the trial's set-up; without this arrangement, the sub-study is unlikely to go ahead due to the considerable costs associated. The research team has since continued to use this approach for other studies. In addition, the study used a novel design using highest-quality imaging data to deduce data that would have been obtained through the simpler (standard) imaging approach, avoiding the ethical dilemma of having to assign one patient group to a potentially lower quality treatment.

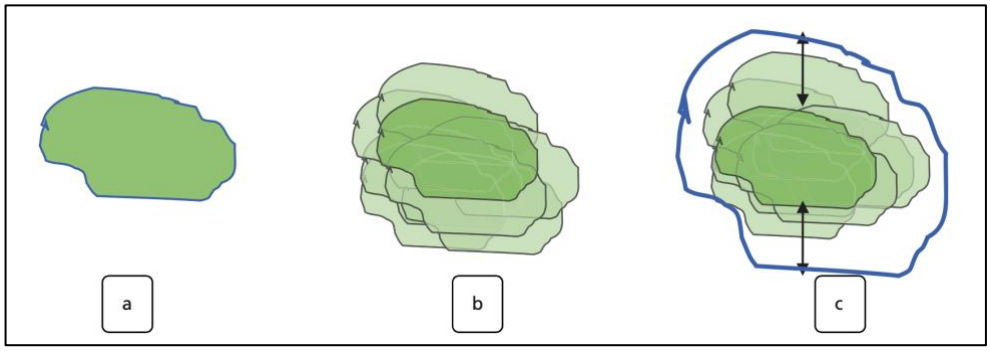
Background

Breast cancer is the most common cancer in females in the UK, accounting for 30% of all new cancer cases (around 55,000 women in the UK per year) and for 7% of total cancer deaths.[1] Breast conservation surgery, where only a part of the breast is removed, is the most common breast cancer operation.[2] It is usually accompanied by subsequent radiotherapy to destroy any possible remaining cancer cells and thus minimise cancer recurrence in the breast. Approximately 30,000 women are given radiotherapy for early breast cancer in the UK every year.[3] Still, approximately 1200 patients (2%) experience a relapse near the site of the tumour.[4]

Most cancer recurrences are known to occur close to the primary tumour, a site called the tumour bed. Hence for some patients, especially younger women who have a higher tumour recurrence risk, a high radiotherapy dose boost is aimed at the tumour bed to prevent relapse. However, irradiation of surrounding healthy tissue needs to be kept to an acceptable level to avoid tissue damage and long-term side effects such as fibrosis and damage to the heart and lung.[5]

Standard imaging to guide delivery of radiotherapy to the tumour bed used to rely on bone anatomy. However, the accuracy of this imaging approach was limited due to variations in patient and breast position between treatments and due to breathing motion during treatment. To avoid "geographical miss" of the tumour bed being treated, a safety margin was added to the target area (see figure below). Using the standard imaging approach, this margin was fairly wide, at 0.5-1 cm, resulting in up to twice as much breast tissue than needed receiving a high radiotherapy dose.[6] To avoid damage, the total radiation dose had to be limited, with potential impact on cure rates. A balance was struck: The level of boost treatment provided typically reduced local relapse risk by around 50%, at a 'cost' of a 30% increase in moderate or severe hardening of breast tissue due to fibrosis.[7]

Safety margins in radiotherapy treatment



a) Target area requiring radiotherapy

b) Day-to-day variation in the position of the radiotherapy target area

c) Safety margins (black arrows) around the target area

Precision and accuracy of treatment delivery can be enhanced through image-guided radiation therapy (IGRT), i.e., the use of imaging during radiation therapy. Radiation therapy machines are equipped with technology that allow images to be taken before and during treatment. To help align and target the radiation, IGRT procedures may use a range of "reference points" such as markers – gold seed or titanium clips - implanted around the tumour bed during surgery. Other procedures use x-ray images of bone structure, MRI, ultrasound, CT scans, or coloured ink tattoos on the skin as reference.

Prior to the EME-funded IMPORT IGRT study, novel IGRT techniques were being developed and put into use to reduce the safety margin and thus decrease the level of radiation (and damage) to healthy tissue while allowing an increase in the total dose delivered to the tumour bed.[8,9] However, a quantitative comparison of approaches and best practice in their uses had not been established. Thus, in 2012, the NHS National Cancer Action Team's guidance for implementation and use of IGRT pointed to the need for evidence on IGRT methods.[10]

The EME award

The EME-funded IMPORT IGRT study evaluated clip-based IGRT following breast conserving surgery in women with early-stage breast cancer. In this technique, breast cancer surgeons mark the walls of the tumour bed with small titanium clips. These are visualised during radiotherapy treatment to guide targeted delivery of radiation. A pilot study for the IMPORT HIGH trial had suggested that this approach was likely to allow a narrower safety margin.[9] This work led to a shift towards clip-based IGRT in medical practice; however, the technique had not been directly compared with standard imaging to provide quantitative evidence underpinning this change. It was also unknown whether a reduction in side effects could be predicted from the reduction in the volume of irradiated breast tissue.

IMPORT IGRT set out to address both these questions:

The primary objective of IMPORT IGRT was to determine whether radiotherapy for early breast cancer can be delivered more accurately using the clip-based approach when compared to the standard approach based on bony anatomy and lung position. The study's secondary objectives were to estimate the reduced risk of late adverse effects resulting from the smaller tissue volume irradiated, to determine adequate radiotherapy safety margins around the tumour bed to avoid geographical miss, and to determine the reduction in volume of normal tissue irradiated to a high dose using IGRT compared to standard imaging

IMPORT IGRT was implemented as an observational sub-study to the IMPORT HIGH trial, a phase 3 multi-centre trial funded by Cancer Research UK investigating the effect of different levels of radiotherapy treatment after tumour surgery.[11] The IMPORT IGRT study was based on data from 218 participants of the IMPORT HIGH trial, receiving treatment in five UK radiotherapy departments.[6] All patients received breast radiotherapy guided by clip-based IGRT; standard imaging data were then deduced from the clip-based IGRT images. Running IMPORT IGRT as a sub-study to IMPORT HIGH trial hence provided an opportunity to maximise value from the IMPORT HIGH trial: The necessary data was already being collected as part of the IMPORT trial, with organisational and administrative arrangements in place (e.g. patient recruitment; data sharing agreements between sites; PPI).

The IMPORT IGRT team was overseen by Prof Philip Evans (Institute for Cancer Research/ICR and University of Surrey), Professor Judith Bliss (ICR Clinical Trials & Statistics Unit), and Prof Charlotte Coles (University of Cambridge/Cambridge University Hospitals NHS Foundation Trust), with Prof Coles leading the IMPORT HIGH trial. The study included two funded posts, held by Dr Emma Harris, a research physicist at the ICR with expertise in radiotherapy physics, and Dr MB Mukesh, who was completing his medical doctorate at the University of Cambridge. This collaboration was described as 'extremely effective' by bringing together complementary expertise, from the technical and medical sides, to enable successful study implementation.

Findings

The IMPORT IGRT study demonstrated that clip-based IGRT can target radiotherapy treatment more precisely than standard imaging and quantified this difference: While the use of standard imaging requires a safety margin of at least 8 mm to avoid geographical miss of the tumour bed, a margin of 5mm is sufficient if clip-based IGRT is used.[6] This decreases the volume of tissue receiving a high dose of radiotherapy. The sub-study was hence able to evaluate the benefit of the technological development – clip-based IGRT – in a quantitative, rigorous manner. By enabling more precise targeting of radiotherapy, clip-based IGRT has opened the door for treatments tailored to the individual patient, rather than the "one size fits all" approach that had been prevalent.

The study also sought to estimate the level to which the decrease in irradiated breast volume reduces the long-term side effect of fibrosis. However, a literature review and an analysis of data from two completed trials was not conclusive: While the literature review identified studies that showed a link between the volume of breast tissue irradiated and breast fibrosis,[12] the analysis of trial data implied that the radiotherapy dose is a more important factor than the volume irradiated.[13] Since then, further research evidence has confirmed the benefit to patients from reducing the irradiated volume of tissue, as enabled through the use of clip-

based IGRT: Compared to whole breast irradiation, partial breast irradiation results in a lower proportion of patients reporting changes to the breast five years after treatment.[14] Reductions in the safety margin may also reduce the dose to other tissues, such as the heart and lungs, which differ in their sensitivity to damage. For example, cardiac toxicity has been reported for all levels of irradiation;[15] hence even small decreases in the dose reaching the heart may be important.

Impact

Clip-based IGRT for breast cancer was widely adopted as a result of the IMPORT trials, supported by the evidence generated by the IMPORT IGRT sub-study. Following the conclusion of the trial, a questionnaire was sent to all 26 IMPORT HIGH recruiting centres to determine whether the trial had influenced non-trial breast radiotherapy techniques [11]. The study found that after joining the trial, centres increasingly used titanium clips and imaging information for boost treatments, with the number of centres using this technique rising by 60% (from 10 to 16). Capabilities in clip-based IGRT built as a result of participation in the IMPORT trial, along with the favourable assessment provided by the IMPORT IGRT study, are likely to underpin this change. A 2019 editorial noted that clip-based imaging had been widely adopted by the surgical community as a result of the IMPORT trials and has become standard practice.[16] The technique is also recommended in guidelines, such as those of the Royal College of Radiologists: "Tumour bed clips should be considered the standard of care to improve planning (and delivery) of the boost."[17]

IMPORT IGRT successfully employed a novel study design to compare imaging techniques. Using highest-quality imaging data gathered by the IMPORT HIGH trial, the research team was able to deduce data that would have been obtained through the simpler (standard) imaging approach. This avoided the ethical dilemma of having to assign one patient group to potentially less accurate imaging for boost radiotherapy. This study design and method could also be adopted for other technologies, such as imaging approaches.

The IMPORT IGRT sub-study also provided a model for the research team of how to derive full value from data collected in clinical trials. Nesting a technical study within a trial makes use of data that was being collected anyway, thus reducing research cost and avoiding duplication. - without this arrangement, the sub-study would have been unlikely to go ahead due to the considerable set-up costs associated. The research team has since continued to use this approach for other studies, e.g. the PRIMETIME trial, which includes a sub-study assessing the use of video to support decision-making for patients considering participating in the research.[18,19]

Career development

The EME award supported career development for early career researchers: As a result of the research, the study's co-CI, Dr Harris, was able to expand her technical skills and publication record, and gain crucial experience in grant writing and managing project teams. This was an important factor in the successful outcome of her subsequent application for a faculty post at the ICR. To date, Dr Harris continues to collaborate with Prof Coles' group in Cambridge on diagnostic scans of breast cancer recurrence after surgery.

Dr MB Mukesh completed his medical doctorate (MD), for which he received the Cambridge University's Ralph Noble prize in 2017/18 in recognition of his outstanding work in clinical medicine and the high quality of his MD thesis.[20,21] He moved on to the position of Consultant Clinical Oncologist at Colchester General Hospital, where he was able to bring his knowledge of radiotherapy techniques gained at Cambridge to the setting up of a new radiotherapy unit for treating patients. Dr Mukesh' experience and skills in clinical research acquired as part of his MD have led to further active involvement in research, e.g. as member of Trial Management Groups of radiotherapy trials, and through participation of the unit at Colchester General Hospital in clinical trials – including national studies led by Professor Coles.

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5 Nutritional Evaluation and Optimisation in Neonates (NEON) trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition: a randomised double blind controlled trial

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Lead CI:	Dr Sabita Uthaya
Lead institution:	Imperial College London
Reference:	08/99/04; researcher-led call

Summary

Very preterm infants are born with limited energy stores and need nutrition to support metabolic needs and growth. However, a sufficient volume of milk feeds cannot be provided immediately as the infant gastrointestinal tract is still immature. Early postnatal nutrition is therefore provided intravenously, in the form of parenteral nutrition (PN).

The Nutritional Evaluation and Optimisation in Neonates (NEON) trial was a randomised clinical trial (RCT) led by Dr Sabita Uthaya, Chelsea and Westminster NHS Foundation Trust/Imperial College London, involving infants born below 32 weeks of gestation across four hospitals in London and the South East of England. At the time, limited evidence was available on the optimal level of amino acids and types of lipids in the PN formulation. Also unknown was whether PN could be provided as a standardised formulation rather than individualised to each infant (which was the standard of care at the time). The NEON trial set out to test the effect of two different amino acid and two lipid formulations on the babies' body composition and liver function. It was the largest RCT of PN in very preterm babies.

The research found no significant differences between the formulations in NEON's primary outcome measures – lean body mass and liver fat and function – when the babies reached the age at which they would have been born. This highlighted a need for re-assessment of international guidelines, which advocated for higher levels of amino acid intake, and emerging practice in the lipids added to PN. The trial also demonstrated that standardised PN can be provided safely to premature infants.

Evidence from the NEON trial contributed to policy on neonatal PN composition, including a recent NICE guideline. In addition, all neonatal units in hospitals in North West London Operational Delivery Network switched to a standardised formulation (used in the control arm of the NEON trial) and the NEON regimen is now one of two formulations recommended for use in London. Among other benefits, this standardised approach minimises prescribing errors and clinical variation, and allows cost savings through bulk purchasing. The latter has led to an estimated £150,000 of savings per year in purchasing for the NHS in London. These savings are

set to increase further, with the 2020 NICE guideline recommending the use of standardised PN for all hospitals in England.

Background

An estimated 60,000 babies are born prematurely in the UK every year.[1] Approximately 1-1.5% of these infants are 'extremely preterm', with close to 9000 infants born 'very preterm' before 32 weeks of gestation in 2018/19.[2–4]

Very preterm infants have to spend several weeks or months in intensive care as they are at risk of complications related to their prematurity. Inside the womb, the late period of gestation would see rapid growth. Outside the womb, the nutritional demands to enable equivalent growth are difficult to meet. As the gut of very preterm infants has not yet matured, some nutrition is initially provided intravenously – so-called parenteral nutrition (PN).

Early nutrition has a significant impact on the short- and long-term health of preterm infants. Preterm infants tend to require NHS resources throughout life.[5–7] A 2006 study in the UK and Ireland estimated that health and societal costs for extreme preterm children at 6 years of age exceeded that of a child born at term by around 2.5 fold, at an average of £9541 compared to £3883.[8]

PN aims to provide the right amount of protein and energy. Too little or imbalanced nutrition can delay growth, while too much can overwhelm preterm infants' immature systems. This nutritional 'calibration' is complicated by the fact that the optimal growth velocity in the womb is uncertain, and that reference data to chart the growth of preterm infants is still subject to debate.[6,9,10] There is hence substantial variation in the commencement, duration, and composition of PN across hospitals.[7]

Traditionally, the amount of PN provided was started below the Recommended Daily Intake (RDI) of key nutrients to make sure the babies could cope with the nutrition, and then gradually increased over time. This practice was not based on robust evidence, and there were concerns it resulted in nutritional deficits.[11] Preterm infants receiving conventional PN formulation were shown to have less protein and a higher proportion of fat tissue compared to term-born infants.[12] These differences in the infant's nutritional status and body composition affect long-term metabolic health,[13] but are not captured by the routinely-used outcome measure, weight gain.[14]

Thus, despite widespread use, the impact of administration of PN on key clinical outcomes had not been evaluated in randomised controlled trials (RCTs).[15,16] As a result, and in the absence of national recommendations, practice in relation to the prescribing and administration of PN for extremely preterm infants was inconsistent and based largely on historical evidence. Some practitioners were calling for more 'aggressive' nutritional interventions such as higher amino acid intakes[17,18] - also reflected in international consensus guidelines.[19] Similarly, the use of PN

containing a combination of lipids, called SMOF lipid, was being promoted and increasingly being provided to neonates with liver problems but there was no evidence to suggest that SMOF lipid used from birth could prevent liver problems from developing in the first place.[14,20] Robust evidence to support these changes was not available.[21]

Standardising parenteral nutrition

At the time of the EME-funded NEON trial, NHS hospitals provided individualised bags, attempting to match the individual needs of PN-dependent babies. The PN composition was prescribed on examining the infant, and then prepared in individualised bags by the hospital pharmacy before return to the neonatal unit and administration to the infant.[7] Each day of PN typically cost the NHS £80–100 per infant (with wider variation between hospitals), and a typical specialist neonatal hospital unit spent up to £150,000 per year on PN.[14] A 2020 guideline estimates a cost of £175,000 for a large tertiary neonatal unit.[22] In addition, there were concerns about safety. For example, a 2011 report involving 116 hospitals concluded that current practice among neonatologists with respect to PN varied widely and was based on limited evidence.[23] There was also considerable variation in the preparation of PN and guidelines for use. However, evidence on whether healthcare professionals should use standardised or individualised PN formulations was, and remains, limited.[7]

While the individualised approach allows tailoring the PN formulation to meet specific needs of individual babies, the use of standardised bags provides several safety and cost advantages: they are immediately available in the neonatal unit when needed and suitable for most babies; they help to minimise prescribing and dispensing time and errors and clinical variation (e.g. differences between hospitals); they can improve compliance with national recommendations on quality control of PN manufacturing, dispensing, prescribing and administration; and they cost less and allow bulk purchasing.[24]

The EME award

The NEON trial was a randomised, 2 × 2 factorial and double-blind controlled trial in four UK centres in London and south-east England, led by Dr Sabita Uthaya, a consultant with the Chelsea and Westminster NHS Foundation Trust, and sponsored by Imperial College London.[14]

The two main research objectives of the trial were to study the effects of two PN interventions in extremely preterm infants, with the aim of providing robust evidence to inform guidelines and general practice:

- The effect of providing the full RDI of amino acids immediately after birth, rather than starting at a lower level and gradually increasing the amount, on lean body mass (primary

objective) as well as other indicators of growth and on insulin resistance (secondary objectives)

- The effect of providing SMOF lipid on fat deposited in the liver and liver function

The trial's 2 x 2 factorial design enabled it to address both research questions simultaneously.

NEON was the first RCT testing nutrition in preterm babies, investigating the impact of amino acid intake in PN on body composition in extremely preterm infants.[14] Infants were assessed using whole-body magnetic resonance imaging (MRI) to allow a better understanding of the effect of PN on body composition (lean body mass vs adipose tissue), an approach Dr Uthaya had developed as part of her MD project. In addition, the level of fat in liver cells (hepatic lipid), a marker for the liver disease cholestasis associated with prolonged use of PN,[25] was assessed through *in vivo* magnetic resonance spectroscopy (MRS).

The trial was supported by parent representatives who reviewed communication material to inform parents of preterm babies during the recruitment phase. Following their advice, the information leaflet was simplified and shortened to communicate the trial's aims and risks more clearly. This is likely to have contributed to NEON's swift recruitment and high retention rate, as parents understood the purpose of the trial and that their babies would only receive PN formulations already in routine use, rather than a novel intervention.

Challenges encountered

While the trial met its recruitment target, the research team encountered a range of organisational and regulatory challenges – some of which are commonly cited by chief investigators -, including:

- Prolonged administrative and reporting processes, associated with gaining MHRA approval and agreement on excess treatment costs (ETC) with each of the participating hospitals. For example, NEON was classified as a 'Clinical Trial of an Investigational Medicinal Product' (CTIMP) by the regulator. This was unexpected by the research team as the interventions tested, different PN formulations, were already in routine use. The CTIMP classification added considerable complexity, reporting requirements, and cost to trial implementation. It also increased ETC, which in turn complicated gaining agreements with participating hospitals.
- Problems with sourcing the intervention to be tested: While the PN formulations were already used widely in practice, their use in a CTIMP required the bags to be prepared in a specifically licenced pharmacy. The team contacted every pharmacy in England – only one, a private pharmacy in Bath, was able to prepare the formulation. This led to a substantial increase in trial costs.

- Training needs: Given the target population of the research – very preterm babies – the trial had to be implemented in neonatal intensive care units (NICUs). This required training for neonatal nurses in research methodology and good clinical practice standards, as research nurses within the clinical research network were unfamiliar with the NICU setting and did not have expertise in working with neonates.
- Adjustment of trial processes: The clinical trials unit (CTU) implementing NEON had not previously worked in a NICU setting and had to find ways to align the usual trial processes with intensive care. This included streamlining data collection to focus on routinely recorded data.
- Time demands on the CI: The trial work had to be carried out over and above her responsibilities as a full time NHS consultant (despite funding available to back fill her time).
- Issues with access to trial data held by the CTU for further analysis to inform a follow-up study for NEON, due to the lack of resources after the award closed

Findings

NEON demonstrated that there was no difference in primary outcomes measures between the PN formulations tested[14,26]:

- When the premature babies reached the age at which they would have been born, their lean body mass was not significantly different if they were given the full RDI of amino acids compared to infants who were provided with gradually increasing amounts. This countered the assumption that very preterm infants require higher protein intakes to avoid nutritional deficits. Furthermore, the trial found that immediate 'aggressive' protein intake may be less safe: Infants provided with the full amino acid RDI had a significantly higher concentration of urea in the blood, and there were indications that this PN may result in a lower head circumference. Overall, the results did not support the more aggressive approach to PN reflected in international consensus statements,[19] and indicated that gradual introduction of amino acids may be safer.
- There was no difference in liver fat and function in infants provided with SMOF lipid compared to a routinely used lipid preparation. A switch to SMOF lipid in PN was hence not supported.

The trial results thus highlighted a need to re-assess international guidelines and emerging practice and were published in the American Journal of Clinical Nutrition[26] and the EME Journal.[14] An editorial described the NEON trial as "high-quality",[27] and the findings of the NEON trial were cited in Cochrane reviews [28,29]. Evidence on amino acid and lipid preparations has informed the British Association of Perinatal Medicine's framework for practice,[30] led to a decrease in the recommended amino acid intake in a European guideline on paediatric PN,[31]

and contributed to NICE's first clinical guideline on neonatal parenteral nutrition[22] - with a direct citation of NEON in the evidence for amino acid regimen[7] and taken up indirectly via the Cochrane Review on lipid emulsions.[29,32] Building on her knowledge and experience from the NEON trial, Dr Uthaya became a member of the NICE Neonatal PN Guideline Committee[33] and has been appointed to the NICE Neonatal Parenteral Nutrition Quality Standards Committee.

NEON also demonstrated that the use of standardised PN, rather than PN tailored to the individual infant, is feasible, able to achieve growth and body composition in line with individualised PN, acceptable to clinicians, and safe.[14,34] Based on this finding, Dr Uthaya worked with NHS Improvement to create a standardised procurement framework for London hospitals under the NHS Quality, Innovation, Productivity and Prevention (QIPP) programme. The 'NEON formulation' is now one of the two regimens recommended by the London Neonatal Operational Delivery Network, a network of the 27 hospitals across London which provide neonatal care, and has been adopted by all providers in North West London (Sweeney S. Personal Communication, February 2021). The standardised procurement framework has allowed London hospitals to order PN bags at competitive prices from contracted pharmacies, reducing overall costs as well as cost variation between hospitals (which had ranged from £30 to £115 per bag). This has led to a minimum of £150,000 per year in savings on PN purchasing for the NHS in London alone, a figure that does not include benefits from other benefits associated with standardisation (see Background section). Savings are now set to increase further: A recent NICE guideline recommends the use of standardised bags for PN for all hospitals in England.[22]

Next steps

The NEON trial has helped to address a gap in the evidence and led to changes in clinical practice. However, the level and timeframe of EME programme funding for NEON did not allow differences in functional outcomes over a longer period of time to be determined. To fully understand the impact of early nutrition, the effect of different PN regimen on neurodevelopment, body composition and metabolic health needs to be assessed over the long term. Dr Uthaya is currently conducting a follow-up study with the participants of the NEON trial, now nine years old, to gather further evidence (Uthaya S, Personal Communication, February 2021). Such long-term follow-up studies are currently difficult to finance as a shared infrastructure for neonatal research in the UK, which would lead to efficiencies across research projects, has not been funded and is hence not available.

Further research is needed to refine current guidelines on PN composition. For example, while the NEON trial hinted towards a risk of giving higher amounts of amino acids in early PN, it was not designed to conclusively demonstrate that there was potential harm. Today, some

practitioners continue to advocate for early PN providing full RDI. There is a clear need for evidence to inform these clinical decisions.

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