



EHE Rare Cancer Charity (UK)

23 Geneva Road
Kingston-Upon-Thames
Surrey
KT1 2TW

www.ehercc.org.uk

contactus@ehercc.co.uk

Registered charity: 1162472



A huge thank you to eightcreate.co.uk
for the graphics and design work in
producing this report



We would like to also thank
Bennett Brookes Chartered
Accountants for providing
bookkeeping services to EHERCC



Printed by Optichrome Limited

Cover images

Dr Paul Huang,
Institute of Cancer Research, London.
and
The Bootcamp Commandos.



Rare Cancer Charity UK

Annual Report and
Financial Statements 2021



Epithelioid Haemangioendothelioma (EHE)

EHE Facts

A **destructive vascular sarcoma** that is found in the walls of blood vessels

Commonly appears in **liver and lungs** but can appear anywhere

Can present as **indolent** (passive) or **aggressive**

Typically more aggressive in **young people**

Can re-present after long period with no disease

Often presents with **multiple tumours** called 'multifocal'

Representative image showing the formation of TAZ-CAMTA1 foci, in day 21 endothelial cells cultured as part of Emily Neal's PhD at the University of Manchester (see Research section).



May turn **aggressive at any time** without warning

Clinical signal that onset may be tied to **pregnancy** and **puberty** in young women

Living with EHE causes **enormous psychological stress**

Affects women more than men in a ratio of about **5:1**

One of the **world's rarest cancers**, with 5 to 10 patients per year in the UK

No recognised treatment, so treatment is by trial and error

No known cure. Aggressive disease is **normally fatal**

Find out more at: www.ehercc.org.uk

The London Cancer Hub

Welcome to Innovation Gateway



EHERRC visit to ICR facilities at the London Cancer Hub, Sutton.

Annual Report and Financial Statements 2021

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Post-COVID recovery continues

With the impact of the COVID pandemic in 2020 still being felt in many areas, we entered 2021 not knowing if our activities would 'bounce back', or if the charity would face a longer period of recovery. We are delighted therefore to be able to report that 2021 has been another exciting year for The EHE Rare Cancer Charity UK (EHERCC). Substantial new funds were raised by our supporters, while growing interest in EHE research allowed us to commit to new projects. At the end of the year and for the first time, every pound we have raised since our inception in 2015 had been fully allocated to current and future research projects.

Fundraising is the lifeblood of every charity, and was an area badly affected by COVID. We were not surprised, however, to see our core supporters take up the fundraising challenge again in 2021 with the same amazing energy and determination we had seen in previous years, raising an amazing £101,000 through a variety of events and individual fundraising, including an EHERCC team which ran in the London Landmarks Half Marathon, which was re-established in 2021.

At the same time, instead of a downturn in research interest in 2021, we received and were able to support a number of exciting new research proposals. These involved extensions and expansions of existing projects, as well as committing to new research. Our support for these projects was only made possible by the input and guidance from our Research and Medical Advisory Board (details of the Advisory Board can be found on the EHERCC website at www.ehercc.org.uk). We also want to register our sincere and deep thanks to all our Advisory Board for helping us to understand and evaluate the proposals we received, and to steer us towards the projects most likely to deliver early benefits and greater understanding of EHE.

2021 also saw changes and expansion of the teams associated with the charity. Liz Milligan stepped down from her role as Trustee and Mike Rich left us as Executive General Manager; Sally Baker joined us at the end of the year as Trustee with special responsibility for patient

liaison; Dr Silvia Stacchiotti accepted our invitation to join our Research and Medical Advisory Board; and Mariana Coutinho, based in Portugal, joined the charity as European Coordinator. We want to thank Liz and Mike for all they contributed as trusted friends and colleagues. We also want to thank Sally, Silvia and Mariana for accepting our invitations and joining 'the team'.

As Trustees, we are all acutely aware of the fact that everything the charity achieves is only possible due to the amazing support we get from so many different people. We particularly want to mention our patient community and their families, the people who are at the very sharp end of the EHE story and live with the effects of an EHE diagnosis every day. Your drive and determination to make a difference is inspiring.

So to all our supporters, whether it is as fundraisers, volunteers, EHE advocates, patient supporters, Advisory Board members, researchers, or any of the other forms of support we received through the year, we want to say a huge and simple

Thank you!

Left to right:

Hugh Leonard (Chair of Trustees),

Jeff Collins (Trustee),

Kate Hooper (Trustee),

Sally Baker (Trustee),

Dr Oliver Pearce (Trustee).



01 Patient Support and Advocacy

Although COVID had a major impact in 2020, we continued to support our existing EHE patient community, and of course welcomed those newly diagnosed with the disease. Despite COVID still being a 'live' issue, we were very pleased with the progress that was made in all areas of our patient-support activities through 2021.

Our patient community in the UK remained fully engaged, and actively supported all areas of our activity. This was particularly true with the UK National EHE Biobank, which went live in 2021. The start of the year also saw the UK charity and our members participate in the first EHE360 international patient conference, held online, and coordinated by The EHE Foundation in the USA.

Broader engagement with European patients also progressed, with Mariana Coutinho joining us as European Coordinator, a role in which she started reaching out to EU patients through our social media platforms. We were also delighted to support, encourage and engage with the new Italian EHE association, *EHEItalia Non Solo Laura*.

Our European engagement was further enhanced as the charity participated in the development of a Consensus Paper on EHE, an ESMO (European Society of Medical Oncology) process led by Dr Silvia Stacchiotti from Istituto Nazionale dei Tumori (INT) in Milan, Italy. The process involved more than 80 clinical and other specialists from across Europe. The final consensus paper is of course technically complex. The EHERCC therefore, assisted by the INT team, developed a patients' version of the consensus paper, which was published in early 2022. Please contact the charity if you would like a copy of the patient paper.

In the UK, the charity engaged with all sarcoma centres. As part of our desire to develop pan-European EHE awareness, the charity continued to engage with European patient advocacy groups and in 2021 joined Sarcoma Patients Euronet (SPAEN), the European Cancer Patient Coalition (ECPC), and Rare Diseases Europe (EURODIS).

We were also delighted to welcome Sally Baker to our Board of Trustees with responsibility for patient liaison; Dr Silvia Stacchiotti to our Research and Medical Advisory Board; and Mariana Coutinho (European Coordinator) to the charity management team.

02 Research

2021 saw our ongoing research recover well from the difficulties due to COVID in 2020. One project was extended by a further year. We also received and were able to support two new funding applications with the result that, at the end of the year and for the first time since our inception in 2015, every pound raised for EHE research was fully allocated to current and future projects.

2021 was the third year of the PhD we are funding at the University of Manchester under Dr Valerie Kouskoff. Results from this research continued to be exciting, suggesting that secondary DNA mutations may play a key role in the development and progression of EHE.

In early 2021, the team at the University of Sheffield presented proposals to support extending by a further year the project to develop an EHE zebrafish model. These proposals focused on different strategies to successfully introduce the EHE gene mutation construct into the endothelial cells of the fish. Evaluated by the charity's Research and Medical Advisory Board, with the support of an external genetic specialist, the proposals were approved and a one-year MPhil project was initiated in July.

The UK National EHE Biobank went live in the second quarter of the year. Based at the Royal Marsden Hospital, enrolment of existing and new patients into the biobank has continued through the year.

Finally, the research project to identify cytokines and hormones as possible biomarkers, a collaborative project centred at INT in Milan and involving the Institute of Cancer Research (ICR) in London, collected blood samples from Italian patients, and at year-end had identified one possible biomarker for EHE progression.

The first of the two new projects evaluated for funding at the end of the year and formally agreed in 2022 was an expansion of our INT-ICR research, including the development of PDX (patient-derived xenograft) models to support further research and drug testing. The project will also collect a library of radiological images together with patient clinical records, which will be used to develop better interpretation and evaluation techniques for EHE and so help doctors with prognosis and disease assessment.

The second new project is the development of a pan-European prospective EHE registry, allowing disease progression to be monitored in selected patients over a multi-year time scale, again to help provide information and understanding of EHE progression.

03 Fundraising

We were very pleased to see our EHE patient community and all their supporters continue and grow their engagement in 2021, initiating new fundraising with the same levels of energy, enthusiasm and dedication that we enjoyed pre-COVID. That dedication resulted in the charity receiving over the full year a further £80,000 of funding for EHE research and £21,000 of funding from our single donor to cover administrative costs and entry fees to various events to assist our fundraising.

The charity was again able to participate in the London Landmarks Half Marathon, securing 40 places for our supporters. As always, we were hugely grateful to the 40 runners who took part for their brilliant support, and for the £22,000+ that they collectively raised.

The Bootcamp Commandos, a group of women based in and around Yate, near Bristol, took up training to run a half marathon while carrying a 70 kg log! As part of their training, they also took on the Three Peaks Challenge, climbing the highest peaks in England, Wales and Scotland in 3 days, raising more than £7,000 for EHE research in the process.

Individuals also organised their own events through the year. Kelly Denton, mother of an EHE patient, organised friends and colleagues to take part in the Tough Mudder trial during May, and a quiz night in November. Nicola Henderson decided to combine fundraising, getting fit and mental health by taking up the challenge to walk 10,000 steps a day for the 37 days leading up to her 37th birthday. We also benefited from rowing challenges, birthday campaigns, annual charity lunches, collections of change, and other fundraisers.

The charity once again ran its Giving Tuesday matched-funding campaign in November and secured matched funding for the more than £10,000 raised. The principal funds raised included a wonderful donation of £1,000 received from the Rolls-Royce Nuclear Power Branch of Unite, in Derby, in support of EHE patient Hazel Peake.

At the end of the year, the charity was also well advanced in its planning for its two big 2022 fundraising events, the London Landmarks Half Marathon (40 places) and the Ride-London-Essex 100 sportive (20 places). We look forward to 2022 being another great year.

Objectives and Achievements for 2021

We believe it is important that all stake holders in the charity and its activities can see how we are performing against our stated objectives. We have therefore provided below a summary of our 2021 performance against the objectives we set ourselves. On the facing page we have also provided the objectives we set for the charity for 2022.

What we said we would do... ...and what we achieved

01 Patient Support and Advocacy

Promote UK National EHE Biobank and maximise patients' engagement.	Engaged with patients, 13 patient enrolled at year end.
Join appropriate European patient umbrella groups and expand European patient and clinical/research engagement.	Joined SPAEN, ECPC and EURORDIS. Patient, clinical and research engagement through ESMO consensus paper.
Engage with regulators concerning tissue management and EHE treatment approvals.	Attempting to collate necessary information, and waiting to see response to EHE Biobank start-up.
Maintain contact with sarcoma centres.	Annual reports and updates provided.



02 EHE Research

Promote EHE research and international collaboration.	INT (Milan) and ICR (London) collaborative research established and project expansion approved.
Assist with launch of UK National EHE Biobank.	Notices of EHE Biobank sent to centres. Also working with RMH team to increase profile.
Conclude PEACE project engagement and enrolment into the Biobank.	CRUK funding for PEACE being withdrawn in 2022.
Support existing research projects.	Achieved through regular updates, visits, EHE360 conference, and EHE Group coordination.
Promote and evaluate new research Initiatives.	Two new projects approved at year end so that all funds fully allocated.



03 Fundraising and Finance

Support and encourage grass-roots activity.	Support provided to individuals and fundraising again promoted.
Review fundraising strategy post COVID, including recruiting volunteer fundraising professional.	Decided to delay to see how 2021 developed post-COVID. At year end we are seeking to engage with recommended fundraising specialist.
Develop strategy for longer-term EHE Biobank financing.	Agreed acceptable funding structure with RMH.
Assess possible European grant award to assist with European strategy.	Deferred to 2022 as we progressed actual European projects with INT.



Charity Organisation

Identify and invite patient representatives to join the Board of Trustees.	Sally Baker joined the Board of Trustees; Mariana Coutinho joined management team as European Coordinator.
Continue to seek to expand Research and Medical Advisory Board.	Dr Silvia Stacchiotti joined the EHERCC Advisory Board.
Continue review of appropriate policies.	Ongoing.
Review organization goals and conclude strategy and support required for success in post-COVID environment.	2021 suggests that current structure is viable as we continue to assess the post-COVID environment.



Our Forward Focus for 2022

Because rare cancers are not rare to those who have them

01 Patient Support and Advocacy

- Undertake review with UK patient community as to what support is important to them
- Launch targeted Biobank discussion with all UK patients
- Progress regulatory discussion re acceptance of IRE Ablation for EHE patients
- Maintain Sarcoma Centre engagement in UK
- Relaunch pan-European patient engagement

02 Research

- Continue to support and engage with all existing research projects
- Complete contracting and initiate two approved projects with INT/ICR
- Continue to evaluate new research options, including broad immunotherapy review
- Continue to build/refine EHE Group research coordination and strategy for optimisation
- Coordinate further EHE research review presentations and discussion sessions

2022 AND BEYOND

03 Fundraising

- Support and encourage grassroots fundraising
- Revisit all previous fundraising concepts and strategy post COVID
- Initiate fundraising strategy review with recommended service provider, including possible grant writer
- Assess possible EU funding for EU-based EHE projects, translation etc

Charity Organisation

- Continue to review possible additions to charity bodies, including Board of Trustees, Advisory Board, and management team
- Revisit and relaunch voluntary support post COVID, in coordination with patient review
- Re-establish social media campaigns post COVID and coordinate with voluntary support review
- Continue to assess charity objectives, activities and appropriate policies post COVID

Foreword

Hugh Leonard

(Chair of Trustees)

Dear Reader,

Over the past five years we have invited different people to write the Foreword for our annual reports. This year however, I have decided to write the Foreword myself as there are two very recent events that I want to mention. I dearly wish that these were happy events, but they are not. They both involve the tragic loss of a young member of our 'EHE family' here in the UK.

Harry Medwin was just 28 years old when he passed away this August. Like all our patients, Harry's life and that of his family was turned upside down when he was given his EHE diagnosis. But like most, Harry was determined that his cancer would not control his life. Harry was a vibrant, fun loving young man. He was a son, brother, grandson, friend and colleague. He lived life to the full, and brought joy and fun into the lives of many. Harry was also a husband, marrying Ellen, his sweetheart, in February this year.

Harry's family were also determined that they would do all they could to help him, actively assisting the charity, and engaging in fundraising to help drive research into EHE. Harry's brother, Charlie, rowed the Atlantic with two friends, in the Talisker Whisky Challenge, raising huge sums for us. Sarah, Harry's mother, started holding an annual EHE charity lunch, as well as organising other fundraising activities. Ellen was first and foremost Harry's partner, and engaged in all of these activities, but also acted as Harry's advocate, engaging with the EHE community, keeping us all updated and asking lots of questions.



Harry Medwin 1994 - 2022



Adrianna Glennie was 42 when she lost her battle against EHE, in September. We first met Ads, as we came to know her, at WOMAC's annual charity party in London in 2019 which was dedicated to raising funds for EHE research. She was accompanied by her mother Diana, somebody who became another champion of the EHE cause. Ads had been to the Royal Marsden that day. Just like Harry, here was a young person full of energy, hope, drive and determination. Ads was also determined that she would beat EHE because her brother, Garrith, had previously died from a different form of cancer, and as Ads said, *"one is enough"*.

Ads lived near Aberdeen in Scotland, so meeting up regularly was not possible. However, that did not stop her engaging with us on all charity matters. She was first on the zoom calls, and had multiple ideas for every issue discussed.

One of her great passions was music, and she organised several fund-raising gigs for the charity. Her energy and drive was huge and so infectious; she was just wonderful to be around.

Sadly, in its progressive form, EHE is typically very destructive, and Harry's and Adrianna's EHE was no exception. As 2022 progressed, their family and friends were increasingly aware of the battle they both faced. But despite that understanding, news of Harry's and Adrianna's passing was still truly shocking. Once again the sheer scale of the loss, and our inability to prevent it, were all too apparent. One of the unusual things about working with such a rare cancer is that you get to know all the patient members by name, and interact with most of them, so their loss is very keenly felt indeed.

We spend a lot of time talking and writing about fundraising, research and patient advocacy. We try to present a positive outlook, but I fear that sometimes this may mask why we really do what we do, and that is to dedicate ourselves every day to finding a viable treatment for EHE that will stop tragedies like the loss of Harry and Adrianna. At such a sad time, there is little we can do to soften the sense of loss felt by both of their families. All we can do is send them our love, and promise them that we will relentlessly pursue the objectives we have set because it is the very least that we owe to Harry and Adriana, and all the others who have left us far too early, due to EHE.

And if anybody reading this Foreword feels that they would like to help us, so that future patients can survive EHE, then please get in touch as we would love to hear from you. Together we will defeat this rare sarcoma, and that will happen faster the more people we have involved.

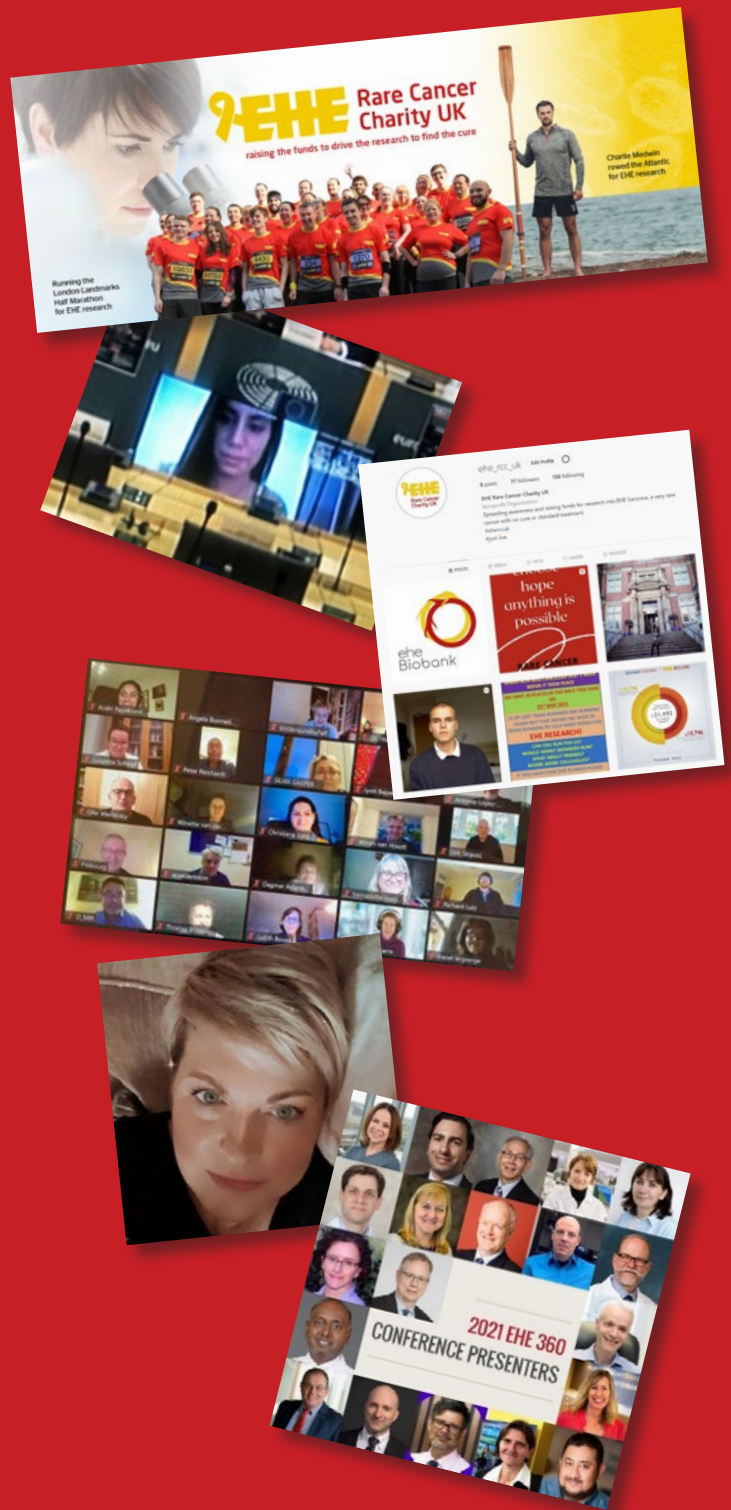
It remains for me to close by simply saying *"Just Live"*, the EHE group motto that both Harry and Adrianna lived by to the very end, and to dedicate this Foreword to these two very special people. We miss them deeply.

01 Patient Support and Advocacy

Unlike 2020, where we all faced COVID lockdowns and severe social restrictions, 2021 was all about trying to return to a more normal life, although 'sensible precautions' continued to be necessary as the year progressed and new waves of the coronavirus were faced. Throughout this period, we remained focused on supporting our patient community wherever possible, and tried to provide the support and information that they needed as they each continued on their own personal EHE journey.

Connectivity and engagement with other EHE patients remains an extremely important part of what the EHERCC, and its sister EHE foundations around the globe, strive to offer. Many of our members were delighted, therefore, to be able to participate at the start of the year in the first ever global EHE international conference, called EHE360. Involving patients, clinicians and researchers from around the globe, the two-day virtual conference included: summary presentations of the multiple EHE research projects that are now in progress; presentations and discussion of the challenges clinicians face in dealing with EHE; and input and dialogue on EHE issues with many participants of the global EHE patient community. Post-conference comments often talked of the optimism and hope that participants gained from the two days, and especially from the multiple research presentations.

Connectivity in the UK has also been supported through social media, and the patients' WhatsApp group. The idea of coordinating a meeting of EHE patients and supporters was not attempted due to the ongoing COVID concerns, but ad hoc chances to meet, such as during the London Landmarks Half Marathon, were grabbed by some. We are pleased that 2022 has seen a further reduction in COVID worries, and that actual patient 'get-togethers' can once again take place. The EHE360 2022 conference will also be taking place, offering further chances for patients to engage and meet



Review by Hugh Leonard

Although the EHERCC is a UK charity based in England, we are also determined to establish a broad EHE patient network across Europe, including the UK.

Our ultimate objective is to create a pan-European patient federation with each country having at least one EHE patient-coordinator acting as a bridge between the EHE global network and their domestic patient cohort. EHERCC will then coordinate the group's communications so that, regardless of language, all European patients will be fully aware of all that the EHE group is doing, possible clinical trials, as well as studies and registries that they can join. In addition, we hope that this will allow us to gather greater group information about many aspects of EHE, leading to greater understanding and knowledge that we can feed into research and clinical management of the disease.

Mariana Coutinho joined the charity in the role of European Coordinator during the year. She has made significant progress in identifying and contacting European patients or their supporters, and is aware of those that are interested in acting as a coordinator for their country. The process of building the patient federation will not start entirely from scratch, as we have had an established patient group and coordinator in Germany for several years. In addition, we were delighted to welcome **EHE Italia Non Solo Laura**, an Italian association established by the Italian patient community which went live at the start of 2021.



As part of our overall European patient engagement, we have also joined three of the most recognised and active European patient advocacy groups. Sarcoma Patients Euronet (SPAEN) is the main sarcoma-focused foundation in Europe and works actively with the EU and all European countries on behalf of sarcoma patients; the European Cancer Patient Coalition (ECPC) advocates for cancer patients generally; while Rare Diseases Europe (EURORDIS) is the patient advocacy group for all rare disease. We look forward to working with these different bodies going forward.



We hope that the building of greater interaction amongst European EHE patients will take place in parallel with a growing engagement with European clinicians experienced with EHE. A significant step forward in this area was the publication in 2021 of the paper '**Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts**', led by Dr Silvia Stacchiotti from Istituto Nazionale dei Tumori (INT) in Milan, under the auspices of the European Society of Medical Oncology (ESMO) and including a large number of European and international sarcoma experts.



In addition to the consensus paper, the charity has agreed to fund the establishment of a European EHE prospective study which will also be coordinated by Dr Stacchiotti and her colleagues at INT, providing further engagement opportunities with the clinical community.

Charity organisation

A key component of our patient support and advocacy work is to ensure that we continue to review and supplement the EHERCC with key personnel so that we have the resources to achieve our objectives. In 2021, a number of individuals joined the charity to continue this process of renewal and growth.

Changes to the Board of Trustees saw Liz Milligan step down from the Board in March. At the end of the year, Sally Baker joined the Board, with her main focus being patient liaison and communications. We also supplemented our Research and Medical Advisory Board in 2021 when Dr Stacchiotti kindly accepted our invitation to join it. Finally, our volunteer management team saw Mike Rich step down due to personal commitments while Mariana Coutinho joined the team as European Coordinator.

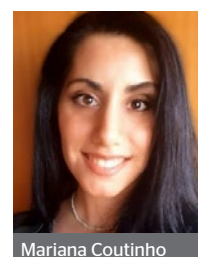
We would like to thank Liz Milligan for her excellent contributions to our Board of Trustees and Mike Rich for his oversight of our activities, both of whom stepped down during the year due to personal commitments.



Sally Baker



Silvia Stacchiotti



Mariana Coutinho

02 EHE Research

As we entered 2021 there was significant uncertainty as to how research would progress through the year, after the impact of the COVID pandemic in 2020. Our existing research was ongoing and we were reasonably confident that momentum and lost time would be recovered. There was greater uncertainty, however, with regard to new research and the likelihood of new grant applications.

As 2021 progressed it quickly became apparent that our existing research was in good health, with the associated labs back up and running at close to full capacity, albeit with the adoption of COVID-related work practices. At the same time, the charity received new funding applications for exciting new research projects, particularly building on the existing collaborative research between the Instituto Nazionale dei Tumori (INT) in Milan, Italy and the Institute of Cancer Research (ICR) in London, UK. Three new grants were ultimately approved and awarded through the year with the exciting result that as at the end of 2021 all funds raised by the charity for research since inception have now been fully allocated to current and future research projects.

We remain excited by the ongoing research and the applications for further funding from highly respected researchers in recognised and established research institutes. We are now involved in a wide variety of research projects, all of which involve significant technical detail that we have in the past worked to summarize into more simplified descriptions in our annual reports. This year we have also provided one example - the Manchester PhD - with significantly more technical detail than normal to highlight the level of technical expertise that is required in projects of this nature.

Manchester PhD

2021 was the third year of this four-year project being undertaken by Emily Neil under the supervision of Dr Valerie Kouskoff at the Department of Biology and Experimental Medicine at the University of Manchester. Emily's PhD project, entitled '*Developing an in vitro model system to study Epithelioid Hemangioendothelioma*' had established a robust model of EHE using pluripotent stem cells that could be differentiated to endothelial cells, and which contained the WWC-CAMTA1 gene mutation. This mutation is activated with the addition of doxycycline so that the TAZ-CAMTA1 fusion protein (TC) is expressed. Emily is then able to explore the impact of TC on the biology of the cells.

Emily's 2021 work programme involved a number of discrete experiments looking at the impact of TC on specific aspects of the biology of the cells, as summarised below:

1. TC expression in endothelial cells results in enrichment of TAZ target genes

Analysis revealed a large number (4,528) of differentially expressed genes (DEGs) in cells within the TC^{high} endothelial populations. Significant enrichment included genes for the EHE-specific gene set, suggesting that the *in vitro* model developed in Manchester is relevant to EHE.

2. TC expression in endothelial cells results in downregulation of the endothelial phenotype

Phenotypically, TC-expressing endothelial cell populations show reduced tube-like formation. Data showed that TC causes transcriptional changes to genes involved in endothelial cell identity, and leads to reduced angiogenic activity.

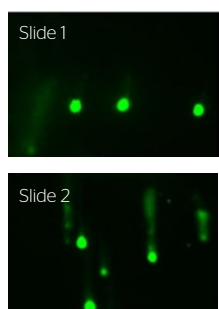
Review by Kate Hooper and Oliver Pearce

3. TC-expressing endothelial cells become arrested in S phase of the cell cycle

As the normal TAZ protein is known to regulate S phase entry in the cell cycle, and proliferation in endothelial cells, experiments were designed to determine if TC expression has a similar effect. Results showed that TC^{high} cells were proliferating at a slower rate than TC^{low} cells, and that TC-expressing cells are indeed becoming arrested in late S phase of the cell cycle.

4. TC expression causes endothelial cells to accumulate DNA double-strand breaks

Emily was able to confirm that TC is causing substantial DNA damage involving double-strand breaks (DSBs) in endothelial cells. These data reveal that endothelial cells acquire a large number of DSBs upon TC expression, leading to S phase cell cycle arrest. A neutral comet assay was performed, where damaged, fragmented DNA migrates to form the comet 'tail', leaving undamaged DNA in the comet 'head'. Cells where TC was not induced had little or no comet tail (upper slide 1) whereas those where TC was induced had a significantly larger percentage of DNA in the comet tail (lower slide 2)



5. DSBs are directly caused by TC, and are independent of its interaction with TEADs

DSBs are seen just four hours after TC is induced, suggesting that they are directly caused by TC. In addition, this effect was also seen in cells expressing TC S51A, which cannot bind TEAD family transcription factors. These results suggest that the accumulation of DSBs is independent of TC interacting with TEADs. The substantial change in the transcriptome 24 hours after TC expression is also suggestive of hypertranscription, an emerging source of replication stress in cancer.

6. Homologous recombination is impaired in TC-expressing endothelial cells

Emily next investigated the ability of these cells to repair DNA damage, initially focusing on homologous recombination (HR), the DNA damage repair pathway most active in S phase of the cell cycle. Emily's results strongly suggest that HR is impaired in TC-expressing cells. Emily has also shown that TC-expressing cells have reduced expression of BRCA1, a key protein in HR, but further experiments are needed to elucidate the mechanism behind this impairment.

7. Homologous recombination impairment leads to cellular senescence and genomic instability

It is known that HR impairment in cancer can lead to genomic instability, potentially allowing secondary mutations to occur, bypassing S phase arrest. Likewise, BRCA1-deficient cells can also become senescent (dormant), as the amount of DSBs overwhelms compensatory repair pathways. To explore these possibilities, Emily separated and re-plated TC^{high}, TC^{low} and TC^{negative} cells to investigate how the level of TC expression affected their ability to proliferate.

Four days after sorting, the TC^{negative} population had grown to confluence, and the cells had retained their endothelial morphology. In TC^{high} and TC^{low} populations, many cells had taken on a flat morphology, characteristic of senescent cells, which was verified by the presence of the protein p16 and by β -galactosidase activity, which marks senescent cells.

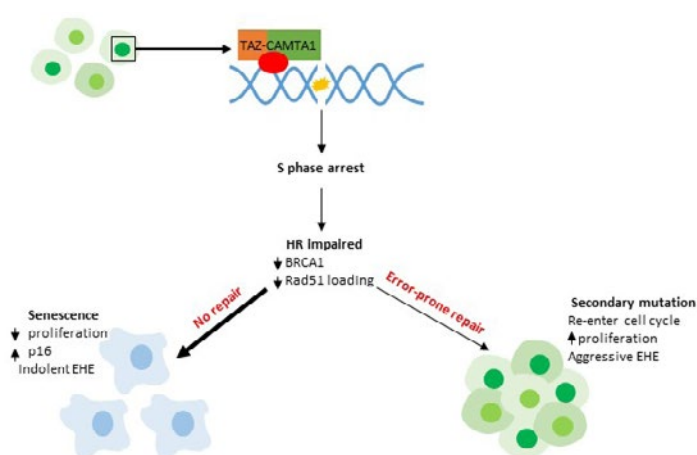
Emily then moved on to determine the p16 expression level in TC-expressing endothelial cells, as this protein is known to positively regulate senescence. Moreover the *Cdkn2a* gene, which encodes p16, is the most common secondary mutation to TC in EHE, and these tumours are often more aggressive. Interestingly, cells with high TC expression did not express p16, but some cells with low TC levels did express p16. This suggests a transition between TC expression and p16 expression, providing further evidence that TC expression may cause oncogene-induced senescence in certain situations.

Emily then generated endothelial cells which were left in culture for 4 weeks, maintaining TC expression. After 10 days, small TC^{positive} colonies began to form, which grew in size over the course of the experiment. These colonies were not present in uninduced populations. Further testing suggested that the DSBs caused by TC expression in endothelial cells often go unrepaired, leading to cellular senescence. However, a subset of cells may acquire a secondary mutation, likely due to the reduced functionality of the HR pathway. These cells do not become senescent, instead gaining a proliferative advantage as seen by the TC^{positive} colonies. This could explain the range of disease presentation and long latency from indolent to aggressive as seen in EHE.

8. Knockout of *Cdkn2a* seems to allow cells to overcome growth arrest in the cell cycle

The *Cdkn2a* gene encodes the p16 protein, which positively regulates cellular senescence. However, *Cdkn2a* is often found mutated in aggressive EHE tumours. Emily used CRISPR/Cas9 assays to knockout *Cdkn2a*, and showed that in *Cdkn2a* knockout cells expressing TC, higher growth rates were observed than in untransfected TC cells, and TC increased over time. This suggests that deletion of *Cdkn2a* allows endothelial cells to overcome the growth arrest imposed by TC expression. This is consistent with data from EHE patient samples, which shows that where *Cdkn2a* is mutated EHE is more aggressive.

O2 EHE Research Continued



Model showing the early consequences of TC expression in endothelial cells. Upon TC expression, cells enter a state of hypertranscription which results in DSB formation. Consequently, cells become arrested in late S phase while DNA damage repair takes place. As HR is impaired in TC-expressing endothelial cells, most will undergo oncogene-induced senescence. In some cases, another, more error-prone pathway will repair the DSBs and allow cells to re-enter the cell cycle. This has a high chance of causing a secondary mutation, resulting in senescence bypass and increased cell proliferation.

Emily's research has produced some very interesting results, providing a possible model for why we see such a wide range in the nature and progression of EHE across the EHE patient community. Her focus in 2022 will involve further experiments to test her hypothesis that secondary mutations play a key role in EHE tumorigenesis, and also exploring some early ideas on possible therapeutic targets. Emily will also be writing and preparing final data for her PhD manuscript. We thank Emily and Dr Kouskoff for their ongoing focus on EHE, and the excellent progress they have made.

All of the research projects EHERCC funds have this level of technical detail. In future annual reports we will provide similar details for our other projects. For this year, summaries of our remaining projects are provided below.

EHE zebrafish model development

In mid-2018 the charity entered a two-year half-time contract with the Bateson Centre at The University of Sheffield to develop a zebrafish model of EHE. The Bateson Centre is one of Europe's largest zebrafish facilities, with an excellent reputation for the development of zebrafish models of human diseases. The EHERCC project is being co-led by Drs Fredericus van Eeden and Robin Young.

The project was delayed by six months due to the COVID pandemic and so reached its initial contractual conclusion in late 2020. At this point the team had still been unable to achieve expression of the TAZ-CAMTA1 oncoprotein in the zebrafish endothelial cells, something that the team found very surprising. Two possible causes were identified:

1. The first is that there are elements in the DNA sequence that encodes the oncoprotein that prevent it from being produced. To check this, the team would 'chop' the sequence first into big, and then smaller pieces, and see if any of these are blocking expression.
2. The second reason might be best described as 'feedback inhibition'. To activate TAZ-CAMTA1 in endothelial cells, a particular well-tryed and tested control sequence is used, known as the *fli1* promoter. Perhaps, when a little TAZ-CAMTA1 protein has been produced, it blocks the function of its own *fli1* promoter.

It was agreed that Dr Van Eeden should undertake a detailed review of the situation with other zebrafish experts as well as with other researchers working on EHE biology and EHE models. That review was carried out through the end of 2020 and the early part of 2021 and highlighted several realistic and viable solutions to the problems seen.

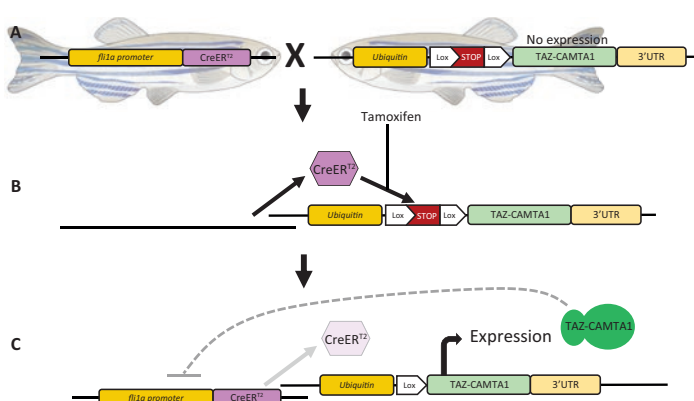


Fig: Strategy for driving TAZ-CAMTA1 in endothelial cells. Fish containing a *fli1a*-driven CreERT2 and a silenced TAZ-CAMTA1 expression construct are crossed together (A). The resulting larvae containing both constructs express an inactive form of Cre in the endothelial cells. When activated with tamoxifen the Cre will remove the stop cassette (B) and lead to expression of TAZ-CAMTA1 under the control of a constitutive ubiquitin promoter. If subsequent feedback of TAZ-CAMTA1 leads to downregulation of the *fli1a* promoter activity and CRE production, this is irrelevant, as removal of the stop cassette is permanent (C).

Reviewed by the EHERCC Research and Medical Advisory Board, and an external genetics expert, it was agreed that the project should be continued as there was a real possibility that an EHE zebrafish could be developed. In July 2021 therefore, EHERCC entered into a further one-year MPhil project, again led by Dr Van Eeden, to progress the zebrafish model development. This was a full-time project with Eleanor Markham the selected MPhil student.

Through the second half of the year the team were making new DNA constructs to understand and solve the issue. By the end of the year ongoing experiments had not yet distinguished between the two proposed reasons, but suggest that it is the CAMTA1 part of the oncoprotein which is at the root of the problem, and not the TAZ element. At year end, Eleanor was chopping up CAMTA1 further, to home in on the precise area. If feedback inhibition is the issue, the team have also created a construct that uses a different promoter, which could bypass this problem. The next step will be to inject these new constructs into fish to create transgenics that will hopefully express the oncoprotein in endothelial cells, progress that we hope to see in 2022.



Eleanor Markham at microscope



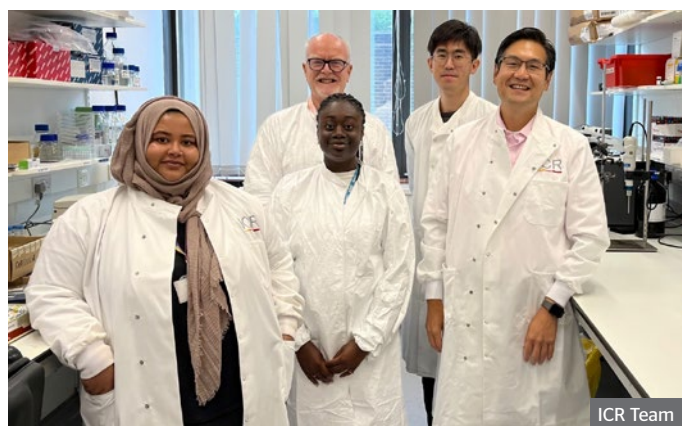
National UK EHE Biobank

A key component for cancer research is the availability of bio-samples, both tissue and fluids, including blood. This is particularly true for rare cancers where samples, by definition, are also very rare. To address this fundamental weakness of research into EHE, the charity funded a two-year project to develop the UK's National EHE Biobank through 2019 and 2020.



This was one project that was impacted by COVID, but we were delighted when The Royal Marsden confirmed in mid-2021 that all arrangements and approvals were in place and that the EHE Biobank would be going live. Patient engagement, managed initially by Emma Perkins and now by Eniola Ayeni, Tissue Manager, has also been positive with 13 patients enrolled and donating samples by the end of the year.

2022 will see the charity remaining focused on patient support and promotion of the biobank in the UK. We will also be working with the Royal Marsden to ensure that sarcoma centres around the UK are aware of and supporting the biobank when they have EHE patients under their care. If you want to learn more about the EHE Biobank please visit our website: [The National EHE Biobank \(UK\) | EHERCC](https://www.ehebiobank.org/)



ICR Team

Hugh Leonard visiting the Institute of Cancer Research. Left to right are: Nafia Guljar, Eniola Ayeni (front), Hugh Leonard (back), Leo Tam and Paul Huang.

02 EHE Research Continued

Collaborative biomarker research project

In the second quarter of the year, the research project involving collaboration between The Istituto Nazionale dei Tumori (INT) in Milan, Italy, and The Institute of Cancer Research (ICR) in London, UK was started. This project is jointly funded by EHERCC together with the EHE Foundation in the USA.



FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

ICR The Institute of
Cancer Research

The project, *'The evaluation of cytokines and hormones as biomarkers for EHE'*, is seeking to explore groups of compounds which may be involved with the development and progress of EHE, as described below:

1. Cytokines and hormones, known to play a role in the mediation of processes which may affect tumour progression, metastasis and therapeutic outcomes.
2. Estrogen receptor proteins, which have been implicated in the development of cancers such as breast cancer.
3. MicroRNAs (miRNAs), which are small non-coding pieces of RNA that can negatively regulate gene expression, as proven in several types of human cancer, and which can be reliably detected in both tissue and blood samples.

This project has several research objectives, split between clinical research and translational research. Clinical objectives are focused on understanding the disease, including factors such as: the demographics of the patient population; the presentation, natural history and treatment pattern in patients with advanced EHE; symptoms and their changes over time, pain assessment, etc.

Translational changes will assess: the longitudinal profiles of circulating cytokines, hormones and miRNAs; the estrogen receptor expression and its impact in tumour tissues, according to the clinical course of the disease; and seek to identify novel biomarkers (that can be used to improve prognosis and/or predict response to drugs) as well as potential new therapeutic targets.

To this end the analysis is being conducted on the whole study patient population compared to healthy controls, and by stratifying EHE patients who will enter the study in 3 subgroups according to disease behaviour (non-growing disease, slow-growing disease, highly aggressive disease).

The plan is to include in the project over a 36-month period, between 50 and 70 patients at INT in Milan, and 18 patients at the ICR in London. Profiles of targeted compounds over time in the EHE patient group will be compared to the profiles of the same compounds in healthy individuals.

By year end INT had recruited 23 EHE patients into the project, and 23 healthy subjects matched for age and gender, and had begun to see interesting results, as follows:

Circulating cytokines

INT have found differentially expressed cytokines in plasma samples from EHE patients compared to plasma samples from healthy individuals. At year end three cytokines shown to be significantly over-expressed were being validated in the EHE patients' cohort, prospectively collected in the first year of the project.

In addition, INT were able to investigate whether one of these circulating cytokines, GDF-15, was contributed by tumour cells using a patient-derived xenograft (PDX) together with the corresponding *in vitro* cell line. Results indicated that GDF-15 was indeed released from EHE cells, as the cytokine was detected in the blood of SCID mice carrying the PDX as well as in the culture medium of the EHE cell line. Interestingly, Sunitinib, one drug that overall has proved positive in the management of EHE, was found to down-regulate GDF-15 release in both *in vivo* and *in vitro* EHE models.

Circulating miRNA profiles

Twenty three miRNAs were found to be differentially expressed between EHE patients and healthy donors. In addition, six miRNAs were differentially expressed in patients with the aggressive variant of EHE compared to those with a more 'indolent' disease. At year end these miRNAs were being validated in the EHE patients' cohort prospectively collected in the first year of the project.

Research expansion with INT

2021 saw the ongoing EHERCC research relationship with INT and ICR expand, as grant applications for two new EHE research projects were assessed by the charity. These projects, summarised below, represent an exciting expansion of the overall EHE research being undertaken. Following positive recommendations from the charity's Advisory Board, the grant applications were approved and contracting was finalised in 2022.

Project 1:

This expansion of the current collaboration between INT and ICR is setting out to improve our understanding, assessment and treatment of EHE, and consists of an additional three-year project with three key objectives:

1. The generation and characterization of patient-derived preclinical models of EHE to assess the activity of anticancer agents and identify/validate novel therapeutic targets
2. The validation of circulating microRNA differentially expressed in EHE patients compared to healthy donors
3. The assessment of radiological features and response to treatment

Project 2:

The second project involves the setting up of an observational prospective EHE patient registry in Europe. This project will be managed and coordinated by INT in Milan but will involve multiple other institutions in Europe. The study will be established within the STARTER project which will be creating a pan-European registry for all cancers.

This study initially plans to include approximately 100 patients (range: 80-120), in 36 months, with a follow-up time of at least 3 years. The study aims to provide a description of the population affected by EHE, giving an insight into the natural history of the disease and its variants, identifying reliable clinical prognostic and predictive factors, and analysing the broad spectrum of treatment approaches and subsequent outcomes, and so allowing some of the outstanding questions on EHE management to be answered.

Dr Silvia Stacchiotti and Dr Nadia Zaffaroni are joint Principle Investigators of the EHE research projects that the charity is funding.



Nadia Zaffaroni



Silvia Stacchiotti

03 Fundraising and Finance

2021 was an inspiring year, largely due to the energy and enthusiasm of our members to engage and drive fundraising, even though many were still feeling the effects of the 2020 COVID crisis. We recognise that the EHE patient community has a huge interest, one we share, in seeing research deliver new treatments, and ultimately a cure for the disease. But we are also very cognisant of the challenges they faced in 2020, living with both EHE and COVID19. Despite this, however, they continued to engage with inspiring enthusiasm and creative ideas.

It was not just our individual members and their supporters who contributed to our fundraising programme. We were delighted to see the London Landmarks Half Marathon return to the annual events calendar in August, following cancellation of such events in 2020. As in previous years, we quickly filled the 40 places secured in the event by the EHERCC. We could not be more grateful for their great support.

With fundraising rejuvenated through the year, we once again turned our minds to the issue of our ongoing fundraising strategy, and how this might be expanded to include foundation and corporate support. Such a programme was under review in late 2019 but was suspended due to the COVID pandemic. Clearly the fundraising landscape has been changed by COVID, but at the end of the year we resumed our strategy discussion with a view to re-engaging with appropriate advisers in 2022 and the aim of confirming an advisor during 2022 to assist in this critical next step in the charity's fundraising development.



Review by Jeff Collins

2021 saw a significant recovery in the fundraising activities for the charity, both in fundraising directly organised by EHERCC and also fundraising organised by our members. This, coupled with the energy, enthusiasm and planning we were seeing for 2022 events meant that we ended the year optimistic about our ability to continue to fund expanding EHE research.

Strong engagement from many of our wonderful supporters meant that 2021 was another successful year, raising an amazing £100,900. Their enthusiasm and desire to raise funds was particularly important, demonstrating that the 2020 COVID downturn would not have a long-lasting effect on our ability to fund future EHE research.

As always, fundraising events came in different shapes and sizes. The Bootcamp Commandos, a group of women based in Gloucestershire, used their major fitness training programme including the Three Peaks Challenge to raise over £7,000. Kelly Denton, mother of an EHE patient, organised multiple events including a Tough Mudder challenge and raised over £8,000 during the year. Nicola Henderson raised over £1,000 in her 37-day walking challenge, and Sarah Medwin raised nearly £4,000 with her annual charity lunch. At the end of the year we were also delighted when a single donor agreed to match up to £10,000 of fundraising around Giving Tuesday, a sum that our supporters reached. Many other smaller events and regular giving all contributed to the total sum raised in the year.

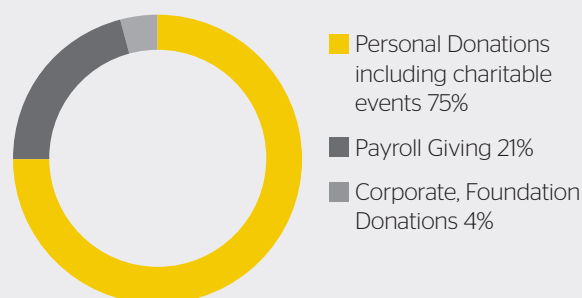
In 2021, we once again received the generous support of a single donor who funded 100% of the charity running costs. As in all previous years, we segregated these funds, donated for administration purposes, from those received from all other sources, which can therefore be allocated to fund our key objectives, in particular, EHE research. It is the intention of the Trustees that the same will be true in 2022.

Key objectives

In the 2021 calendar year our supporters raised a total of £80,000 for the charity's key objectives. The sources of these funds are summarised on the pie chart above.

During 2021 we provided funding for our two UK research projects, at the Universities of Manchester and Sheffield. We also funded the EHE National Biobank and Tissue Manager at the Royal Marsden. We jointly funded with the EHE Foundation in the United States the collaborative research project between INT in Milan and the ICR in London.

Source of funds



Administration/business running costs

The charity received funding of £20,900 for its administration and business running costs account. During 2021, £16,700 of expenses had been incurred, which included an accrual of £1,200 for the independent examiner's fee. The remaining £4,200 will be carried forward to cover future administration and business running costs.

The spend of £15,500 (excluding the £1,200 independent examiner's fee) included the fees associated with fundraising events conducted in 2021, and publishing costs, in addition to ongoing website maintenance.

"We were so pleased to see our supporters engage with such enthusiasm in fundraising activities in 2021 and assist us in raising important funding for critical EHE research. As always, we worked hard to keep our costs as low as possible, with a group of dedicated and committed volunteers running all the charity's activities. 2020 demonstrated why our underlying policy of ensuring we do not expose the charity to funding commitments beyond our means is so important, and is a policy that we continue to apply. As in all previous years, the wonderful support the EHERCC receives comes in many different forms. We would like to thank all those who continue to provide this amazing support so generously. I would also like to thank the companies and organisations who have provided their services to us at no or reduced costs. Special mention again goes to Bennett Brookes Chartered Accountants who for the seventh year running have donated their bookkeeping services to the charity. Thank you."

Jeff Collins

Wonderful support for EHE in 2021

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The following pages highlight some of the amazing fundraising events that raised funds for EHERCC in 2021.

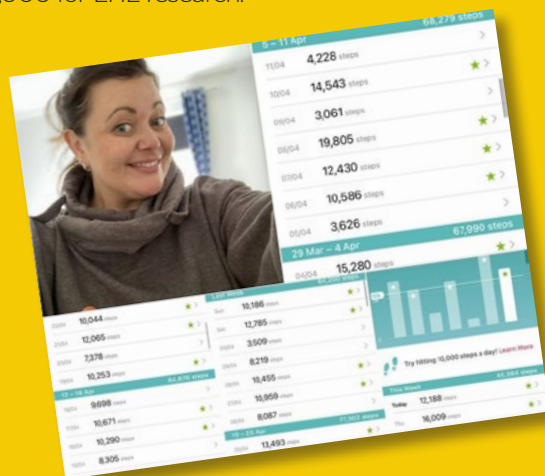
Saving the loose change all adds up

Fundraising is not always about mega events and huge sporting challenges. Sometimes it's about saving little and often. Hugh and his family decided to do this, following Jessie Hayman's Jessie Jars challenge, by putting their loose change most days in their own EHE jar at home. The last collection started in 2019, and by June this year had expanded into a second jar, despite there being little to contribute during lockdown. The result? After counting and bagging, just over £240 was raised for EHE research.



Nicola was on the march in April!

As a liver transplant patient, Nicola Henderson had to endure greater levels of social distancing, including in her own home. Recovering from a major transplant is a physically and psychologically daunting process at any time, but adding COVID restrictions on top of all of this makes the process so much harder. Fed up with COVID and having endured a significant period of shielding, Nicola decided that it was time to get out and get motivated after she was vaccinated! Her self-imposed challenge was to simply walk 10,000 steps every day for 37 days leading up to her 37th birthday on 7th May. And on her birthday Nicola was delighted to confirm that she had in fact walked 372,981 steps and, in the process, raised over £1,000 for EHE research.



Allana's birthday fundraiser

Allana Parker shared her birthday fundraiser in June and was once again overwhelmed by the support she received. This was largely due to Allana's brilliant communication skills and her dedication to helping others, even though she was battling through some challenges of her own due to her EHE. Allana also took responsibility for setting up the charity's social media sites and managing these. Everybody was therefore devastated when news was posted that Allana had passed away later in the year. She was a much-loved member of the team and is much missed by all who knew her.



London Landmarks Half Marathon

After the disappointment of the 2020 event being cancelled one week before it took place, the EHERCC was delighted that the 2021 London Landmarks Half Marathon was back, on 1st August. The charity had a team of 40 runners taking part to raise awareness of EHE and also to raise funds for EHE research.

It was a wonderful turn out by so many of our supporters, either running or cheering, and everybody who took part said that it had been a fantastic experience. At the end of the day the event helped raise over £22,000 for EHE research.



03 Fundraising and Finance Continued

Bootcamp Commandos are on the charge!

Nicola Henderson has always had an amazing group of supporters. Kerry Marks, Leanne Woodruff, and several others, set out to raise funds for EHERCC and two other charities, while completing an arduous training regime, known as the 'Bootcamp'. This included running while carrying a log, half marathons, and multiple other exercise regimes.



The Commandos also completed the Three Peaks Challenge, climbing the highest mountain peaks in England (Scafell Pike), Wales (Snowdon) and Scotland (Ben Nevis) with a combined height of 11,182 feet. They completed it in 3 days and raised over £7,000 for EHE research, in the process! They showed true grit and determination in completing the Three Peaks Challenge and Nicola was rightfully super proud of every one of them.



Another great charity lunch

Sarah Medwin held her first EHE charity lunch in December 2019, when her son Charlie was rowing the Atlantic with two friends to raise funds for EHE research. Brilliantly supported by a great group of friends, Sarah then decided she would hold an EHE charity lunch annually. So, when December 2021 came around, Sarah and her friends once again set about organising a special lunch event to raise money for EHE research. Together, this fantastic group, coupled with great support from local businesses, raised £1,850 in support of Sarah's son Harry and EHE research. When added to the JustGiving matched funding campaign, this rose to £3,700.



UK supporters take on Tough Mudder

Tough Mudder is an organisation in the UK that sets up assault courses to test participants to their maximum. Normally this involves large amounts of water and mud, and huge amounts of energy. In September, a group of employees from Raft Furniture, organised by Kelly Denton, took on the Tough Mudder course in support of somebody they know who has EHE. As the weather had been so hot, the normally wet and soggy course was in fact rock hard and totally dry. But that did not stop the group having a great day during which they raised over £7,300 for EHE research.



EHE Quiz night asks lots of questions

Kelly Denton and her friends had already raised substantial funds for EHE research, but Kelly wanted to do more. So, when her local pub, The Bridge House Pub in Penge, offered to host an EHE Quiz Night in December, Kelly was very grateful and super excited. The pub sold tickets at £5 each and local media outlet, Community Magazine SE20, sent details to 4,000 local addresses. Kelly organised a raffle and organised her best sales team to sell raffle tickets on the night. Kelly's quiz raised £1,075 on the night which, with the charity's matched funding campaign, rose to £2,150.



Matched Funding

The EHE Rare Cancer Charity (UK) was once again able to run a matched funding campaign, tied to Giving Tuesday, thanks once again to a generous donor who was prepared to match all funding that the charity raised, up to £10,000 between Giving Tuesday and the end of the year. The call therefore went out to all the charity's supporters to seek their assistance, including sharing the campaign as widely as possible. Once again we saw such generous engagement from so many people. The campaign received a £1,000 donation from the Rolls-Royce Nuclear Power Branch of Unite, in Derby, in support of their colleague, Hazel Peake, who was diagnosed with EHE earlier in the year. The charity also collected £185 pounds from text donations. By the end of the year the target of £10,000 had been exceeded, securing the £10,000 in matched funding.



Hazel Peake gets wonderful support

Hazel Peake received her EHE diagnosis in late 2021, and like all our EHE members, her life was turned upside down. But like many of our members, this is often followed by amazing and uplifting support. Hazel has seen such support from her wonderful colleagues at the Rolls-Royce Nuclear Power Branch, in Derby, and the local branch of her trade union, Unite. As soon as her branch of Unite heard that the EHE Rare Cancer Charity had launched a matched-funding campaign in December, they stepped up with an immediate £1,000 donation. And her work colleagues are also organising a quiz night for the charity in early 2022, and the funds raised there will also be matched.

The Trustees want to thank everybody who has raised or donated funds to the charity, whether it was through participation of one of the events listed above or not. It is the combination of so many small donations that deliver the funds needed to drive critical EHE research. Thank you.

EHE Rare Cancer Charity UK

Financial Accounts for 2021

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EHE Rare Cancer Charity (UK)

Independent examiner's report

Independent examiner's report to the trustees of EHE Rare Cancer Charity (UK)

I report to the charity trustees on my examination of the accounts of EHE Rare Cancer Charity (UK) (the Charity) for the year ended 31 December 2021.

Responsibilities and basis of report

As the Trustees of the Charity you are responsible for the preparation of the accounts in accordance with the requirements of the Charities Act 2011 ('the Act').

I report in respect of my examination of the Charity's accounts carried out under section 145 of the Act and in carrying out my examination I have followed all applicable Directions given by the Charity Commission under section 145(5)(b) of the Act.

Independent examiner's statement

I have completed my examination. I confirm that no material matters have come to my attention in connection with the examination giving me cause to believe that in any material respect:

- 1 accounting records were not kept in respect of the Charity required by section 130 of the Act; or
- 2 the accounts do not accord with those records; or
- 3 the accounts have not been prepared in accordance with the methods and principles of the Statement of Recommended Practice for accounting and reporting by charities [applicable to charities preparing their accounts in accordance with the Financial Reporting Standard applicable in the UK and Republic of Ireland (FRS 102)].

I have no concerns and have come across no other matters in connection with the examination to which attention should be drawn in this report in order to enable a proper understanding of the accounts to be reached.

(signed) "RJP LLP"

Simon Paterson FCCA

RJP LLP
Ground Floor
Egerton House
68 Baker Street
Weybridge
Surrey
KT13 8AL

Date: 18 October 2021

EHE Rare Cancer Charity (UK)

Statement of Financial Activities

for the period ended 31 December 2021

	Notes	Unrestricted funds £	Restricted funds £	Total 2021 £	Total 2020 £
Incoming resources:					
Donations	2	80,026	20,900	100,926	53,067
Total incoming resources		80,026	20,900	100,926	53,067
Resources expended:					
Costs of generating donations		1,751	10,450	12,201	4,448
Charitable activities		134,264	-	134,264	118,365
Governance costs		-	1,200	1,200	1,200
Other administrative costs		85	5,032	5,117	9,110
Total resources expended	3	136,100	16,682	152,782	133,123
Net surplus for the year		(56,074)	4,218	(51,856)	(80,056)
Transfer between funds		-	-	-	-
Balance brought forward		379,556	350	379,906	459,962
Funds carried forward	8	323,482	4,568	328,050	379,906

Funds carried
forward for 2021
£328,050

EHE Rare Cancer Charity (UK)

Balance Sheet

as at 31 December 2021

	Notes	Unrestricted funds £	Restricted funds £	Total 2021 £	Total 2020 £
Current assets					
Debtors	5,9	143,674	10,074	153,748	230,769
Cash at bank and in hand		307,353	4,026	311,379	324,986
Total current assets		451,027	14,100	465,127	555,755
Creditors: amounts falling due within one year	6,9	(102,490)	(9,532)	(112,022)	(112,748)
Net current assets (liabilities)		348,537	4,568	353,105	443,007
Creditors: amounts falling due after one year	7,9	(25,055)	-	(25,055)	(63,101)
Net assets (liabilities)		323,482	4,568	328,050	379,906
Funds carried forward					
Unrestricted funds		323,482	-	323,482	379,556
Restricted funds		-	4,568	4,568	350
Total funds	8	323,482	4,568	328,050	379,906

The Charities Act requires the Trustees to prepare financial statements for each financial year which give a true and fair view of the state of affairs of the charity at the year end and of the surplus or deficit for the year then ended.

In preparing these financial statements, the Trustees are required to select suitable accounting policies, and then apply them on a consistent basis, making judgements and estimates that are prudent and reasonable. The Trustees must also prepare the financial statements on the going concern basis unless it is inappropriate to presume that the charity will continue in business.

The Trustees are responsible for keeping proper accounting records which disclose with reasonable accuracy at any time the financial position of the charity and to enable them to ensure the financial statements comply with the Charities Act 2011. The Trustees are also responsible for safeguarding the assets of the charity and hence taking reasonable steps for the prevention and detection of fraud and other irregularities.

These accounts were approved by the Trustees Committee on 13 October 2022 and signed on its behalf by:

(signed) "Hugh Leonard"

Hugh Leonard
Chairperson

EHE Rare Cancer Charity (UK)

Notes to the Accounts

for the period ended 31 December 2021

1 Accounting Policies

Basis of preparation: The financial statements of the charity, which is a public benefit entity under FRS 102, have been prepared in accordance with the Charities SORP (FRS 102) 'Accounting and Reporting by Charities: Statement of Recommended Practice applicable to charities preparing their accounts in accordance with the Financial Reporting Standard applicable in the UK and Republic of Ireland (FRS 102) (effective 1 January 2019)', Financial Reporting Standard 102 'The Financial Reporting Standard applicable in the UK and Republic of Ireland' and the Charities Act 2011. The financial statements have been prepared under the historical cost convention.

Incoming resources

Recognition of incoming resources: These are included in the Statement of Financial Activities when:

- The charity becomes entitled to the resources;
- The trustees are virtually certain that they will receive the resources; and
- The monetary value can be measured with sufficient reliability.

Deferred income: Where grants are received in advance and specified by the donor as relating to specific accounting periods, these are deferred on an accruals basis to the period to which they relate.

Tax reclaims on donations and gifts: Incoming resources from tax reclaims are included in the Statement of Financial Activities at the same time as the gift to which they relate.

Incoming resources with related expenditure: Where incoming resources have related expenditure, the incoming resources and related expenditure are reported gross in the Statement of Financial Activities.

Volunteer help: The value of any volunteer help is not included in the accounts.

Investment income: Investment income is included in the accounts when receivable.

Expenditure and liabilities

Resources expended are inclusive of VAT where applicable which cannot be recovered.

Liability recognition: Liabilities are recognised as soon as there is a legal or constructive obligation committing the charity to pay out resources.

Costs of charitable activities: A research grant is recognised when the Charity formally notifies the recipient of the award following scientific review. The liability is measured as the total of expected payments for the award. Grant payments that are contingent on a successful outcome of and payable after a future scientific review are disclosed as commitments. Liabilities for awards payable more than one year after the balance sheet date are recorded at the value the Charity expects to settle the grant or award.

Governance costs: These include the costs of preparation and examination of statutory accounts, the costs of any general meetings and the costs of any legal advice to trustees on governance or constitutional matters.

Administrative fund

This fund has been established by the Trustees to fund all governance and administrative costs and is funded by a single donor for these restricted purposes.

2 Analysis of incoming resources

Donation income:

	2021 £	2020 £
Unrestricted funds:		
Personal donations including fundraising events	76,125	51,055
Corporate and Foundation donations	3,901	812
	80,026	51,867
Restricted funds:		
Administration fund	20,900	1,200
	20,900	1,200

3 Analysis of resources expended

	Unrestricted funds £	Restricted funds £	Total 2021 £	Total 2020 £
Costs of generating donations:				
Just giving fees	539	562	1,101	987
Fundraising event entry and other fees	-	9,888	9,888	2,700
Credit card and other processing fees	1,212	-	1,212	761
	1,751	10,450	12,201	4,448
Costs of charitable activities:				
University of Manchester PhD Study	43,736	-	43,736	33,433
Royal Marsden Biobank	31,612	-	31,612	56,000
Zebrafish Study University of Sheffield	26,483	-	26,483	28,932
Fondazione IRCCS and ICR Biomarkers	32,433	-	32,433	-
	134,264	-	134,264	118,365
Governance costs:				
Independent examiners' fee	-	1,200	1,200	1,200
	-	1,200	1,200	1,200
Other administrative costs:				
Design and publishing	-	3,041	3,041	3,810
Website maintenance	-	1,883	1,883	1,750
Other professional fees	-	-	-	3,348
Bank fees	85	108	193	202
	85	5,032	5,117	9,110

Trustees' expenses

£6,293 of expenses were incurred by Trustees during the period, primarily associated with fundraising event entry fees paid by Trustees and reimbursed by the Charity (2020 - £Nil).

4 Taxation

The Charity is exempt from Corporation Tax on its charitable activities.

EHE Rare Cancer Charity (UK)

Notes to the Accounts (continued)

for the period ended 31 December 2021

5 Debtors

	Unrestricted funds £	Restricted funds £	Total 2021 £	Total 2020 £
Prepayment to the University of Manchester	50,533	-	50,533	94,269
Prepayment to Royal Marsden	32,805	-	32,805	51,333
Prepayment to Fondazione IRCSS Istituto Nazionale Dei Tumori	31,477	-	31,477	67,840
Prepayment to the University of Sheffield	26,483	-	26,483	-
Other debtors	2,376	10,074	12,450	17,327
	143,674	10,074	153,748	230,769

Included within the debtors figures above are amounts of £25,055 (2020 – £63,101) due after more than one year.

6 Creditors: amounts falling due within one year

	Unrestricted funds £	Restricted funds £	Total 2021 £	Total 2020 £
University of Manchester	29,182	-	29,181	49,101
Royal Marsden	9,820	-	9,820	25,667
Fondazione IRCSS Istituto Nazionale Dei Tumori	37,005	-	37,005	33,920
University of Sheffield	26,483	-	26,483	-
Accrued independent examiners'	-	1,200	1,200	1,200
Other creditors	-	8,332	2,860	2,860
	102,490	9,532	112,022	112,748

7 Creditors: amounts falling due after one year

	Unrestricted funds £	Restricted funds £	Total 2021 £	Total 2020 £
University of Manchester	-	-	-	29,181
Fondazione IRCSS Istituto Nazionale Dei Tumori	-	-	-	33,920
Royal Marsden	25,055	-	25,055	-
	25,055	-	25,055	63,101

8 Details of funds

Administrative Fund

This fund has been established by the Trustees to fund all governance and administrative costs and is funded by a single donor for these restricted purposes.

9 Commitments and contingencies

In July 2018, the Charity contracted with the **Bateson Centre at the University of Sheffield** to develop an EHE zebrafish model. In August 2019, a second phase of the project was agreed with two payments required in August 2019 and February 2020 of £21,699 each. In July 2021, the Charity contracted with the Bateson Centre to fund an additional one-year, full-time MPhil student to further assess the EHE zebrafish model that the Charity had funded in 2018 through 2020. The total cost of the project is £52,965 and commenced in July 2021. In 2021, £26,483 of payments were made and recorded as charitable activity cost (2020 - £28,932). The amounts committed to for 2022 have been included within Debtors and Creditors as appropriate.

In October 2018, the Charity contracted with the **Department of Developmental Biology and Medicine at the University of Manchester** for the carrying out of a four-year PhD study to research the impact of EHE on endothelial cells. The total cost of the contract was £173,237 to be incurred over four years from January 2019 as follows:

2019	£45,535
2020	£49,420
2021	£49,101
2022	£29,181

In 2021, £49,101 of payments were made and recorded as charitable activity cost offset by £5,365 of amounts refunded as not spent during 2020 (2020 - expense of £33,433). The amounts committed to for 2022 have been included within Debtors and Creditors as appropriate.

In April 2019, the Charity contracted with the **Royal Marsden Trust** to fund a two-year position of Tissue Manager with the Royal Marsden and ICR Sarcoma Research Centre. The project commenced in 2019 with a total cost of £112,000 over two years commencing from the date of hire of the Tissue Manager on 17 June 2019. In 2021, no payments were required to be made but £25,667 was recorded as charitable activity cost (2020 - payment of £56,000 and £56,000 as charitable activity cost).

In March 2021, the Charity agreed to fund costs associated with the establishment and administration of an EHE Biobank with the **Royal Marsden Cancer Charity and the Royal Marsden NHS Foundation Trust** with an estimated total cost of £38,750 over five years commencing in April 2021, when the first payment of £3,875 was made. £5,945 has been recorded as charitable activity cost (2020 - £Nil). The amounts committed to for future years have been included within Debtors and Creditors as appropriate.

In December 2020, the Charity contracted with **the Fondazione IRCCS Istituto Nazionale Dei Tumori in Italy and the Institute of Cancer Research: Royal Cancer Hospital, UK** to fund a project to assess the presence of novel biomarkers in EHE patient blood and tissue samples to inform patient management as well as potential therapeutic targets. The total cost of the project is €115,000 (£95,530) to be incurred over a maximum of 30 months and separately, the Charity agreed that the EHE Foundation based in the United States would fund €40,000 (£33,576) of the total costs. In 2021, payments of £25,949 were made and £32,433 was recorded as charitable activity cost. The remaining amounts payable by the Charity have been included in Debtors and Creditors as appropriate.

10 Subsequent events

In June 2022, the Charity agreed to expand the project contracted with the Fondazione IRCCS Istituto Nazionale Dei Tumori in Italy and the Institute of Cancer Research: Royal Cancer Hospital, UK to look in greater detail of the mRNA analysis and to develop additional PDX models of different variants of EHE. Total costs of the expansion over the two years of the project are estimated at £113,595 with costs funded 50% by the Charity and 50% by the EHE Foundation in the United States. As the commitment was not incurred as at the balance sheet date, no amounts have been recorded as liabilities in the 31 December 2021 financial statements.

In June 2022, the Charity contracted with the Bateson Centre at the University of Sheffield to extend the one-year, full-time MPhil student for a further year to continue assessing the EHE zebrafish model that the Charity had funded since 2018.

The total cost of the extension is £57,430 which commenced at the end of the existing project in July 2022. As the commitment was not incurred as at the balance sheet date, no amounts have been recorded as liabilities in the 31 December 2021 financial statements.

With the recent and rapid development of the Coronavirus outbreak, the Charity has considered the unique circumstances and the risk exposures of the Charity and has concluded that there is no immediate material impact to the Charity's financial position. The Charity will continue to monitor the situation closely and will re-assess in case the period of disruption becomes prolonged.

Trustees' Declaration

As Trustees of the EHE Rare Cancer Charity (UK), the undersigned have fully reviewed the content of this Report of the Trustees and confirm that they each consider it to be a true and fair reflection of the EHERCC's activities and operations for the year ending 31st December 2021. They each confirm that there are, to the best of their knowledge, no exceptional or special events that have occurred or that should be reported.

The Trustees also confirm that they have undertaken their respective roles and responsibilities with due regard to the public benefit requirements of the charity, and have taken into account the Charity Commission's public benefit guidance when making any decision and producing any reports relating to EHERCC's charitable objects and its associated activities.

Signed this 22nd day of October, 2022

(signed) "Hugh Leonard"
Hugh Leonard Chair of Trustees

(signed) "Jeff Collins"
Jeff Collins Trustee

(signed) "Kate Hooper"
Kate Hooper Trustee

(signed) "Oliver Pearce"
Oliver Pearce Trustee

(signed) "Sally Baker"
Sally Baker Trustee

Charity Information

Charity Name:

The EHE Rare Cancer Charity (UK),
A Charitable Incorporated Organisation (CIO)

Also known as:

Also known by its acronym, EHERCC

Charity number:

1162472

Web address:

www.ehercc.org.uk

Registered address:

23 Geneva Road, Kingston Upon Thames,
Surrey, KT1 2TW

Charity Trustees:

Mr Hugh Leonard (Chair)
Mr Jeffery Collins
Dr Katharine Hooper
Mrs Elizabeth Milligan (resigned 10th March 2021)
Dr Oliver Pearce
Ms Sally Baker (from 12th November 2021)

Established in 2015.

Also working closely with EHE foundations in USA, Australia, Canada and Italy.

Managed and run by volunteers.

All running costs funded by single donor.

100% of all donations received therefore available to deliver core objectives.

The Pledge

The Pledge is the quarterly newsletter of the EHE group of foundations. It is produced in London and provides details of the groups' worldwide activities in their key areas of advocacy and patient support, research, fundraising, and any other stories of interest. If you would like to be added to the distribution list to receive a copy of *The Pledge* each quarter, please contact your local EHE charity or foundation.

