EHE RARE CANCER CHARITY (UK)

England & Wales · Charity number 1162472

Details

Other names	EHERCC
Status	Registered
Legal form	CIO
Registered	2015-06-30
Register	View on the Charity Commission register

Contact

Address	23 Geneva Road Kingston upon Thames KT1 2TW
Phone	02089745643
Email	contactus@ehercc.co.uk
Website	www.ehercc.org.uk

Activities

Objects: 1. THE RELIEF OF SICKNESS BY PROMOTING RESEARCH INTO THE NATURE, CAUSES, DIAGNOSIS, PREVENTION, TREATMENT, AND CURE OF CANCER INCLUDING BUT NOT LIMITED TO EPITHELIOID HEMANGIOENDOTHELIOMA AND PUBLISHING THE USEFUL RESULTS THEREOF,2. THE RELIEF OF PERSONS SUFFERING FROM CANCER BY IMPROVING METHODS OF TREATMENT.3. THE ADVANCEMENT OF EDUCATION IN THE CAUSES AND TREATMENT OF CANCER.

Activities: The EHE Rare Cancer Charity (UK) has three key objectives. Firstly we provide support to patients diagnosed with epithelioid haemangioendothelioma (EHE), a very rare form of vascular sarcoma. Secondly we are raising funds to support and fund research into EHE. Thirdly, we are working to raise awareness of EHE and to secure greater attention and improved care for people diagnosed with EHE.

Classification

- **How:** Makes Grants To Organisations, Provides Advocacy/advice/information, Sponsors Or Undertakes Research
- **What:** The Advancement Of Health Or Saving Of Lives
- **Who:** The General Public/mankind

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Geography

- Australia
- France
- Germany
- Italy
- United States
- Throughout England

Finances

Period end	Income	Expenditure	Assets	Employees
2024-12-31	£132,868	£53,510	-	-
2023-12-31	£73,837	£172,970	-	-
2022-12-31	£106,559	£163,721	-	-
2021-12-31	£100,926	£152,782	-	-
2020-12-31	£53,067	£133,123	-	-

Trustees

Name	Role	Appointed
HUGH LEONARD	Chair	2015-04-17
Dr Oliver Matthew Thomas Pearce		2020-09-16
JEFFERY IAN COLLINS		2015-04-17
KATE HOOPER		2015-04-17
Sally Jane Baker		2021-11-19

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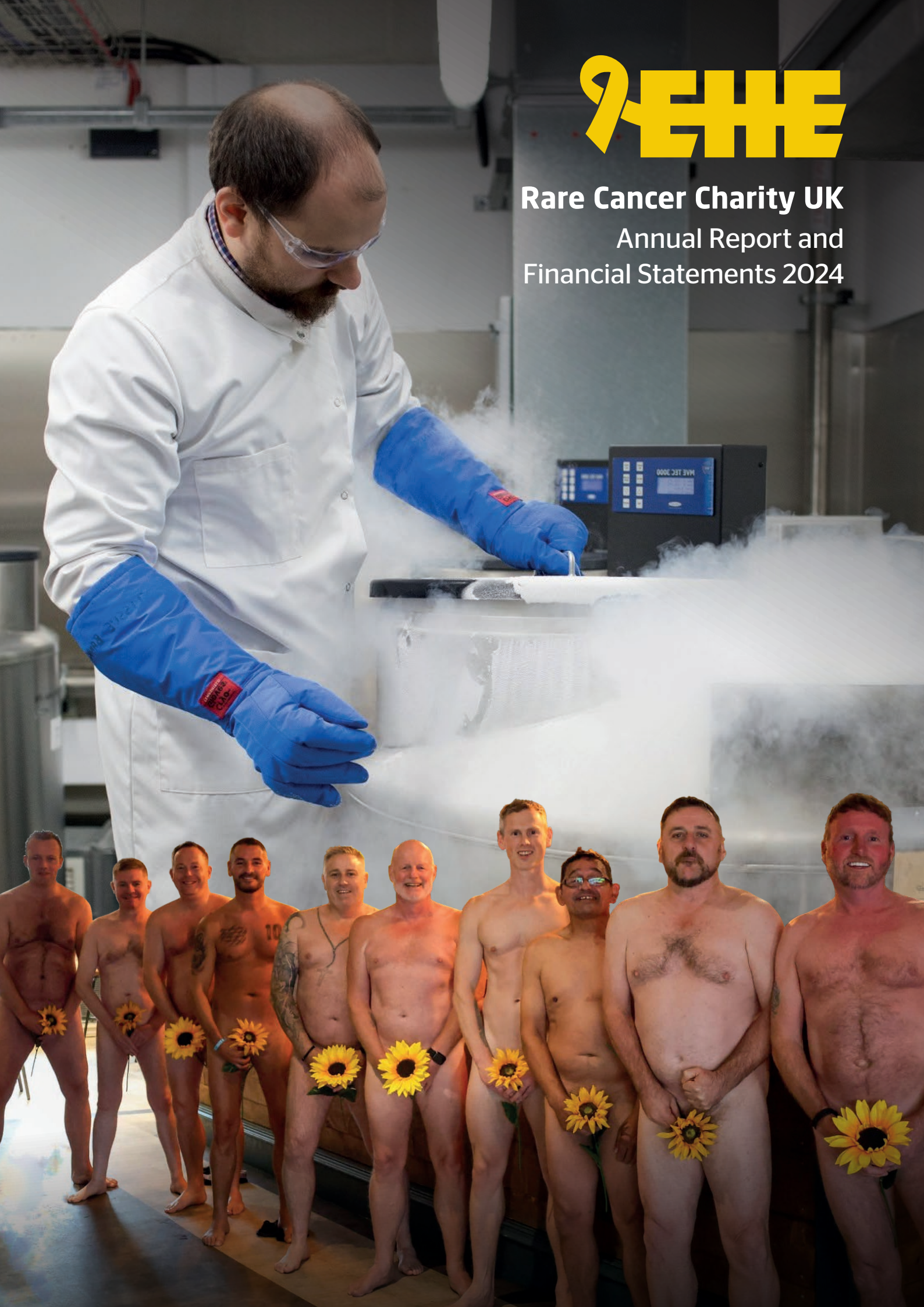
EHE RARE CANCER CHARITY (UK)

England & Wales - Charity number 1162472

Accounts



Rare Cancer Charity UK

Annual Report and Financial Statements 2024

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'

Background slide showing endothelial cells treated with inhibitor (blebbistatin) to show location (pink areas) of TAZ-CAMTA1

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 both males and females but is **more prevalent in women**

One of the **world's rarest cancers,** with approximately 20 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

EHE Rare Cancer Charity UK

Annual Report and Financial Statements 2024

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Message from the Trustees

In 2024, we once again enjoyed great support from our patient community, saw excellent progress in the research we are supporting, and made advances in important areas of advocacy for better EHE treatments. These outcomes resulted in 2024 being another excellent year for the EHE Rare Cancer Charity (EHERCC or 'Charity').

The EHE research activities we are funding continued to produce exciting results. The European collaborative research involving Istituto Nazionale dei Tumori (INT) in Milan, Italy and the Institute of Cancer Research (ICR) and the Royal Marsden Hospital (RMH) in London continues to study different aspects of the disease, and the researchers believe they have identified a biomarker for EHE, one of the key objectives. The UK National EHE Biobank, funded by the Charity, continues to grow, capturing critical EHE biosamples for use in research. The international EHE research programme we support has also continued to grow and produce important results.

Our patient support and advocacy activities have continued to grow. Patient support and information sharing has been provided on a patient-to-patient basis through the group's global EHE Patient Support Facebook page. At the same time, every opportunity has been taken to engage with the general public, regulators, hospitals and other key stake holders to ensure that awareness of our EHE global community and the Charity continues to grow.

We are also excited by the Charity's engagement with the European Medicines Agency, seeking a label extension of the drug sirolimus for the treatment of EHE, an important goal for the EHE patient community. This has been led by the European Organisation for Research and Treatment of Cancer (EORTC). The Charity is also a participant and Executive Committee member of the PUSH project (Pushing Ultra-rare Sarcomas beyond Hope), a new global platform designed to promote, support and run ultra-rare sarcoma studies, trials and other forms of disease investigation.

2024 was also another excellent year on the fundraising front, with grass-roots fundraising by our patients and their supporters. As we prepare this annual report, we want to again acknowledge that all the activities we are proud to report on have only been possible because of the extraordinary commitment of our patient community and their supporters. This is even more extraordinary when we recognise that EHE patient numbers will always be tiny due to the extreme rarity of the disease. That makes their achievements all the more amazing.

We will also never forget the amazing contribution made by the sarcoma clinical and research communities that we work so closely with. They strive every day to discover and deliver better treatment options for EHE patients. We could not be more grateful. As always, therefore, we want to recognise every single person who provided their support, in whatever form, to the Charity and the global EHE community in 2024 by saying a simple but profound "Thank you"!

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

In 2024 the Charity, working side by side with the other internationally-based EHE foundations and our EHE patient community, continued to engage with all stake holders with the core objective of increasing understanding and awareness of EHE.

In early January, Hugh Leonard, Chair of Trustees, participated in a very positive workshop hosted by the European Medicines Agency (EMA) and the European Organisation for Research and Treatment of Cancer (EORTC), to discuss the challenges faced by ultra-rare sarcomas in securing approvals for new or repurposed drugs. Hugh presented the experience of EHE patients as a case study for ultra-rare sarcomas in general. Senior clinicians from Europe, the UK and USA also participated, addressing a number of key areas.

In parallel with the EMA process above, the Charity is also a participant in the PUSH project, a new global platform with the aim of maximising the knowledge that is gained from interacting with, and treating, every single patient affected by an ultra-rare sarcoma and to support the development of new treatments to improve outcomes and quality of life. Ultimately it is hoped that a substantial number of institutes and academic centres across the globe will join the project, forming the PUSH Consortium, giving the PUSH Platform real momentum and an ability to change the landscape for ultra-rare sarcomas.

Collaboration is also a key feature of the Charity's advocacy initiatives. Global collaboration between the different national EHE foundations has continued to provide a common approach across international EHE programmes and initiatives. The Charity is working closely with 'EHE Italia Non Solo Laura' (Italy), particularly on European-focused matters, and with the EHE foundations in the USA, Australia and Canada, seeking to promote and expand the international EHE research and clinical collaborations for EHE.

Ensuring engagement with the UK EHE patient community is also a core objective. The UK EHE patient WhatsApp group continues to be an active and hugely positive component of our activities, although we continue to regularly communicate with the patient community through multiple social media and other communication routes.

02 Research

A key focus for our funded research was again the ongoing European collaboration involving Istituto Nazionale dei Tumori (INT), Milan, the Institute of Cancer Research (UK), and the Royal Marsden Hospital (RMH), London. This multi-faceted programme is researching a number of key aspects of EHE, one of the key objectives being to try and find a biomarker for EHE. We were therefore thrilled when the research team identified Growth and Differentiation Factor-15 (GDF15) as a strong likely biomarker for the disease.

A core component of this international collaboration is the ongoing non-interventional observational study of EHE patients. The study cohort was approaching 50 patients by the end of 2024, providing a unique data set for EHE. At the same time, the Charity continues to fund the first ever EHE-dedicated, prospective observational registry, a pan-European initiative, which is part of the European STARTER project, and is managed and coordinated by a dedicated team also based at INT in Milan.

The National EHE Biobank, funded by the Charity and based at The Royal Marsden Hospital in London, continues to gather critical bio-samples. The Charity and the Royal Marsden are continuing to promote awareness of the biobank with hospitals across the UK, supported by enthusiastic support from the UK patient community.

The above is all very exciting, but we do have to accept that not all research will be successful. One such case was the continued work we were doing with the Bateson Centre in Sheffield, where the team were seeking to generate a zebrafish model of EHE. Ultimately the team were unable to generate research-useful fish, and this, coupled with the ongoing successful development of PDX, mouse and human EHE cells lines globally, meant that the difficult decision to halt this research project had to be made.

03 Fundraising

Fundraising is the life blood of the Charity, providing the very foundations for all that we do, and in particular our ability to fund key research. Once again, our fundraising through the year was a combination of grass-roots activity driven by our patient community and their supporters, and charity-driven events.

The largest of our two charity-driven events is the London Landmarks Half Marathon, and 2024 saw great turnout from our supporters, with more than 50 runners registered for the run. It was another fantastic day with the runners enjoying near perfect conditions.

The RideLondon-Essex 100-mile-long cycling sportive was also well supported, with 14 riders taking on this major challenge. Hugh Leonard, Chair of Trustees, again felt that he needed to participate, having spent several years encouraging others to get involved, his third time riding in the event.

Fundraising can be both inspiring and deeply emotional as it is often organised in memory or support of a loved one. The Charity received great support from so many different groups and individuals. Every single one of these acts, which come in so many different forms, is priceless. We are so grateful for every single one, and so seldom single out any particular event. We did, however, love the group of men who decided to bare nearly all to create an EHE calendar to raise funds for EHE research. We loved the use of the sarcoma symbol of sun flowers to maintain a minimum level of modesty, and hope you don't mind us using it on our front cover.

More information about these and other events can be found in this report.

Objectives and Achievements for 2024

We believe that an honest assessment of our year's activities and achievements against the goals we set ourselves is important for all our supporters and stakeholders. Below is the 2024 assessment; on the oppositive page you will see our objectives for 2025 and beyond.

	What we said we would do...	...and what we achieved
01 Patient Support and Advocacy	Continue sirolimus repurposing	Dialogue ongoing with EMA with two Scientific Advice procedures completed
	Support PUSH platform	The Charity is a consortium member with Hugh Leonard a member of the Executive Committee
	Revitalise other social media	Social media relaunched. Delivery of news and messaging ongoing
	Engage with European patient community	Limited progress made. Exploring UK-Italy collaboration
02 EHE Research	Support existing projects	All projects supported
	Develop and promote coherent EHE research strategy	Limited progress made with this complex matter. Currently reviewing best way to develop the concept
	Organise additional research review meetings	Further online meetings held
	Coordinate with EHE Group entities	Close and proactive ties maintained with US, Canadian, Italian and Australian organisations
03 Fundraising	Support and encourage grassroots fundraising	Continued to work with our brilliant supporters
	Coordinate key charity events (LLHM and RideLondon100)	Both organised and delivered with great engagement
	Continue to review fundraising strategy with NOVA fundraising	Limited progress as we worked on the broader research strategy
	Coordinate review of research strategy and develop draft fundraising programme	Limited progress as requires completion of actual research strategy first
Charity Organisation	Consider appropriate support for research strategy	Dr Paul Huang joins Research and Medical Advisory Board
	Implement fundraising strategy	Grass-roots ongoing, but new broad strategy delayed
	Establish structures for European engagement	In progress and under review with EHE Italia
	Evaluate need for additional structures and personnel for the above	In progress

Our Forward Focus for 2025

Because rare cancers are not rare to those who have them!

01 Patient Support and Advocacy

- Continue to promote sirolimus repurposing
- Engage with other repurposing groups and platforms
- Remain engaged with PUSH
- Support UK patient community, and international patients where possible
- Attempt to define European strategy

02 EHE Research

- Support existing research
- Execute research extensions where possible
- Continue to search for new research opportunities
- Identify joint funding opportunities within the EHE Group

2025 AND BEYOND

03 Fundraising

- Support and encourage grassroots fundraising
- Promote **10 for 10** fundraising campaign across 2025
- Re-evaluate timing of fundraising strategy with NOVA fundraising
- Evaluate ways to systemise fundraising engagement ideas through website modifications

Charity Organisation

- Consider appropriate support for research strategy
- Implement fundraising strategy
- Establish structures for European engagement
- Evaluate need for additional structures and personnel for the above

Foreword from Associate Professor John M. Lamar

I am honored to write this foreword for the UK EHE Rare Cancer Charity (EHERCC) Annual Report—particularly because it was the EHERCC and its sister foundations in the United States and Australia that provided the initial funding that enabled my laboratory to begin our work on epithelioid hemangioendothelioma (EHE).

I am a cancer biologist who has spent much of my career studying YAP and TAZ—two proteins that, although vital for normal cellular function, can drive cancer development and progression when not properly controlled. Like many of my colleagues, I was initially unaware of EHE, despite the fact that virtually all cases of this rare cancer are caused by mutant forms of YAP or TAZ. That changed when Dr. Guy Weinberg reached out to ask if I would help organize a scientific workshop. His goal was to bring together researchers studying YAP and TAZ with those focused on EHE, believing that this connection could accelerate progress for EHE patients.

At our inaugural YAP/TAZ-TEAD at the Crossroads of Cancer workshop, I met Drs. Brian Rubin and Munir Tanas and learned of their pioneering work on EHE. At the time, the field was still in its infancy. There were no reliable research models, and many fundamental questions about the disease remained unanswered. Yet I was immediately captivated by EHE and by the fusion protein TAZ-CAMTA1, which is present in more than 90% of all cases. In 2018, with seed funding from the EHERCC and the EHE foundations in the United States and Australia, my laboratory began our own EHE research in collaboration with Dr. Rubin's group.

The seven years since have brought extraordinary progress. Through the collective efforts of EHE researchers and clinicians worldwide, we now understand much more about how the TAZ-CAMTA1 and YAP-TFE3 fusion proteins drive EHE formation and progression. Robust mouse models, human and mouse EHE cell lines, and patient-derived xenograft models have been developed, providing essential tools to study this disease and identify therapeutic opportunities. EHE patients have been enrolled in clinical trials, and promising new drug targets are emerging from preclinical studies. The first biomarker has been identified, and the establishment of EHE biobanks and a global EHE patient registry is providing vital resources for researchers. A consensus paper authored by more than 80 experts now guides evidence-based best practices for managing primary and metastatic EHE.

Equally transformative has been the growth of the EHE research community. Awareness of EHE among cancer scientists has expanded dramatically, as has the number of laboratories working on the disease. Today, EHE is discussed regularly at international conferences, and pharmaceutical companies are increasingly interested in testing compounds that target YAP and TAZ in EHE models and including EHE patients in clinical trials.

Much of this progress has been made possible through the vision and dedication of the EHERCC and its sister foundations in the United States and Australia, and more recently Italy, together with dynamic patient groups in countries such as Canada and Germany. These organizations have been instrumental not only in funding critical research and supporting patients, but also in fostering collaboration between scientists and clinicians, a partnership that is absolutely essential to translating new discoveries into life-saving therapies.

Despite these remarkable advances, our work is far from done. There are still no approved treatments for aggressive EHE, and many questions remain about its biology and vulnerabilities. Continued progress will depend on expanding our research tools, developing new models, and sustaining the support of donors committed to this mission.

I am inspired by how far the EHE community has come in such a short time. With the continued leadership of the EHE foundations, I am confident that the coming years will bring even more significant breakthroughs and, ultimately, new hope for patients living with EHE.

The Lamar Lab team (from left to right): Jessica Scarchilli, Emily Norton, John Lamar, Seth Lecuyer and Sarah McMullan

John M. Lamar Ph.D. is an Associate Professor at the Molecular and Cellular Physiology Department at the Albany Medical College in Albany, New York. He obtained his Bachelor of Science in Biochemistry at SUNY Geneseo, Geneseo, NY in 2000; his Master's Degree in Biology at Albany Medical College in 2006; and his Ph.D. in Biology at Albany Medical College in 2008. After completing spells first as a Postdoctoral Researcher and then a Research Scientist at Koch Institute at MIT, he returned to Albany Medical College where he has established his own laboratory focused on the study of cancer metastasis, which is responsible for greater than 90% of all cancer mortality. His work is heavily focused on the Hippo Pathway and its two effectors, Yes-associated protein (YAP) and Transcriptional coactivator with PDZ-binding motif (TAZ), and in particular, their involvement in EHE.

01
Patient Support and Advocacy

Our patient support and advocacy activities lie at the core of the Charity's activities and comprise two simple objectives. The first, inward focused, supports the whole patient community, while the second, outward looking, is about spreading awareness of EHE and the impact that an EHE diagnosis has on patients.

Support for EHE patients is largely provided through EHE social media platforms, both local and global, by the patient community itself. These are the people with real EHE understanding, allowing them to share experiences and provide valuable information on a range of topics.

Our outward-looking advocacy objectives are to take every opportunity to bring these facts to people's attention. We therefore take every opportunity to engage in dialogue as we continue to believe that there is no better way to spread awareness than by speaking to actual audiences.

We also share news about the Charity and its activities, in the EHE Group quarterly global newsletter, The Pledge, edited and produced here in the UK. We will also share this Charity Annual Report with as many people as we can as part of our awareness and patient support programme. We hope that people find the content of these different publications inspiring and share them as widely as possible.

Review by Sally Baker

"2024 has been another good year with regard to our patient support and advocacy activities. We were delighted with the continued engagement with the European Medicines Agency as we sought approval for the drug sirolimus for the treatment of EHE. We also continued through the year as a member of the Push Consortium, with Hugh Leonard our Chair of Trustees being a member of the PUSH Executive Committee. We were also delighted in 2024 when Dr Paul Huang from the Institute of Cancer Research agreed to join the Charity's Research and Medical Advisory Board. More information is provided below concerning our Patient Support and Advocacy activities through the year".

EMA engagement and sirolimus approval

In early January, Hugh Leonard was delighted to participate in a workshop hosted by the European Medicines Agency (EMA) and the European Organisation for Research and Treatment of Cancer (EORTC), to discuss the challenges faced by patients with ultra-rare sarcomas and those treating them. Hugh Leonard presented the perspectives of patients with these ultra-rare diseases, using EHE as a case study.

The core objective of the workshop was to consider how the regulatory pathway for approval of new treatments for ultra-rare sarcomas can be improved. Senior clinicians from Europe, the UK and USA also participated, addressing a number of key areas. In addition, more than 300 people participated online, including clinicians, health care professionals, researchers, patient advocates and members of the public.

A second such workshop was held in late May, also at the EMA offices in the Hague. Hugh Leonard again had the chance to participate, presenting the EHE Group's experience with mobilising and accessing patients and their information. Denise Robinson from the EHE Foundation in the USA updated the meeting on the history of sirolimus involvement in treating EHE, including some of the data from the EHE Group's sirolimus survey which was the subject of a scientific paper published in February 2024 (see the Research section of this Report).

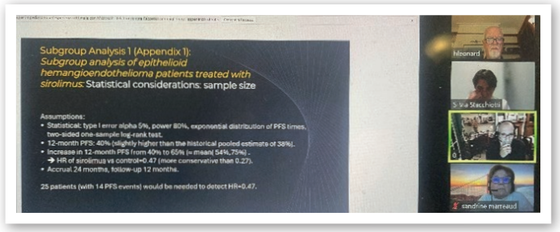
Both workshops were positive, with strong alignment between the clinicians, patient groups and the regulators, all keen to continue the dialogue and to find improved ways to approve new drugs or the repurposing of existing drugs for ultra-rare cancers.

The focus on repurposing is of particular importance for EHE as the EHE Group continues to seek approval of sirolimus for the treatment of EHE. Hugh Leonard explained:

"Getting a marketing authorisation approval for sirolimus will allow more EHE patients to have access to this important drug. This is necessary because, without formal regulatory approval, sirolimus is only available to patients if their doctor, hospital, and health system, and/or insurance companies will all allow off-label use. The only alternative may be to self-fund. As a result therefore, because of these off-label limitations, many of our patient community cannot access sirolimus".

01 Patient Support and Advocacy - continued

In addition, because EHE is so rare, many of the standard practices that regulators would expect an applicant to use in support of a drug approval, new or repurposed, are just not possible. The clinical team, led by Dr Stacchiotti, had therefore worked hard to develop a prospective observational study protocol which would generate data about the disease and the effect of sirolimus, in a manner that is as close as possible to those standard procedures.



In the technical exchange with the EMA, known as Scientific Advice, the application team provided a further set of detailed questions to the regulator, seeking feedback as to whether their latest study proposal would be likely to meet regulatory requirements.

The Scientific Advice response letter was received in mid-December 2024. Although it included a number of observations and identified concerns, the EMA did recognise the difficulties presented by such a rare disease and indicated that with some further small changes, the study protocol could be acceptable.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CONFIDENTIAL
Doc Ref: EMADOC-360526170-2106638
Case No.: EMA/SA/0000178254
Human Medicines Division

Amsterdam, 12/12/2024

Follow up Scientific Advice
Sirolimus

On 10/06/2024, the Applicant European Organisation For Research And Treatment Of Cancer requested scientific advice for their product Sirolimus pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

The Charity believes that this is a positive response, and hopes that it will soon be possible to start to actually gather data under the study protocol. Success of the study is not guaranteed but will of course be dependent on the actual results achieved, which must in fact meet or exceed the target results that are included within the protocol itself and which define the outcomes that will be necessary to demonstrate an acceptable level of efficacy.

We look forward to further EMA engagement and progress in 2025.

New member joins the Charity's Advisory Board

In mid-January, the Charity was excited to be able to confirm that Dr Paul Huang had joined the Charity's Research and Medical Advisory Board. Dr Paul Huang is Head of the Molecular and Systems Oncology Laboratory at the Institute of Cancer Research in London, UK. He received his PhD in Biological Engineering from Massachusetts Institute of Technology in 2008. His laboratory focuses on understanding aberrant signalling networks and drug resistance in sarcomas, with the goal of developing biomarkers and new therapies for these diseases. Dr Huang is the Deputy Director of the Joint Royal Marsden-ICR Sarcoma Research Centre, one of the largest sarcoma research centres in Europe. He serves as Vice Chair of the Pathology & Translational Research Committee of the EORTC Soft Tissue and Bone Sarcoma Group and on the Board of Directors of the Connective Tissue Oncology Society. He was elected a Fellow of the Royal Society of Biology in 2020.

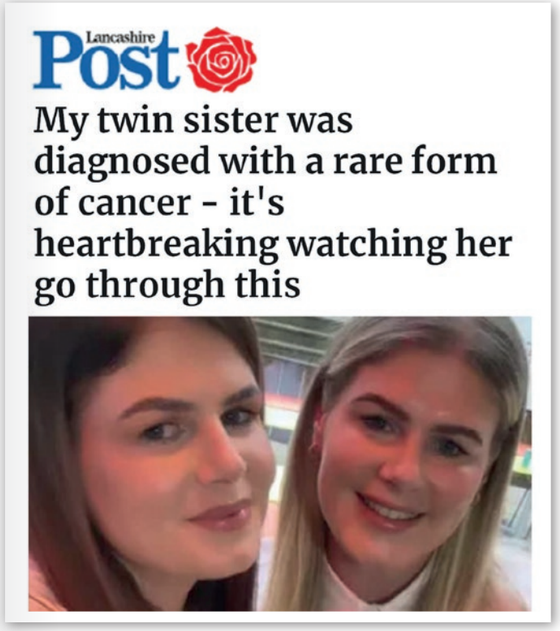
Hugh Leonard, Chair of Trustees, was thrilled to be able to welcome Dr Huang:

"We are really delighted to be able to confirm that Dr Paul Huang has joined the Charity's Research and Medical Advisory Board, and welcome him to the team. Dr Huang works at the Institute of Cancer Research, which is a sister organisation of the Royal Marsden Hospital, where he continues to be a great champion of the EHE cause. He is a key collaborator with Dr Stacchiotti and her team in Milan on the research that the EHE Group continues to fund, including research to identify possible EHE biomarkers. It is hard for us to overstate how delighted we are to have Dr Huang join our Advisory Board".

Twins tell their story to spread awareness

One of the objectives of the EHE Group globally is to spread awareness of the disease. This can be done in several different ways, but it is generally recognised that one of the most powerful formats is when EHE patients tell their stories. That sounds easy but, to open yourself to the public in such personal circumstances is very tough and requires considerable bravery and determination from those who do it.

One such case is Kym and Emma, twins from the UK, who wanted to share their story. As twins, the sisters are facing and dealing with the disease from a particularly unique viewpoint. Their story was first picked by up local press, and then nationally by the Mirror Group.


Lancashire Post

My twin sister was diagnosed with a rare form of cancer – it's heartbreaking watching her go through this

Emma was diagnosed with EHE in 2024, and Kym spoke openly about how heart-breaking it is to see her sister suffering and how hard she is working to support her sister and striving to make sure she is getting the best care possible. Kym said:

"With her being my twin, it's been so hard for me not being able to control this situation and make her better as she is literally my other half. Over the last six months Emma has shown more strength and resilience than I have ever seen in a person. Some days she is fine and others she will wake up in agony. She's on a lot of pain relief and anti-sickness drugs. She's fighting against this disease everyday whilst remaining the world's best mummy to her two boys and partner".

Emma wanted to thank Kym for her brilliant support at such a tough time.

"I don't know what I'd have done without Kym. From day one after getting my diagnosis she's been full into research, fundraising, gathering all sorts of different contacts to help me, whilst having her own young family to care for. She's the real superwoman".

Twin's heartbreak as sister's 'flu' turns out to be something far worse

Mirror

At the Charity, we could not be more grateful to Kym and Emma for doing so much to spread awareness at such an incredibly difficult time. Once again we are inspired and amazed by the commitment and compassion that patients and their families, like Kym and Emma, have when faced with an EHE diagnosis.

01 Patient Support and Advocacy - continued

Quality of Life study

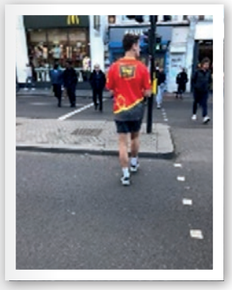
To better support drug development and improve overall outcomes for people diagnosed with EHE, the European Organization for Research and Treatment of Cancer (EORTC) has been conducting an international study on Quality of Life (QoL) in people with rare cancers, including EHE. The EHE Foundation, on behalf of the EHE Group, engaged with EORTC to enrol EHE patients in this study, as Denise Robinson explained:

"The EHE Foundation has been working to enrol people with EHE in this quality-of-life study. This is an easy way for patients to help with EHE research from the comfort of their own homes! The overall objective of the study is to develop a document that can be used to help measure the quality of life in EHE patients, and which can then be used also to assess the impact of a specific drug on such patients. While QoL assessment will never be sufficient on its own to justify drug approvals, the reality with ultra-rare diseases is that all evidence is important, and for this reason, this study is important, and one that the Foundation wanted to support. As always, the EHE patient community was keen to help, and were able to provide EORTC with the EHE participants they needed, another excellent example of how patient involvement is so important to our overall EHE objectives. We want therefore to thank all those who took part in this important study".

This is an important collaboration of the EHE Group, aligning with ongoing efforts to work with regulators to look at repurposing drugs, specifically sirolimus for the treatment of EHE, as well as novel drugs for ultra-rare sarcomas. In repurposing drugs or to get a new investigational drug into review, the issue of establishing the efficacy of a drug has arisen. Regulators rely on a standard called RECTIST v1.1 to measure efficacy, but recognise that this does not work well in the case of some ultra-rare diseases such as EHE.

We are grateful to EORTC for undertaking the development of a standardised instrument that can be used to objectively assess the change in symptoms experienced by the patient, measuring the effect on the QoL of those taking a drug, or during active surveillance. QoL assessment is an established and recognised process in the clinical and research world. The EHE Group completed such a survey of QoL for EHE patients in 2019, led by Dr. Marije Weidema from the Reboud University in Holland, but this assessment was of the disease generally, and not undertaken with specific reference to treatment outcomes or a specific drug. (The published paper for this assessment can be found in the EHE Library on The EHE Foundation website or at https://www.tandfonline.com/doi/full/10.1080/0284186X.2020.1766696).

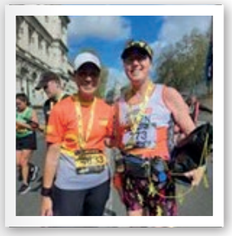
Spreading EHE awareness



Spreading awareness of EHE takes different forms, one of which is people wearing EHE merchandise with our EHE logos on them. Jake Leonard, Hugh Leonard's and Sally Baker's son, who lives in London posted a photo of somebody out jogging at lunch time wearing an EHE Rare Cancer Charity running shirt. Sally Baker noted:

"It's great to see our running shirts out and about. We hope one or more people might have asked what the charity does!"

Michelle Hughes was also thrilled when her running shirt led to an approach from another runner at the finishing line of the London Landmarks Half Marathon:

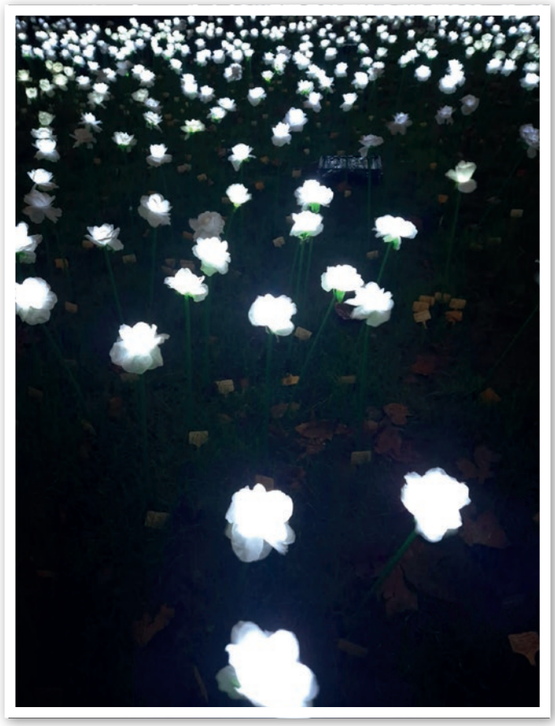


"When I came across the finish line a fellow runner who had seen my shirt came up to me and said she is a nurse who treats EHE patients. She proceeded to tell me about her hope for our cancer. It was incredible to hug her knowing how much she cared".

We love these impromptu stories of EHE awareness and engagement.

Remembering those who have left us

One of the things that our global community always wants to do is to remember those who left us far too early, of whom there are far too many. Kim Alexander-Bird posted news of just such an opportunity when she visited the Royal Marsden Cancer Charity's 'Ever After Garden' in Grosvenor Square in London.



The Ever After Garden is a tranquil haven where anyone can come to remember treasured friends and family they have lost, offering a space to pause and reflect over the Christmas period. Visitors are invited to dedicate a rose in memory of a loved one, whilst making a donation to The Royal Marsden Cancer Charity, helping to fund groundbreaking research which improves the lives of cancer patients everywhere.

02
EHE Research

The Charity, and indeed the global EHE Group, is both excited and inspired by the levels of EHE research engagement we see in the UK and globally. Thanks to our wonderful supporters we are also delighted that we have been able to expand and extend our existing research while also considering new research projects, together with our sister EHE Group entities.

In 2024, the collaborative EHE research being led by Istituto Nazionale dei Tumori in Milan, and the Institute of Cancer Research and the Royal Marsden Hospital in London has delivered important results together with a number of new and exciting research ideas. The observational study and the prospective registry of EHE patients has also continued to grow, both also managed by INT in Milan.

We are also delighted at the excellent support for, and progress of, the National UK EHE Biobank. This important infrastructure is maintained at the Royal Marsden Hospital, collecting critical EHE bio-samples for future research, funded by the Charity.

Summaries of these research programmes can be found on the following pages.

Review by Dr Oliver Pearce and Dr Kate Hooper

European collaboration

The Charity, together with the EHE Foundation (USA), is funding this major European collaboration involving the Istituto Nazionale dei Tumori (INT), Milan, the Institute of Cancer Research (ICR) in London, and the Royal Marsden Hospital (RMH) in London.

The overall research program entitled 'Evaluation of Cytokines and Hormones as Biomarkers for EHE' was initiated at the end of 2020 and extended and expanded at the end of 2022. The resultant overall research comprises a number of different objectives or projects as follows:

i) the identification and validation of novel circulating and tissue biomarkers to inform patient management (prognosticators and predictors of response to medical agents) as well as potential therapeutic targets **(Project 1)**

ii) the development of patient-derived xenograft (PDX) models **(Project 2)**

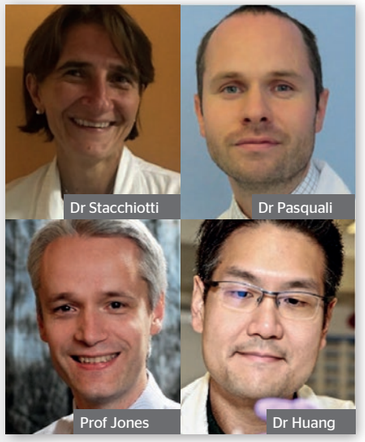
iii) the assessment of the activity of drugs relevant for the disease **(Project 3)**

iv) the generation of PDX-derived cell lines to investigate the cellular and molecular determinants of drug activity and to be submitted to a CRISPR whole-genome screen to identify new therapeutic targets **(Project 4)**

v) the identification and evaluation of miRNAs **(Project 5)**

vi) the description of the radiologic characteristics of EHE and their correlation with the clinical outcome **(Project 6)**

Dr Silvia Stacchiotti, one of Europe's leading sarcoma clinicians, and Dr Sandro Pasquali, one of our leading sarcoma researchers, are joint Principle Investigators (PIs) of the project at INT; Dr Paul Huang is the PI at the ICR, and Professor Robin Jones is the PI at the RMH.



Biomarker focus

A key focus of this research continues to be the assessment of circulating cytokines, hormones (and miRNAs), and estrogen receptor expression, etc, and the identification of a novel biomarker for EHE.

Using a protein array able to simultaneously detect the expression of a hundred different cytokines in plasma samples of EHE patients (n=15) and healthy individuals (n=6), a small panel of inflammatory cytokines was found to be differentially expressed. Among them the researchers focused on Growth and Differentiation Factor-15 (GDF-15), a member of the TGF-β super-family, which has multiple roles in a wide variety of cellular processes. Using a specific ELISA assay, they looked at the concentration of circulating GDF-15 in a retrospective series of 23 EHE patients and observed a statistically significant association of GDF-15 levels with EHE aggressiveness. These results were confirmed in a second cohort of 21 EHE patients prospectively collected within the currently ongoing observational study.

Dr Pasquali and Dr Zaffaroni reviewing research results with the EHE Group

The research team also used their models to test the results by measuring GDF15 levels before and after treatment with drugs that were seen to clinically benefit patients.

Following further validation, the Charity was delighted to see the research paper, entitled 'GDF-15 predicts epithelioid hemangioendothelioma aggressiveness and is down-regulated by sirolimus through ATF4/ATF5 suppression', published in *Clinical Cancer Research* at the end of the year.

02 EHE Research Continued

Results of this groundbreaking research show that:

a) In the two models used, a patient-derived xenograft (PDX) and paired EHE cell line, EHE cells produce and release GDF-15. GDF-15 is a cytokine that cancer cells produce and is used as a biomarker for the severity of many diseases.

b) These results indicate that GDF-15 could be a useful novel biomarker to predict EHE aggressiveness and disease progression.

c) In the EHE models used, sirolimus was shown to reduce GDF-15 expression.

d) Additionally, sirolimus (not yet approved for EHE treatement) had a higher anti-tumor activity than doxorubicin (approved for soft tissue sarcoma) when compared in the model systems.

For EHE patients, these findings give hope for further preclinical drug development using human-derived EHE models, better-informed treatment decisions, and the ability to monitor disease progression, all with the goal of improving patient outcomes.

The paper can be found it at:
https://pubmed.ncbi.nlm.nih.gov/39283723/

Interesting results relating to other potential biomarkers such as miRNAs have also been seen and remain under investigation.

Critically, in addition to the lab-based work, a key component of this research was the creation of a clinical observational study in to which INT and RHM had enrolled more than 50 EHE patients by the end of 2024. Each patient is being treated under a standard protocol, creating a significant, high quality study of the disease which will inform ongoing thinking regarding EHE research and treatment.

Research extended
The original proposal from the research group was for a three-year research project. It was agreed at the outset that the EHE Group would commit to fund the initial two years and review funding of the third year based on the results of the first two years. The research work and results achieved and the importance of the observational study, as shown by its application, with appropriate amendments, to the sirolimus approval programme, were summarised by the research team at the end of the second year in July 2024. That detailed summary was at the core of the EHE Group's assessment, leading to The EHE Foundation and The EHE Rare Cancer Charity agreeing to jointly fund the third year of the project.

In addition to the third year of the project, the research team also submitted a proposed work scope and budget amendment to enable continuation and expansion of the observational study, increasing its target cohort from 50 to 100+ patients, and its duration to the end of 2027, allowing data to be collected for a larger group over a longer period, leading to a better and more accurate understanding of the disease. This observational study has now also become a fundamental component of the ongoing work with regulators to have sirolimus approved for the treatment of EHE. With agreed modifications to the original protocol and increased verification of protocol compliance, the study will now become a prospective observational study. It is also hoped that this new study may be joined by other institutions from around the globe.

Dr Pearce commented:

"The work and progress made has been exceptional and we are so grateful to the whole research team for their ongoing dedication and focus on EHE. After a thorough review, we were pleased to approve the third year funding for this excellent project, and remain excited by its ongoing potential".

Dr Hooper was also excited by the growing observational study:

"We are excited by the development of the observational study into a prospective observational study with the result that a sub-set of the patients who are prescribed sirolimus can be used to support the work we are doing to seek approval for this drug from regulators. Canada joining the study is also an excellent development, and we will be working hard to introduce the study to other institutions".

EHE Prospective Observational Registry

The need for pan-European registries for rare cancers was recognised by the European Reference Network in Rare Adult Solid Cancers (EURACAN). The STARTER project was therefore established in 2022 on the basis that gathering data on rare cancers will support research, help to develop and/or improve clinical practice guidelines, support multidisciplinary discussion and consultations for patients with rare cancers, and ultimately improve quality of care across Europe.

The Charity was therefore delighted when it was informed that EHE had been selected to be the first rare cancer within this important new data-gathering initiative, and immediately committed to funding the setting up of the first such prospective observational registry for the disease. The registry Principle Investigators (PIs) are Dr Annalisa Trama and Dr Silvia Stacchiotti, from INT in Milan, with Dr Anna Maria Frezza providing clinical support. The registry involves more than 22 hospitals across Europe. Patient enrolment into the registry started in 2023, with 20 patients enrolled at the end of 2024.

Dr Hooper was delighted to see the number of hospitals that engaged and the number of patients being enrolled into the registry:

"Joining the registry is not compulsory so we were delighted to see that 22 hospitals had joined the project. The registry team hope to add more hospitals in the future, including international centres who have expressed interest. It is also encouraging to see 20 patients already enrolled by the end of 2024. Only new patients recently diagnosed can be included, so with the ultra-rare nature of EHE, building patient numbers will always be slow. But, capturing this data is so important and over time the study will provide high-quality valuable information that will be important for generating hypotheses and further interrogation of disease treatments. This was why we did not hesitate to provide funding to INT for the registry when we were approached".

PUSH Platform continues to grow

2024 also saw important progress on new infrastructure called the PUSH Platform (**P**ushing **U**ltra-rare **S**arcomas beyond **H**ope). This platform is being developed to help address the significant challenges that patients, clinicians and researchers of ultra-rare sarcomas face, such as:

- Having minimal data on the natural history of their disease;
- An acute lack of research funding to comprehensively study ultra-rare diseases;
- Few if any defined treatment options (in EHE there are no disease-specific approved systemic treatments);
- Major hurdles to, and in most cases the impossibility of, designing and performing large, randomised clinical trials within a reasonable timeframe and cost, due to the extreme rarity of patient populations; and
- Difficulties in drug development and access due to no or minimal interest from commercial drug developers and their perception of high costs and risk of failure when engaging with regulators.

PUSH PLATFORM

02 EHE Research Continued

It is ultimately hoped that a significant number of institutes and academic centres across the globe will join the project, forming the PUSH Consortium, giving the PUSH Platform real momentum and an ability to change the landscape for ultra-rare sarcomas. The first two sarcoma studies to be included under the PUSH Platform were EHE and Chordoma. Two additional multi-centred disease studies were also added in 2024 for: Low Grade Fibromyxoid Sarcoma/Sclerosing Epithelioid Fibrosarcoma (LGFMS/SEF); and Adult-type Rhabdomyosarcoma (RMS).

The PUSH Platform will include collating relevant prospective and retrospective data from substantial numbers of patients from around the world, including real-world data from patient registries such as the EHE Global Patient Registry managed by the EHE Foundation in the USA. PUSH will incorporate data from a large range of different sources that will in turn be used, with regulatory involvement and input, to define and undertake appropriate new prospective studies and associated analyses to help deliver new treatments for patients in faster, lower-risk, well understood and defined processes. PUSH is designed to also include prospective clinical trials. PUSH is particularly important for patients with ultra-rare diseases such as EHE, who face significant unmet needs in terms of the availability of effective treatments.

The PUSH Platform is also a component of the ongoing discussions with the EMA and the USA Food and Drug Administration (FDA) concerning the processes and procedures relating to drug approvals for ultra-rare sarcomas, as reported in the Patient Support and Advocacy section of this report. There is recognition that changes need to be made to reduce the time, risk and costs of such processes, and so encourage pharma involvement in the development of such drugs.

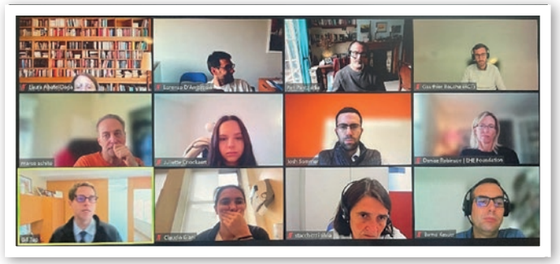
The Charity is actively supporting the PUSH Platform, with Hugh Leonard, and Denise Robinson from the EHE Foundation in the USA, both being members of the PUSH Executive Committee. There is a huge amount of work in progress, as Hugh explained:

"Establishing major new infrastructure like PUSH takes a huge amount of work, focus and determination. Multiple working groups have been established looking at a wide range of relevant issues, such as data collection, legal issues, operational management, trial protocols, translational research and regulatory/pharma liaison. Right at the moment a key area of focus is how we resource and run PUSH to ensure that the daily operation and administration of the platform is fully covered, effective and efficient. Exciting discussions are underway and we hope we can report further progress over the coming months".

Drug Repurposing for EHE

'Drug repurposing' is the process whereby researchers and clinicians test drugs that are already approved for human use for other diseases to see if they show sufficient activity against another disease (that it is not approved for), such as EHE. This is a growing area of drug development research and is a hugely important part of any cancer research programme. It is also a critical pathway to produce approved drugs for ultra-rare diseases, as developing truly novel compounds is almost certainly uncommercial in these cases. Repurposing is therefore a core part of the EHE Group's ongoing research programme and future EHE strategy.

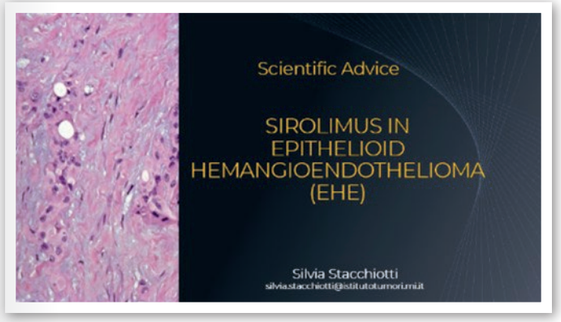
The EHE Group is funding different drug screening projects and has already identified a number of good candidates. At the same time, the Charity continues to work hard to secure an approval from the EMA for a label extension of sirolimus for the treatment of EHE. This process was started in 2022 when the AntiCancer Fund in Belgium submitted an application, 'sirolimus-for-the-treatment-of-EHE' for the EMA's new repurposing pilot process. The application was successful and the AntiCancer Fund then reached out to Dr Stacchiotti in Milan and to the Charity to seek support in taking the application forward.



EHE Repurposing Group videoconference

In January 2024, Hugh Leonard participated in an EMA public workshop in Amsterdam, to discuss ways that the drug repurposing process could be improved, which used EHE as a case study. Hugh's presentation addressed the challenges faced by ultra-rare diseases and why efficient repurposing was so essential. At the end of March an additional informal meeting was held with the EMA to review two new study proposals submitted by the EHE repurposing group, and to answer questions the group had with regard to the Scientific Advice being sought. Scientific Advice is the EMA process where applicants can provide and pose questions relating to their supporting data and whether it is sufficient to support the repurposing of the drug.

The EHE Group continued through the second quarter to engage with the EMA regarding the approval of sirolimus for the treatment of EHE.



The Scientific Advice we received clarified that some additional data would be required. It also appeared to clarify for the regulator that their standard approach with its prescriptive and rigid structure was not suitable when considering ultra-rare diseases.

One of the key issues under discussion with the regulators is how efficacy of the drug is measured, because the traditional methodology, using a process called RECIST v1.1, does not work well for EHE.

The EHE repurposing group was therefore focused on addressing the points raised by the EMA, including the development of disease-specific criteria for evaluating whether a drug is working. This is necessary because the traditional criteria for assessing a drug are based on common cancers where tumour shrinkage is expected. As the EHE patient community understands, a key objective with EHE is to re-establish disease stability once EHE has become progressive, but which is likely not to include shrinkage. The group were therefore pleased that the EMA appeared to understand these challenges of testing the activity of a drug in such rare diseases and were actively engaging to help find solutions. The team at INT in Milan in particular completed some amazing work looking at different assessment criteria, culminating in acceptance of their presentation 'Redefining Radiological Responses in Epithelioid Hemangioendothelioma: Beyond RECIST?' for oral presentation at the prestigious CTOS 2024 Annual Meeting.

The EHE patient community has also been able to add important data to these discussions, from its survey of EHE patients globally, helping to provide further evidence of the beneficial effects of sirolimus. The results of the survey and the resultant published paper are described in the article below ('Sirolimus patient perspectives survey results published').

The discourse with the EMA continued with a further round of Scientific Advice submitted in late summer 2024, including revised data generation plans. At the end of the third quarter, the EMA provided a list of further questions that needed to be addressed. These were answered and discussions were ongoing at the end of the year.

As the year closed, it looked likely that further data would need to be collated on the disease and its treatment with sirolimus, through a new prospective observational study, building off the existing EHE observational study that was started by INT in 2022. The Charity hopes that further progress can be made in 2025, helping to bring forward approval of sirolimus.

02 EHE Research Continued

Sirolimus patient perspectives survey results published

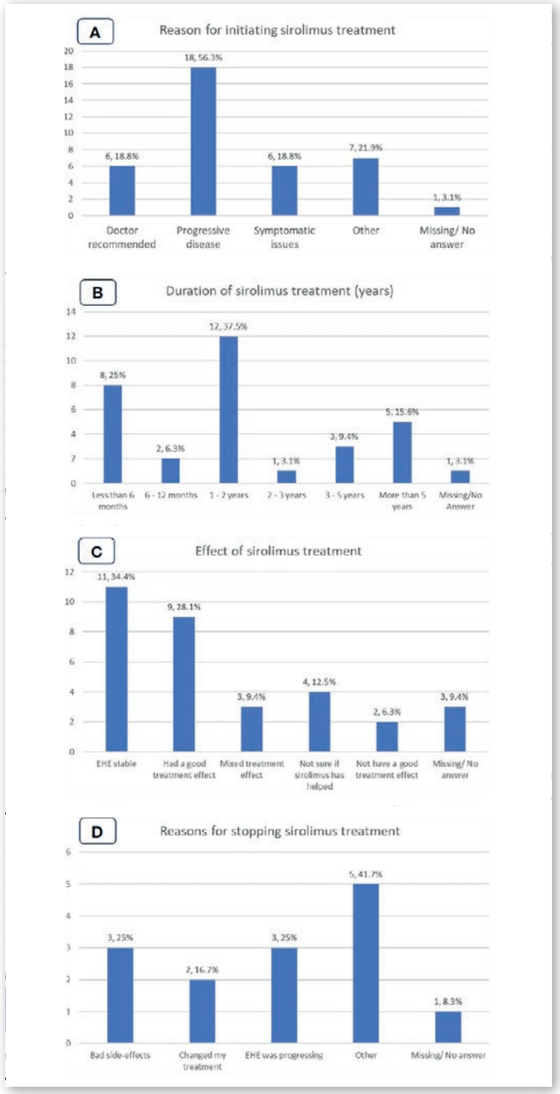
The EHE Group were delighted to report that a paper addressing the important issue of patient access to the drug sirolimus (one of a class of drugs known as mTOR inhibitors) had been published in *Frontiers in Oncology*, a prestigious, peer-reviewed scientific journal, on 26 February. This paper, entitled 'The patient perspective on sirolimus for epithelioid hemangioendothelioma (EHE): results of a community survey highlighting the importance of equitable access to treatments' presented the results of a survey of the global EHE patient community, conducted in 2023, about their access to, and results of treatment with, sirolimus.

The survey, coordinated by Denise Robinson, Director of Research at The EHE Foundation, and Hugh Leonard, Chair of Trustees of The EHE Rare Cancer Charity UK, was undertaken to support the ongoing application to the European Medicines Agency (EMA) for a label extension of sirolimus (also called rapamycin and marketed by Pfizer under the tradename Rapamune®) to include the treatment of EHE. Although sirolimus has been globally approved and widely used for many years, mainly as an immunosuppressant, it can still only be prescribed to EHE patients 'off label' as it has not been formally approved for the treatment of EHE. This means sirolimus is only available to patients who access the drug off-label, resulting in inequality of access to this important treatment.

There is a growing body of significant evidence, including the experience of our patient community, that sirolimus is now the leading front-line drug for the systemic treatment of EHE. In 2021 the ESMO paper 'Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts' recognised, when comparing different drugs used to treat EHE, that ***"the highest clinical activity has been reported for mTOR inhibitors"*** and confirmed that ***"the panel [of experts] agrees that these [mTOR inhibitors] represent the preferred treatment options for patients with advanced and moderately progressive disease".***

The EHE Group survey collated the experiences from 130 patients, 32 of whom were non-liver-transplant patients that had experience of treatment with sirolimus. A high percentage of these patients had experienced good results, with some having been on the drug for more than 5 years.

The results of the sirolimus survey are an excellent example of why patient data is so important. The data, summarised in the graphs shown here, supports the position expressed in the ESMO paper described above, namely that mTOR inhibitors like sirolimus are being successfully used in the treatment of EHE. Its responses also confirmed that these drugs are not equally accessible for all patients because they are only available off-label.



Patient experiences of the Group S (sirolimus) cohort. **(A)** Reasons for initiating sirolimus treatment. **(B)** Duration, in years, of sirolimus treatment. **(C)** Patient perspective on the effect of sirolimus treatment. **(D)** Reasons for cessation of sirolimus treatment.

Hugh Leonard expanded on why the published paper is important to the regulatory process, not only with the EMA in Europe, but also with other regulators like the FDA in the USA:

"Regulators want to hear and understand the experience and perspective of the patient community. However, in presenting such information, we need to be able to show that the data was collated and analysed in a rigorous manner, in line with accepted scientific practise, and that the results and conclusions drawn are supported by the underlying data. The publication of the results in a peer-reviewed paper confirms all these requirements have been met and allows the survey to be accepted and considered by regulatory bodies in their deliberations".

The Charity wants to thank the other authors of the paper, Giacomo Giulio Baldi, MD; Pan Pantziarka, PhD; Silvia Stacchiotti, MD; Robin Jones, MD; and William Tap, MD, for their contribution, guidance, and commitment in helping to produce the paper. Huge gratitude is also extended to The EHE Rare Cancer Foundation Australia, EHE Canada, and EHE Italia Associazione Non Solo Laura ODV, all of whom were instrumental in mobilising support and participation of EHE patients. But the biggest thanks, without doubt, goes to each and every one of the 130 EHE patients who took part in the survey. Without their fantastic support, there would have been no data to work with.

If you wish to read the paper, it can be found at:

https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2024.1367237/full

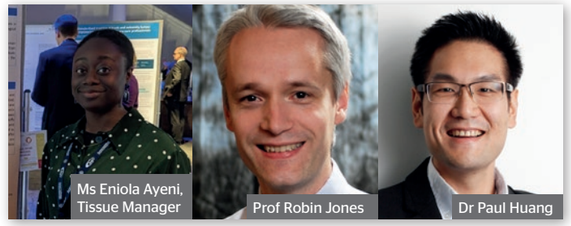
The importance of biobanking

The collecting of biological samples is critical for future research into any disease. With common cancers, tissue and fluid samples are abundant and collecting these samples is relatively easy. For a disease as rare as EHE, however, banking biological samples is absolutely critical. With so few patients, many of whom do not undergo surgery, tissue samples in particular are ultra-rare. It is hard to over-state how important tissue donation is for moving EHE research forward. For these reasons the Charity funded the establishment of the National UK EHE Biobank at the Royal Marsden Hospital, and continues to fund the annual costs for collecting the samples.

ehe Biobank

Progress has been very good. During 2024 a total of 17 new patients enrolled in the biobank, taking the total to 53 patients. At the end of 2024, 32 patient blood samples, 37 FFPE samples; and 3 live tissue samples were held within the biobank:

This is encouraging progress, but capturing and storing the samples is of little value if they are not used for research. Access for researchers is now critical, but has to be very tightly controlled, both under the ethics approval granted for the biobank, and under the relevant UK legislation relating to human tissue use. Professor Robin Jones, Principle Investigator for the biobank, Dr Paul Huang, and Eniola Ayeni, the Biobank Tissue Manager, were therefore instrumental in establishing the Biobank Access Committee which we hope will meet in 2025.



02 EHE Research Continued

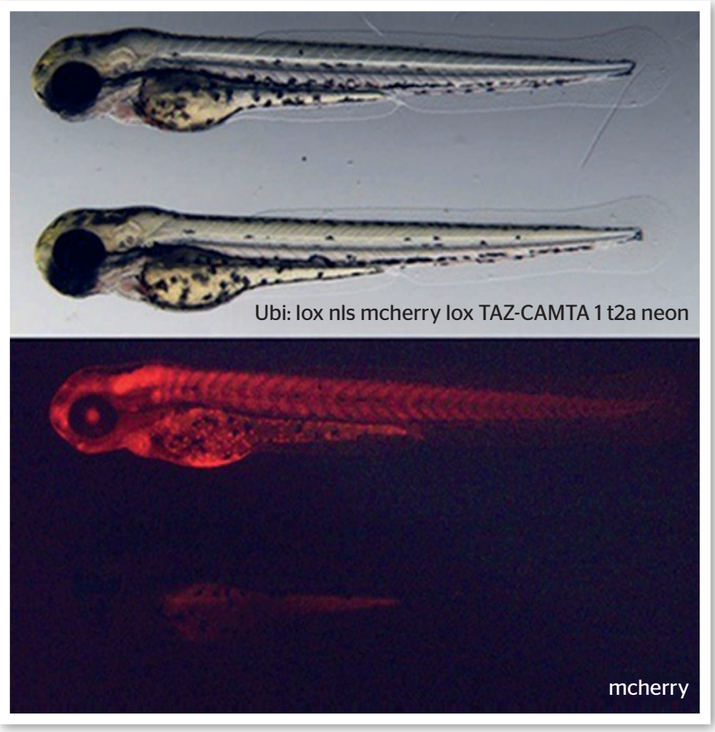
Zebrafish research suspended

In 2018, the Charity initiated research at the Bateson Centre at the University of Sheffield. The Bateson Centre is one of the largest and oldest zebrafish facilities in Europe, and researchers there are experts in developing models of human diseases in zebrafish. Zebrafish are used because they are cheap and quick to produce, if you are successful in creating the model you want. They are also largely transparent, making it easy to see morphological changes as the fish develops.

The primary reason for initiating this research project, seeking to develop a zebrafish model of EHE, was the complete lack of any viable EHE models of any kind. In 2018 there were no PDX mouse models, no PDX-related cell lines, no genetically-engineered mouse (GEM) models, and no human cell lines. Work was underway in these different areas, but with no guarantees of success with any specific model; the continuation of work on all models was essential. The Charity understood that creating a zebrafish model would be a challenge, but all EHE models were proving to be very difficult to establish, so the zebrafish model could not be ignored.

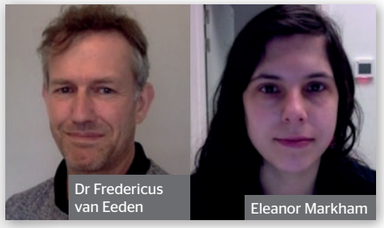
The team at the Bateson Centre was led by Dr Fredericus van Eeden, with Eleanor Markham undertaking most of the painstaking technical work. Over the following five years, the team introduced the gene translocation constructs into the fish, requiring an unbelievable attention to detail to ensure the constructs were correctly located. Many challenges were faced, but each time the team found solutions that allowed them to move on. This included introducing a switching mechanism into the fish so that the gene translocation constructs could be turned on, as they seemed to be fatal at the embryonic stage of the fish. Multiple variations of the construct were tried, with minute adjustments made to its structure and positioning in the fish.

Ultimately the team were able to create EHE fish with switchable mechanisms for both the TAZ-CAMTA1 and YAP-TFE3 variations of the disease. But although the gene translocations could be turned on, and low levels of the fusion proteins seemed to be present, they were in very small quantities, making the fish unviable as EHE models.



But while the zebrafish remained stubbornly resistant to producing a viable EHE model, model developments were progressing in other areas. Dr Brian Rubin was finally able to get his GEM model to work, creating an unbelievably robust model for all presentations of the disease. Cell lines soon followed. At the same time, Dr Silvia Stacchiotti and the team at INT in Milan created the first viable EHE PDX mouse model from a patient tissue sample. This also led to a further cell line. More recently there has been exciting progress with human cell lines in the USA. With all this excellent model progress elsewhere, the Charity could not justify further expenditure on this project.

The decision was therefore taken in August 2024 to suspend the research project. All the work completed has been carefully documented, and any important constructs stored. In the final 6 months the team also investigated if EHE cells could be injected into zebrafish and kept alive, as a xenotransplantation model. These xenotransplant fish provide a life support system for the EHE cells which might then be exposed to treatment with drugs. This will be a possible future development, should the use of such xenotransplant fish become important.



03 Fundraising and Finance

2024 was another year in which we have enjoyed unbelievable support from our patient members and their supporters. Together, bringing their energy, enthusiasm and determination to the role of fundraising, they have raised substantial funding for critical EHE research.

In 2024 we received more than £132,000 from all sources. Of this sum, £15,000 was received from a single donor, specifically to fund our charity running costs. That means that 100% of the remaining sum of £117,000, received from all other sources, is available for EHE research. These funds are critical to a charity that is dealing with a disease as rare as EHE, as without this we would not be able to support the research that continues to deliver such exciting results. In the previous section we provided an overview of our current research, none of which would have been possible without the amazing support we continue to receive.

And it is not just the UK that is enjoying such progress. Our sister foundations in the USA, Australia, Italy and Canada are also making great advances. We cannot thank our supporters across the globe enough for their dedication and wonderful support.

Review by Jeff Collins

Every year, the EHE patient community and their supporters provide us with amazing support and raise significant funds for EHE research. 2024 was no different, with the Charity receiving more than £132,000 in donations. That support means that we can again not only support our ongoing research, but look at ways to expand it, as well as consider new projects.

In 2024, our grassroots fundraising was strong, with our patient community and their supporters again supporting the charity. We also enjoyed wonderful support in our two major charity-organised events, where we had more than 50 runners in the London Landmarks Half Marathon, and 14 riders in the RideLondon-Essex 100 event. Particular mention goes to Sam who rode the 100 miles on a stationary bike in his lounge due to having broken his wrist during training!

We saw huge support for Emma, a newly diagnosed patient, championed by her twin sister, Kym, and all her family. Collectively, they threw themselves into fundraising for EHE research with amazing support from so many people. Their 2025 calendar, '10 men with sunflowers', seen on the front cover of this report, was a particularly imaginative fundraising idea. We also received substantial donations from Luke Harrison, also diagnosed with EHE in 2024. Team Dean, supporting Paul, were again amazing, with a large contingent not only running, but also hosting fundraising events in Birmingham.

Kelly Denton held her annual EHE Quiz Night at the start of the year and her bottle tombola at the Penge Festival in the summer. Lorraine Faulds and her daughter, Louise, walked 96 miles from Glasgow to Fort William in Scotland in support of Lorraine's mother, and Katy ran the London Marathon in support of Nicola Henderson. Nicola and the Charity also enjoyed yet more wonderful support from Darran and Kerry Marks as they both took on the Sodbury Slog.

Judith Gordon and friends were on the fundraising trail in Scotland, participating in both the Edinburgh Shine and Super Nova events. James and Kirsty, organised a raffle in support of Issy Payne, their mother. Issy's colleagues at the Royal Mail also wanted to support her and Issy was delighted to report that they had collected a substantial sum for the Charity. Steph Scott and Adam Patrick held raffles to add to their fundraising page.

Key objectives

In the 2024 calendar year our supporters raised a total of £132,868 for the charity's key objectives. The sources of these funds are summarised on the pie chart above.

During 2024 we provided funding for our UK research project at the University of Sheffield. We also funded the EHE National Biobank and Tissue Manager at the Royal Marsden. We jointly funded the collaborative research project between INT in Milan and the ICR in London.

Source of funds

Administration/business running costs

In 2024, 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 2025.

The charity received funding of £15,000 for its administration and business running costs account. During 2024, £9,900 of administrative expenses had been incurred, which included an accrual of £1,200 for the independent examiner's fee.

The remaining spend of £7,700 (excluding the £1,200 independent examiner's fee) included the fees associated with fundraising events conducted in 2024, and publishing costs, in addition to ongoing website maintenance.

"We are once again so grateful to our patient community, their supporters, and the corporate groups and foundations who supported us through the year. A particular and huge thanks must go to Luke Harrison for his wonderfully generous donation. We are also grateful to all those who helped us and volunteered so that we could keep our charity running costs as low as possible. I also want to thank all the companies and service providers who have supported us with their services, often provided at no or reduced cost.

In 2023 we noted that the prevailing financial climate meant that 2023 and years beyond would continue to be financially challenging. It is thanks to our amazing patient community and their wonderful supporters that we have in fact been able to continue to raise substantial funds for the Charity through this period including 2024, for which we are hugely grateful. We will however continue to ensure that we already hold the funds for any funding commitments we enter into. We will also continue to manage all funds with the utmost care to ensure that we get the maximum benefit from every pound that we have so generously received".

Jeff Collins

Wonderful support for EHE in 2024

The following pages highlight some of the amazing fundraising events that raised funds for Charity in 2024.

Quiz nights are booming!

The start of the year saw two great quiz nights taking place to support the EHE Rare Cancer Charity.

The first was the annual EHE quiz night organised by Kelly Denton and the members of Laptops and Lipstick, a women's business network based in South London. Laptops and Lipstick adopt a charity each year to support, and selected the Charity for 2022/2023. They then extended their support for a further year, holding their annual charity quiz night on 12 February 2024 at the brilliantly supportive Bridgehouse Pub in Peckham.

The event was a huge success, as Kelly explained:

"Last year's quiz was fantastic, but this year's was even better. We again filled the pub, who did an excellent job hosting the event. We also had a lot of brilliant raffle prizes. Hugh Leonard was present and gave a brief update on the research that was taking place, thanks to the generosity and support for evenings like ours. It was also special having four actual EHE patients there on the night, bringing home the reality of EHE. And to top it all, we raised £1,960 during the evening for EHE research. I was so proud of everybody who organised and participated in the event. Without them we would not have raised those critical funds".

The second quiz night was organised by Jo and Phil Lane in support of Paul Dean, EHE patient. Jo organised a similar event in 2023 in the build up to the London Landmarks Half Marathon, and decided to do the same for the 2024 event. Jo and Phil have been wonderful supporters of Paul and the Charity and the three together form a formidable team.

Paul Dean, EHE patient, runner and cyclist, with Jo and Phil Lane, quiz night organisers and hosts.

Easter raffles raising research funds

People find many different ways to raise funds to support EHE research. Steph Scott and Adam Patrick were running the London Landmarks Half Marathon in April, and received great support on their fundraising page. But they wanted to do more and came up with the idea of holding small raffles with limited numbers of tickets through social media to raise research funds.

Their first raffle was very easter-focused, with a tantalising array of chocolates. Selling 60 tickets only at £3 each, they raised £180 for research. Not content with this, they then launched a second raffle for a prize comprising several different spirits. We want to thank them for such a great idea.

Runners turn out in force for EHE

Each year the Charity coordinates a team of runners to run in the London Landmarks Half Marathon. And 2024 was no exception, with more than 50 people running to raise funds for EHE research. This year we had three EHE patients taking up the challenge, including Michelle Hughes and her friend from Canada. Hugh Leonard posted a pre-run photo of many of those taking part with a very simple message – *"Love these guys!!!"*

Hugh also posted news of the build up to the run:

"Sally and I are on our way up to meet our EHE runners pre-race. It's looking like the weather will be lovely. And we have the wonderful Michelle Hughes running with the team this year. Huge thanks to every single one of them for running, and to everybody who has supported their fundraising efforts. They are an awesome band. Just live! Just run!"

03 Fundraising and Finance Continued

In addition to Michelle Hughes, patient Paul Dean also ran, supported by 19 other members of his fantastic support network.

Paul was the fastest of the EHE running cohort and wanted to thank so many for helping:

"Today was London Landmarks Half Marathon 2024! No PBs for me this year, as expected as I'd had some non EHE related ailments, but pleased with how it went! Firstly a huge well done to all the runners that ran for EHE Rare Cancer Charity today, so far my dream team is just shy of raising £10,000! An incredible achievement for such a small charity. Some great performances out there today and some real battles of will going on. Really proud of everyone. All in all it was a great day. It was a pleasure to meet up with some of you and our Canadian friends. well done everyone".

People also wanted to post photos of their runners post-race:

Darran Marks, who ran in support of Nicola Henderson, was enjoying a beer while proudly showing off his race medal!

Tracey Betts posted a photo of her two sons, Josh and Connor, who ran in support of their mother and to raise research funding.

Riders join the cause

The EHE community in the UK not only find runners every year to help their cause, but also put up a group of riders who take on the 'Ride London 100' event, a 100-mile cycling sportive on closed roads in Essex, north-east of London. Sally Baker said:

"This is the UK's biggest cycling event and sees more than 20,000 riders riding 100 miles to raise funds for so many fantastic causes. We were thrilled to have 14 riders riding for us this year".

Four brilliant women rode in support of a dear friend, Sarah, who was diagnosed with EHE late in 2023. Her brilliant friends were determined to raise money and awareness for EHE on the day. One of them even had to buy her first bike for the event as she'd never really cycled before.

Kelly, whose daughter has EHE, also had great support from her nephew Sam, and several other riders recruited to the cause by Sam. Unfortunately Sam in the end had to take part from his lounge, as he had recently broken his wrist and could not take part in the actual Ride London 100 event. Sam rode a 100 mile virtual route based on a ride in France!

Kelly also recruited several other riders who did a great job and raised significant funding for EHE Research. She wanted to thank Jeremy Adams particularly for his great support.

Kelly's at the Peckham Show

Fundraising is not just about big organised events. A significant amount of the funding raised by the EHE community comes through the accumulation of many small events and donations. There is no amount of money that is too small to matter, particularly for ultra-rare diseases, so we are always delighted when we see somebody raising funds for us, regardless of the amount.

One champion of our cause is Kelly Denton who every year runs a bottle tombola at the Penge Festival in South London, always supported by her daughter Neve and their dog Max! Here is a photo of Kelly's stall at the 2024 Peckham Show where she raised an amazing £230. Thank you so much Kelly for another great effort. And please say thank you to Neve and Max too!

Lorraine and Louise are on the march!

Lorraine's mother was an EHE patient. Like many EHE patient family members, Lorraine and her daughter Louise wanted to help, and so decided to get walking! Sadly, Lorraine's mother passed away before they could make the walk, but they were even more determined to complete the 96 miles

"Hi everyone, Louise and I set off this morning on our 96-mile trek from Milngavie, Glasgow to Fort William. Raising awareness and money for EHE was something we felt we could and wanted to do to help combat this horrible disease. I know that my wonderful mother would want us to do this, and she would have been cheering us on".

In describing their walk, Lorraine also explained how they had used technology to help raise funds:

"We wanted to try and collect funds during our walk, as we felt we would have the chance to meet many other walkers and with our Charity t-shirts on, we felt there might be interest in, and an opportunity to talk about, EHE. We also are aware that a lot of people don't carry cash around these days, so we decided to set up and carry a QR code so that if people asked we could show them the code and link them straight to our fundraising page. And it did work, helping us raise £2,772 for EHE research!"

03 Fundraising and Finance Continued

Judith organises participation at Edinburgh events

Judith Gordon and friends participated in the Edinburgh Shine night in September, and were joined by Lorraine Foulds, as Judith explained:

"Here we are having a ball doing the Edinburgh Shine night, raising funds and attention for EHE and enjoying the clear night and good vibes while doing that".

Lorraine echoed Judith's comments:

"Our attendance was all instigated by Judith. It was good to catch up with her and hear her good news".

Then on Saturday 2 November, Judith and David Gordon, and Judith's two best friends, Lynda Harvie and Mary Hughes, all joined the Edinburgh Super Nova 10km run/walk. Judith again wanted to use the event to raise both awareness of EHE and funds for EHE research. Both Judith and David were wearing their EHE bibs in support of the charity, and the four together raised close to £2,000 on the night.

Katy runs the London Marathon

Nicola Henderson was delighted to be able to share news of a special person taking on the London marathon:

"We have EHE representation at the marathon today! My childhood friend Katy. Rooting for her as she has a terrible virus as well poor thing! She's raising funds for EHE and Fertility UK".

Massive support for Emma

In the Patient Support and Advocacy section of this Annual Report, we reported on how twin sisters, Kym and Emma, had used Emma's story to raise awareness of EHE following Emma's diagnosis with the disease. But raising awareness was not all Kym was determined to do. In addition to all she was doing to help Emma, Kym also set about driving a dynamic fundraising programme, including taking on different challenges herself.

Kym started with the Lancashire Loop Trail Run in late November. Kym ran together with her and Emma's brother, Ben Snape, her running partner Jessica Daggers, and Emma's Auntie-in-law, Ginny. Emma was also pleased that the Charity was able to provide two of their charity running shirts to help spread awareness of EHE.

All four set off on 24 November to complete the event in atrocious conditions, and complete what Kym described as ***"the hardest thing I have ever done".*** Kym cannot thank her fellow runners enough for getting her through the run.

Baring all for EHE research

Emma's family and friends quickly became champions of the EHE cause. So we were not surprised when Emma's step-father, Kevin, posted news of a new and brilliant fund-raising campaign. Kevin explained:

"As a lot of you are now aware, my step-daughter Emma was diagnosed with a very rare form of cancer in July. Her twin sister Kym and Brother Ben (amongst others) have already started to raise money to donate to the EHE Rare Cancer Charity here in the UK to help fund research of, and treatments for, this sarcoma. Well.....to that end we've done 'a thing'!!! A couple of weeks ago a few brave lads bared all and a very kind (if not traumatised) photographer took some pictures and we made a calendar!! We're all very proud of how it's turned out and they are now on sale for £10. If you would like to buy one, please comment below and I'll send you a private message on how to pay etc... thank you. Oh... and please feel free to share the heck out of this post!"

We loved the idea; we loved the 'naked ambition' and commitment; we loved the sunflowers; and we loved the compassion of the 10 lads who did indeed bare all, and in so doing have raised over £200 for EHE research.

03 Fundraising and Finance Continued

Micro pub with mega performance

Following on from their superb EHE calendar, the Albion Ale House micro pub next organised a festive 5km run and walk to help raise funds for EHE research. The take-up and turn-out was again brilliant, helping to raise more than £2,500. Emma and Kym were both there to say thank you and to join the festivities.

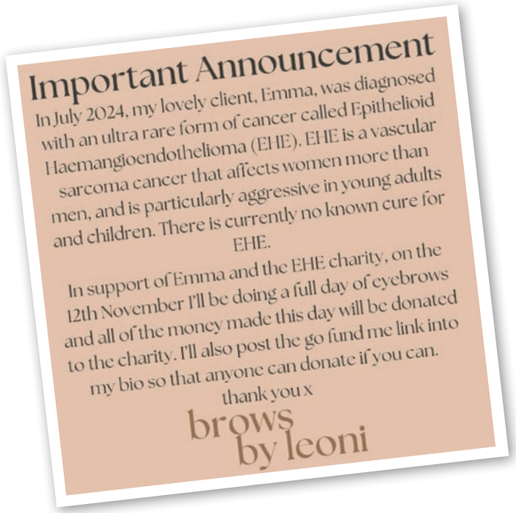
Next up was a festive carol singing session at The Albion which Beccy shared:

"Good Afternoon and Merry Christmas to you and all your loved ones. This is a little clip of our Christmas Carols Afternoon, which we held for the charity on behalf of Emma and Kym. It was a happy and fun afternoon and we made a nice sum of £1,255 for the charity. Not bad for a little micropub. All the very best to you all. Becs (Emma's mum-in-law.) Xx".

Sadly we cannot include the video posted by Beccy here, but we can tell you that the energy and volume of the carols was fantastic. We love the spirit and determination to ***Just Live!***

Support from many directions

Emma and Kym's story caught the attention and compassion of so many people who want to help. Kym shared news of one such supporter, Leoni, who also wanted to do something to help Emma. This young woman who does Kym's and Emma's eye brows, held a charity day on 12 November for EHE and raised £380. Emma and Kym were so grateful for her wonderful support.



The Payne family raffle

Isolde (Issy) Payne was an EHE patient who lived in the UK. Issy and her two children, James and Kirsty, wanted to help raise funds for EHE research, and came up with the idea of holding an online auction. As is often the case, the family were amazed at the generosity of so many people, both donating the prizes and buying raffle tickets. Issy said:

"We were so grateful that people helped us raise over £800. Prize donations were fabulous and we could not have hoped for more in terms of people buying the raffle tickets. We also got to say thank you personally to those who picked up their prizes, as you can see in this photo".

Sadly, Issy passed away in early 2025, but in that short period she had seen the amazing love and support for her from so many people.

The Sodbury Slog!

One of the Charity's most supportive groups, from our inception, has been and continues to be the amazing family and friends of Nicola Henderson. 2024 was no exception with many people again supporting us. Kerry and Darran Marks continued their year-on-year support, not only with Darran running in the London Landmarks Half Marathon at the start of the year, but with both Kerry and Darran taking on the Sodbury Slog, an aptly named run deliberately through muddy fields. It is a slog indeed, but Darran and Kerry took up the challenge with their usual good humour and enthusiasm as we think can be seen in these photos.

Our sincere thanks

The Charity could not be more grateful for the wonderful support received from so many people over the year, as shown by the inspiring stories above. Sally Baker, herself an EHE patient, wanted to register that gratitude on behalf of all the Trustees:

"Once again, I am humbled by these wonderful acts of kindness and support. The stories above of course only capture a small number of the contributions made. There are literally hundreds and hundreds of donations that make up the total sum raised, and it is impossible for us to include them all. We do, however, want to say thank you to every person who organised or participated in an event, or shared details, or made a donation, no matter what size, for having the compassion to support our cause and join the battle to defeat EHE. On behalf of the global patient community, thank you".

EHE Rare Cancer Charity UK

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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 2024.

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"

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

Date: 30 October 2025

EHE Rare Cancer Charity (UK)
Statement of Financial Activities
for the period ended 31 December 2024

	Notes	Unrestricted funds £	Restricted funds £	**Total 2024 £**	Total 2023 £
Incoming resources:					
Donations	2	117,868	15,000	**132,868**	73,837
Total incoming resources		**117,868**	**15,000**	**132,868**	73,837
Resources expended:					
Costs of generating donations		1,931	3,150	**5,081**	10,468
Charitable activities		41,580	-	**41,580**	146,463
Governance costs		-	1,200	**1,200**	1,200
Other administrative costs		65	5,584	**5,649**	14,839
Total resources expended	3	**43,576**	**9,934**	**53,510**	172,970
Net surplus for the year		**74,292**	**5,066**	**79,358**	(99,133)
Transfer between funds		**-**	**-**	**-**	-
Balance brought forward		167,735	4,021	**171,756**	270,889
Funds carried forward	8	**242,027**	**9,087**	**251,114**	171,756

Funds carried forward for 2024 £251,114

EHE Rare Cancer Charity (UK)
Balance Sheet
as at 31 December 2024

	Notes	Unrestricted funds £	Restricted funds £	**Total 2024 £**	Total 2023 £
Current assets					
Debtors	5,9	86,723	-	**86,723**	128,246
Cash at bank and in hand		211,504	11,837	**223,341**	201,410
Total current assets		**298,227**	**11,837**	**310,064**	329,656
Creditors: amounts falling due within one year	6,9	(50,860)	(2,750)	**(53,610)**	(120,518)
Net current assets (liabilities)		**247,367**	**9,087**	**256,454**	209,138
Creditors: amounts falling due after one year	7,9	**(5,340)**	**-**	**(5,340)**	(37,382)
Net assets (liabilities)		**242,027**	**9,087**	**251,114**	171,756
Funds carried forward					
Unrestricted funds		242,027	-	**243,707**	167,735
Restricted funds		-	9,087	**7,407**	4,021
Total funds	8	**242,027**	**9,087**	**251,114**	171,756

The Charities Act 2011 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 29 October 2025 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 2024

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:

	2024 £	2023 £
Unrestricted funds:		
Personal donations including fundraising events	**116,634**	50,949
Corporate and Foundation donations	**1,234**	2,438
	117,868	53,387
Restricted funds:		
Administration fund	**15,000**	20,450
	15,000	20,450

3 Analysis of resources expended

	Unrestricted funds £	Restricted funds £	**Total 2024 £**	Total 2023 £
Costs of generating donations:				
Just giving fees	560	-	**560**	956
Fundraising event entry and other fundraising fees	-	3,150	**3,150**	8,580
Credit card and other processing fees	1,371	-	**1,371**	932
	1,931	**3,150**	**5,081**	10,468
Costs of charitable activities:				
University of Manchester PhD Study	-	-	**-**	4,314
Royal Marsden Biobank	18,089	-	**18,089**	19,719
Zebrafish Study University of Sheffield	(14,970)	-	**(14,970)**	58,097
Fondazione IRCCS and ICR Biomarkers	13,595	-	**13,595**	36,538
Fondazione Prospective Study	24,866	-	**24,866**	27,795
	41,580	**-**	**41,580**	146,463
Governance costs:				
Independent examiners' fee	-	1,200	**1,200**	1,200
	-	**1,200**	**1,200**	1,200
Other administrative costs:				
Design and publishing	-	4,400	**4,400**	4,675
Website maintenance	-	1,164	**1,164**	10,020
Bank fees	65	20	**85**	144
	65	**5,584**	**5,649**	14,839

Trustees' expenses

£4,269 of expenses were incurred by trustees during the period, primarily associated with fundraising event entry fees and reimbursed by the Charity (2023 - £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 2024

5 Debtors

	Unrestricted funds £	Restricted funds £	**Total 2024 £**	Total 2023 £
Prepayment to Royal Marsden	25,847	-	**25,847**	42,442
Prepayment to Fondazione IRCSS Istituto Nazionale Dei Tumori	12,395	-	**12,395**	52,654
Prepayment to the University of Sheffield	-	-	**-**	29,382
Refund due from the University of Sheffield	44,351	-	**44,351**	-
Other debtors	4,130	-	**4,130**	3,768
	86,723	**-**	**86,723**	128,246

Included within the debtors figures above are amounts of £5,340 (2023 – £37,382) due after more than one year.

6 Creditors: amounts falling due within one year

	Unrestricted funds £	Restricted funds £	**Total 2024 £**	Total 2023 £
University of Manchester	-	-	**-**	-
Royal Marsden	26,107	-	**26,107**	23,717
Fondazione IRCSS Istituto Nazionale Dei Tumori	24,753	-	**24,753**	51,457
University of Sheffield	-	-	**-**	29,382
Accrued independent examiners'	-	2,400	**2,400**	2,400
Other creditors	-	350	**350**	13,562
	50,860	**2,750**	**53,610**	120,518

7 Creditors: amounts falling due after one year

	Unrestricted funds £	Restricted funds £	**Total 2024 £**	Total 2023 £
Fondazione IRCSS Istituto Nazionale Dei Tumori	-	-	**-**	12,712
Royal Marsden	5,340	-	**5,340**	24,670
	5,340	**-**	**5,340**	37,382

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 and July 2021, a second and third phase of the project was agreed and in July 2022, 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 2021. The July 2022 contract was further extended in July 2023 to provide one additional year of funding to support the ongoing assessment of the EHE zebrafish model. The total cost of the additional year of assessment is £58,763 and commenced in July 2023. In 2024, £29,381 of payments were made and recorded as charitable activity cost (2023 – £58,097). The project completed during 2024 and as all elements of the agreed work program had not been completed, a refund of contributions made of £44,351 was recorded in debtors and as a reduction of expenditures incurred. The net expense recorded was therefore negative £14,970 during 2024.

In March 2021, the Charity agreed to fund costs associated with the establishment and administration of an EHE Biobank and the provision of a Tissue Manager with the **Royal Marsden Cancer Charity** and the **Royal Marsden NHS Foundation Trust** with an estimated total cost of £85,150 over five years commencing in April 2021 (four years commencing April 2022 regarding the Tissue manager). In 2024, £18,255 of payments were made (2023 – £27,567) and £18,089 recorded as charitable activity cost (2023 – £19,719). The amounts committed to for future years have been included within Debtors and Creditors as appropriate.

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 £117,396 with costs funded 50% by the Charity and 50% by the EHE Foundation in the United States. In 2024, payments of £20,760 were made and £13,595 was recorded as charitable activity cost (2023 – payments of £37,401 were made and £29,247 was recorded as charitable activity cost). The remaining amounts payable by the Charity have been included in Debtors and Creditors as appropriate.

In December 2022, the Charity contracted with the **Fondazione IRCCS Istituto Nazionale Dei Tumori** in Italy to fund costs associated with a study aiming to provide a description of the population affected by EHE, giving an insight into the natural history of the disease and its variants, leading to the possible identification of clinical and biochemical prognostic and predictive factors. Total costs of the project are €91,500. In 2024, payments of £17,200 were made and £24,866 was recorded as charitable activity cost (2023 – payments of £35,903 were made and £26,654 was recorded as charitable activity cost). The remaining amounts payable by the Charity have been included in Debtors and Creditors as appropriate..

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 Charity's activities and operations for the year ending 31st December 2024. 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 the Charity's charitable objects and its associated activities.

Signed this 30th day of October, 2025

(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
Dr Oliver Pearce
Ms Sally Baker

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 group's 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 the Charity.

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 and all editions of ***The Pledge***

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

100% From well-managed forests FSC® C000000

Printed by Optichrome Limited

Front cover images

Tissue handling at the Royal Marsden biobank facility.

and

Brilliant calendar campaign raises EHE research funding.

EHE RARE CANCER CHARITY (UK)

England & Wales - Charity number 1162472

Accounts

Rare Cancer Charity UK

Annual Report and Financial Statements 2023

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

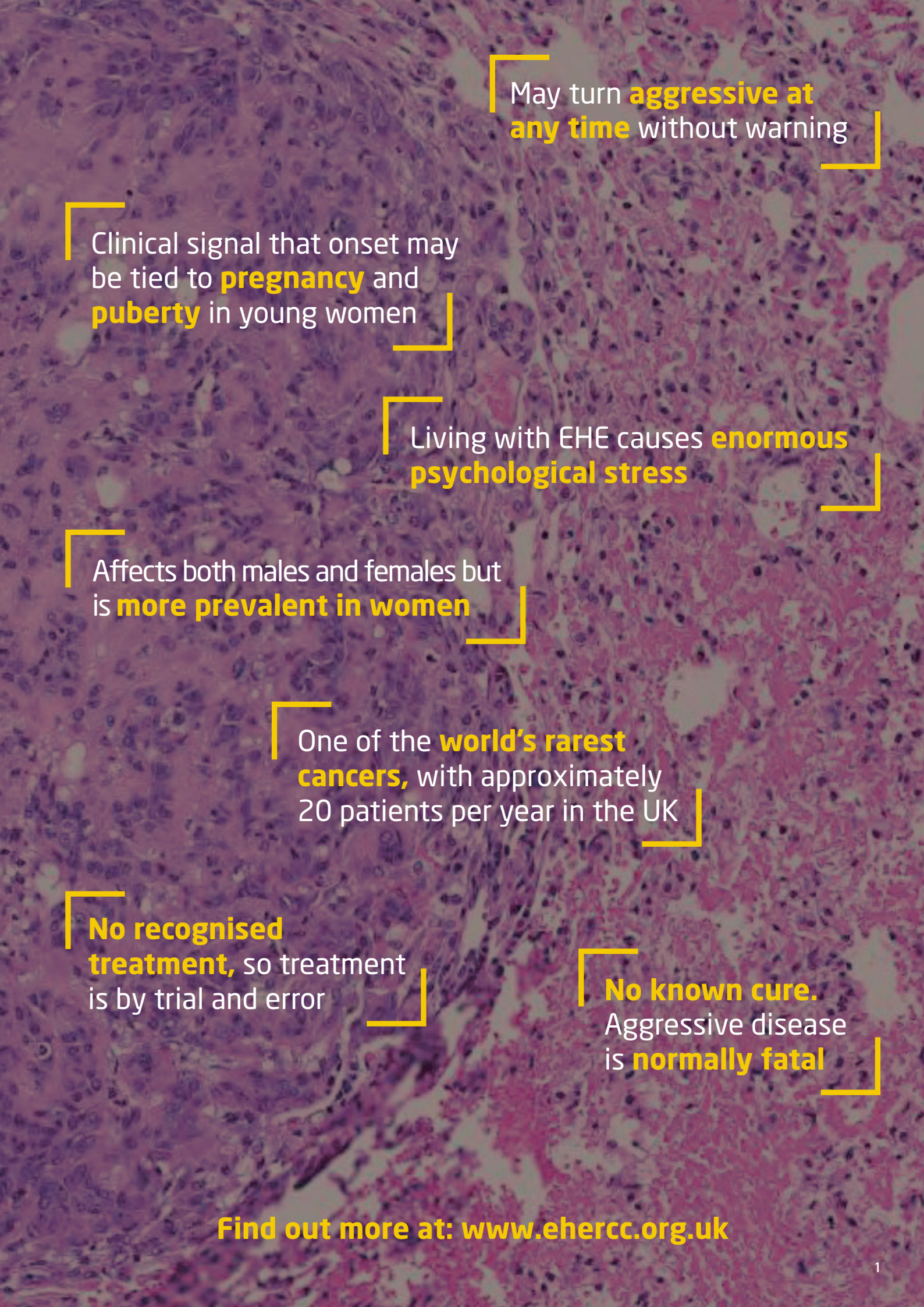
Can present as **indolent** (passive) or **aggressive**

Typically more aggressive in **young people**

Can re-present after long period with no disease

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

Background slide showing Mouse EHE arising in the lung in Dr Brian Rubin's Genetically Modified Mouse Model



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 both males and females but is **more prevalent in women**

One of the **world's rarest cancers,** with approximately 20 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

ICR The Institute of Cancer Research

EHE RARE CANCER CHARITY (UK)

in partnership with The ROYAL MARSDEN NHS Foundation Trust

ehe Biobank

The UK National Epithelioid Haemangioendothelioma Biobank

Eniola Ayeni[1], Stephanie Elston[1], Emma Perkins[2] Robin L Jones[1], Bader Al-Badri[1], Paul Huang[2], Hugh Leonard[3]
[1] The Royal Marsden NHS Foundation Trust, [2] The Institute of Cancer Research, [3] The EHE Rare Cancer Charity

Introduction

The National Epithelioid Haemangioendothelioma (EHE) Biobank supports research into this rare sarcoma subtype where limited tumour material is available for research. The overall aim is to facilitate research into improving diagnostic accuracy, identifying new drug targets and developing new biomarkers to be able to better understand the unpredictable course of this disease.

EHE Biobank Patient Enrolment

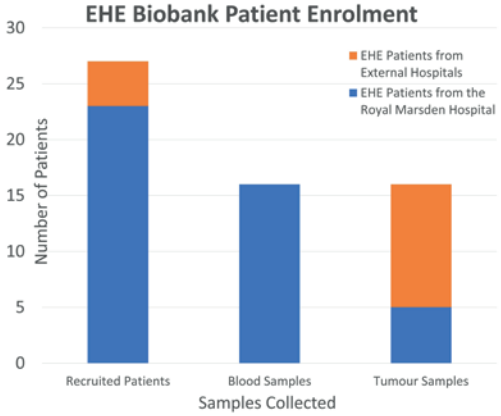


Figure 1: EHE Biobank patient enrolment figures. Recruitment of these patients and the collection of their samples started when the biobank was established in 7th April 2021

Inclusion Criteria

The only inclusion criteria for the biobank is that the patient must have histological confirmation of their EHE diagnosis.

After a formal consent process, the collection and storage of blood and tissue samples from patients will be facilitated by the biobank manager and subsequently stored in the biobank.

Patient Recruitment Process

Patient identified
- Through self-referral
- Through Charity representative
- Through Clinic lists at Royal Marsden Hospital (RMH)

Patient provided information (PIS)
- Patient allowed time to consider PIS
- Opportunity to ask any questions

Patient Consented
- Internally: This is face to face
- Externally: Consented by their local clinician, then remotely by the biobank manager
- Consent forms sent to EHE biobank email

Samples Obtained
- Internally: Collected by RMH staff
- Externally: Collected by local clinical team or requested by the biobank manager
- Courier organised by RMH

Increased National Patient Engagement → Larger bank of samples → Valuable resource for future research → Improved patient outcomes

Method

This research is purely observational and involves the collection of peripheral blood, biopsy cores, surgically resected material and other relevant fluid surplus to diagnostic requirements. Blood samples have been processed, stored and frozen as plasma, buffy coat and whole blood. Core biopsies and surgically resected tissue has been stored as fresh frozen tissue and formalin fixed paraffin embedded (FFPE) tissue blocks. They are processed in this manner in order to reduce the chance of degradation.

Samples Currently Stored in the Biobank

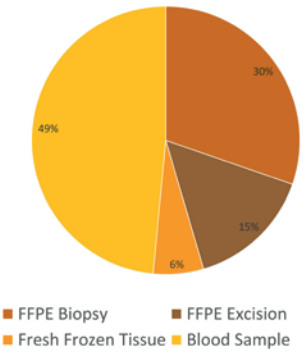


Figure 2: Representation of the EHE Biobank samples currently stored at RMH

Results

Research conducted on these samples will relate to the prevention, diagnosis and treatment of EHE. Currently 16 whole bloods, 2 fresh frozen tumour tissue and 14 FFPE samples have been collected. Though the biobank is still accruing samples and is not yet open to receive applications for tissue/blood access from researchers, we anticipate that in time, the biobank will support collaborative research projects in the UK and internationally. These projects may involve a wide range of biomedical analytic techniques including, for example, microscopy, cellular and in vivo imaging using fluorescent or luminescent probes, nucleic acid analysis, microarrays of DNA and mRNA (whole genome sequencing), protein analysis, small molecule assessment and functional analysis.

EHE Biobank Patients within the UK

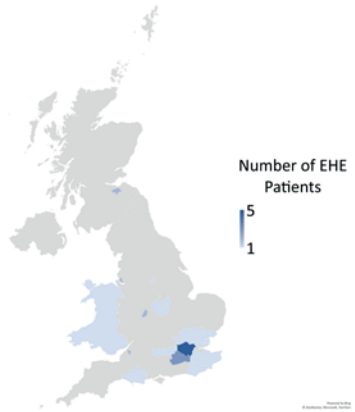


Figure 3: Regional representation of where the samples have originated from

Conclusion

The EHE biobank has been successful in recruiting patients with this rare disease. Despite this, we need more physicians to continue referring new EHE patients to the biobank for the advancement of future research.

For More Information

Including patient consent forms, patient Information sheet and how to recruit patients at local centres:
https://www.ehercc.org.uk/national-ehe-biobank-uk
Email: rmh-tr.ehebiobank@nhs.net

Acknowledgements

The ICR and RMH work in partnership as a National Institute of Health Research (UK) Biomedical Research Centre. This biobank has been funded by the EHE Rare Cancer Charity.

EHE Rare Cancer Charity UK

Annual Report and Financial Statements 2023

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Message from the Trustees

2023 has been another very good year for the EHE Rare Cancer Charity ('EHERCC' or 'Charity'), although not without its challenges.

Our annual patient support programme has once again allowed us to both welcome new patients into the group and at the same time continue supporting and communicating with our existing patient network. As always, this support is largely provided by our patients through their extraordinary energy and compassion for one another. The Charity has also engaged during the year, and become an active participant, in two new closely linked multi-stakeholder programmes. The first is an initiative seeking to obtain a pan-European approval of the drug sirolimus for the treatment of EHE. The second initiative is seeking to set up and establish a platform to streamline and optimise ultra-rare sarcoma clinical trials and research, to reduce costs and uncertainty and so maximise the chance of success. You will find more on both these initiatives later in this report.

The EHE collaborative research we are funding continues to produce positive results. Evaluation of different categories of biomarkers is ongoing, with strong candidates already identified. Our funding continues to support three important initiatives: (i) the EHE observational study involving centres in Milan and London; (ii) the first ever multi-centred prospective observational registry of EHE, coordinated from Milan; (iii) the UK National EHE Biobank centred at the Royal Marsden Hospital. Our research, which is seeking to develop zebrafish models of EHE, based at the Bateson centre in Sheffield, is also ongoing.

Our supporters have once again excelled in the area of fundraising, with their usual determination and energy. This has been particularly important in the current cost-of-living crisis that inevitably means there is less funding available and more people competing for it. So we could not be more grateful for their unbelievable efforts to raise the funding we need to drive EHE research.

Once more, as we prepare our annual report, we are reminded that all our activities have only been possible because of the commitment and passion of our patient community and their supporters, and the dedication and expertise of the doctors and researchers who help in the fight against EHE. As always, therefore, we want to recognise every single person who provided their support, in whatever form, to the Charity and our EHE community, in 2023. Without your extraordinary efforts there would be no EHERCC and no exciting results to present. So please accept our deep and sincere gratitude. "Thank you!"

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

As in all previous years, the Charity was keen to engage with any opportunities where we could talk about epithelioid haemangioendothelioma, explain the challenges faced by our patient community, and all that the Charity and indeed our global EHE Group are doing to help in the fight against this ultra-rare sarcoma. Hugh Leonard was delighted to give such talks at charity fundraising events, including in London and Derby. Awareness is also spread through The Pledge, the quarterly newsletter of the EHE Group that is produced in London (see inside back cover).

We were also delighted to participate in two EHE Group coordinated events held during the year. The first was the Scientific Saturday virtual meeting for our global patient community where Hugh Leonard and Denise Robinson jointly presented a broad overview of the global EHE research that is taking place. The second event was the larger EHE360 Global Patient Conference held in April, where patients, patient-advocates, clinicians and researchers come together to provide a wide range of highly informative talks about the disease; and closes with the ever-popular 'Ask the Experts' Q&A session.

One area where the Charity has made less progress than hoped is the establishment of a coordinated pan-European EHE patient network. This has been delayed partially because we were waiting for the INT-led pan-European prospective observational registry to start. This happened at the end of 2023 and we hope that we can now progress with this important European initiative. Some progress, however, has been made with the Charity engaging and building a strong collaborative relationship with the newest EHE foundation, EHE Italia Associazione Non Solo Laura ODV (EHE Italia), as well as with existing patient groups such as the German cohort.

The Charity is also excited to be part of two important multinational initiatives. The first of these is a European initiative seeking to secure a label extension for the drug sirolimus (marketed as Rapamune®) for the treatment of EHE, as there is now a substantial body of clinical evidence that clearly indicates the efficacy of this drug. As part of this label extension application process with the European Medicines Agency (EMA), the EHE Group undertook a sirolimus-focused survey of its global patient community. Results showed both the activity of the drug in treating EHE, and that results were substantially better than for any of the drugs generally approved for soft-tissue sarcomas, most of which show little or no activity for EHE.

At year end, the Charity also became a member of the Executive Committee of the PUSH Consortium, a new multi-centred international group seeking to establish a new platform to streamline drug approval applications and all pre-application scientific trials and procedures. We hope that this platform will help future EHE drug applications as well as those for all other ultra-rare sarcomas.

02
Research

A key focus for our ongoing research is the European collaboration involving Istituto Nazionale dei Tumori (INT), Milan, together with the Institute of Cancer Research and the Royal Marsden Hospital, in London. This multi-faceted programme has already identified the cytokine protein GDF-15 as a likely EHE biomarker. Six different miRNAs have also been identified as possible EHE biomarkers, with one of these six looking a particularly strong candidate.

The identification of GDF-15 has allowed the team to investigate GDF-15 levels in patient samples for different disease presentations. In addition, and using the PDX cell line developed at INT, they have been able to measure GDF-15 levels as part of the assessment of activity of different drugs. These results have continued to support the identification of this cytokine as a valid biomarker of the disease.

In the UK, our ongoing work with the Bateson Centre to develop a zebrafish model of EHE has continued to be both frustrating and encouraging. We now have a TAZ-CAMTA1 fish, yet levels of TAZ-CAMTA1 seen in these fish are typically lower than would be expected from the recoded activation levels of the TAZ-CAMTA1 transgenic construct. The team are trying to understand this. At the same time they continue to work on the development of a YAP-TFE3 fish, as this fusion protein is far shorter than TAZ-CAMTA1 which may be one reason why the TAZ-CAMTA1 expression is low. Finally, INT are providing cells from their PDX cell lines to allow the zebrafish team to test injecting these cells into fish embryos and so create a new form of xenotransplant where living EHE cells are sustained *in vivo* for use in ongoing research.

The Charity, which has funded the establishment of the first ever EHE-dedicated, prospective observational registry at INT, and involves both European and UK hospitals, was delighted to see the initial launch of the registry in September, and its first patients entered into the registry at the end of the year. A total of 21 hospitals across Europe are engaged in the registry, which is an excellent outcome of which the INT registry team should be very proud.

The National EHE Biobank, funded by the Charity and based at The Royal Marsden Hospital in London (see page 2), continues to gather critical tissue and fluid samples. We are continuing to work with the Royal Marsden to promote awareness of the biobank with hospitals across the UK.

Discussion of the development of a global EHE research strategy was also started late in 2023 and now remains as a priority for the EHE Group, both to ensure our growing research programme is optimised and to act as the foundation for larger, broader and longer-term funding applications.

03
Fundraising

There is no doubt that the most important part of our ongoing activities is our fundraising, as this provides the funding we need to drive all other aspects of our programme of activities. And 2023 was another promising year, despite the cost-of-living crisis, which has had an impact on the funding available to all charities.

Our supporters turned out in numbers for the London Landmarks Half Marathon, matching the 2022 record of 50 runners registered. Once again Team Dean, supporting EHE patient Paul Dean, himself a participant, turned out in huge numbers with a team of 19. Paul Preston also led a team of 19 from Ginger's Fitness from south London, running in support of Kelly Denton whose daughter has EHE. It was an amazing event.

In early summer we had 17 riders participating in The RideLondon-Essex 100-mile-long cycling sportive. As Chair of Trustees, and having spent several years encouraging others to participate for the Charity, Hugh Leonard had ridden in the 2022 event, and decided to ride once more in 2023, this time accompanied by his son, Sam. They were riding in support of Hugh's wife and Sam's mother, Sally Baker, an EHE patient and Trustee of the Charity.

Hugh Leonard attended several fundraising events, to represent and speak about the Charity. These included the second annual Hazel Peak Quiz Night, organised by Hazel's colleagues at the Rolls Royce facilities in Derby in memory of their colleague, and the Laptops and Lipstick quiz night in Peckham, south London.

Perhaps the most vibrant event was a small and intimate music evening hosted by Hannah, cousin of an EHE patient, at one of the Pizza Express music venues in London. Hannah was a successful participant on The Voice, the major UK musical TV talent show. She was accompanied by two other brilliant singers and by her husband (piano) and brother (guitar); the evening was fantastic and was hugely enjoyed by all present, who ended the event dancing around Pizza Express.

This year also saw individuals running in memory of lost friends. Mia Sallet ran for Isabelle Miller, Darren Thomas ran for Janet Griffiths and Adam Patrick and his team ran in the London Landmarks Half Marathon in memory of Allana Parker. These lost friends left us far too early, yet our memories of them burn brightly.

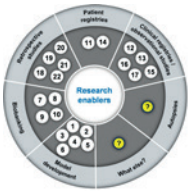
All of these wonderful contributions, together with those in prior years, have combined to provide the amazing fundraising the Charity has enjoyed, which has allowed us to contribute to the vital EHE research described in this and our previous annual reports.

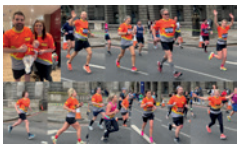
More information about these and other events can be found in this report.

Achievements and Future Objectives

Every year we review our activities and achievement against the goals that we set for ourselves. We believe that this honest appraisal is important so that all our supporters and stakeholders can see how we are progressing. Below is the 2023 assessment; while on the opposite page you will see our objectives for 2024.

	What we said we would do...	...and what we achieved
01 Patient Support and Advocacy	Continue sirolimus repurposing	Engaged throughout 2023 process
	Assist patients with engagement with charity activities	Ongoing promotion of biobank and global patient registry
	Launch new website	Launched by year-end
	Revitalise other social media	Not yet started
	Engage with European patient community	Excellent relationships built with EHE Italia and German patient reps. Full European engagement delayed waiting on pan-European registry from INT
02 EHE Research	Support existing research	Continued through the year
	Review and communicate results	Continued through the year
	Engage with EHE partner foundations in research review	Progress continues regarding EHE strategy
	Develop and promote coherent EHE research strategy	Ongoing, with close coordination with global EHE partners
	Organise additional research review meetings	EHE360 Conference presentations coordinated. No specific research review meetings held.
03 Fundraising and Finance	Support and encourage grassroots fundraising	Continued to promote and support fundraising
	Coordinate key charity events (LLHM and RideLondon 100)	LLHM and RideLondon 100 completed
	Continue to develop fundraising strategy with NOVA fundraising	Reports received and reviewed. Excellent guidance requires implementation
	Coordinate review of research strategy and develop draft fundraising programme	Awaiting research strategy
Charity Organisation	Consider appropriate support for research strategy	Awaiting progress on detailed strategy
	Implement fundraising strategy	Delayed pending research strategy delivery
	Establish structures for European engagement	Delayed
	Evaluate need for additional structures and personnel for the above	Insufficient progress so deferred to 2024





Our Forward Focus for 2024

Because rare cancers are not rare to those who have them

01 Patient Support and Advocacy

- Continue sirolimus repurposing
- Support PUSH platform
- Revitalise other social media
- Engage with European patient community

02 Research

- Support existing research
- Develop and promote coherent EHE research strategy
- Organise additional research review meetings
- Coordinate with EHE Group entities

2024 AND BEYOND

03 Fundraising

- Support and encourage grassroots fundraising
- Coordinate key charity events (LLHM and RideLondon100)
- Continue to develop fundraising strategy with NOVA fundraising
- Coordinate review of research strategy and develop draft fundraising programme

Charity Organisation

- Consider appropriate support for research strategy
- Implement fundraising strategy
- Establish structures for European engagement
- Evaluate need for additional structures and personnel for the above

Foreword from Dr William Tap

William Tap, MD is the Chief of the Sarcoma Medical Oncology Service at Memorial Sloan Kettering (MSK) Cancer Center in New York, and Co-Director of the MSK Sarcoma Center and the Lisa and Scott Stuart Center for Adolescent and Young Adult Cancers. He has a large clinical practice and develops and runs clinical trials of new anti-cancer treatments. His academic research focuses on genetic and molecular nuances of rare cancers, identifying and validating therapeutic targets, treatment biomarkers, and modeling drug resistance.

This has been an amazing year for epithelioid hemangioendothelioma, one that provides me with tremendous satisfaction regarding the accomplishments and spirit of our community, and in turn, hope and excitement for what the immediate future holds. I do not make these comments lightly, as we all have experienced the significant frustrations and devastating impact that is inflicted by an ultra-rare cancer, particularly one as complex and confounding as EHE. Years ago, as our experiences with EHE grew, it became evident that it was not a disease that should be approached, treated, or studied through individual efforts. Rather, it requires an all-in collaborative effort that challenges established academic approaches and is centered around EHE patients. In essence, dissolving artificial barriers and coalescing individual efforts to exact real-time change, redesigning approaches and infrastructures in order to enhance patient care and accelerate research and drug development. Years in development, we are now beginning to experience the strength and promise of this collaborative approach and the foundation it has created.

Central to all of this has been the partnering of patients and patient advocacy groups, such as the EHE Rare Cancer Charity UK, academic sites including sarcoma oncologists and scientists, the Ultra Rare Sarcoma Working Group, the PUSH Platform, not-for-profit organizations focused on drug repurposing and meeting unmet needs in cancer care and research, and regulatory agencies. All are represented with an equal voice, sharing experiences and expertise, and an unbridled passion to better understand EHE, enhance and accelerate research processes and drug development, achieve global equality in treatment paradigms and available agents, and to ensure the patient remains central to the whole process.

Two clinical opportunities emerged that underscored the dramatic need and urgency of this movement. The first is an ongoing effort to make rapamycin (sirolimus) universally available as a treatment for EHE patients in Europe and the second is the potential entry of TEAD inhibitors into EHE specific clinical trials. The former required the collection of 'counterfactual' clinical data in EHE, that is comprehensive data inclusive of the various subtypes of EHE that could be used by data models and machine learning to predict outcomes of certain 'what if' situations under various conditions, i.e., how our best treatments do under the various clinical situations EHE patients experience, examining standard cancer and EHE specific/pertinent outcome measures. This data would be needed to direct retrospective and prospective studies and to guide regulatory discussions. Closely linked to this was the later opportunity which was the entry of a novel and promising class of compounds, the TEAD inhibitors, into the clinic, underscoring the importance of ensuring accurate drug development strategies and clinical trial designs in EHE. This is not a straightforward endeavor due to the complexity of EHE and, as few agents have been tested in clinical trials and there are inherent challenges to ensuring biopharma interest in ultra-area diseases, it is necessary for the EHE community to have developed and aligned on viable approaches that minimized risk and uncertainty.

So, what has been accomplished and why is it so exciting? EHE has now been incorporated as a formal working group in the PUSH Platform. PUSH is a novel and exciting new patient-centric venture designed to change and accelerate research in ultra-rare cancers through the active participation of diverse and vested stakeholders as mentioned above. PUSH facilitates the rapid collection and sharing of comprehensive data with the goal of optimizing research with an emphasis on accelerating drug development and availability. Through PUSH, of which members of the EHE Rare Cancer Charity UK and The EHE Foundation are on the Executive Committee, comprehensive data regarding the natural history of EHE is being collected and organized. This includes comprehensive data extracted from full medical records in the United States with people's consent through the Health Information Exchanges Act, comprehensive clinical and treatment data from academic sites throughout the world through the Ultra Rare Sarcoma Working Group, a multi-centered prospective EHE observational registry in Europe which we hope will go global, and direct information from patients regarding their experiences to better understand how EHE effects them, their family, and caregivers. These data are critical in that it will help us define the natural history of the various clinical and genetic subtypes of EHE, help us better understand how EHE effects the lives of people and how we can better mitigate its symptoms and life impact, provide data about the efficacy patterns of our best treatments, identify meaningful treatment outcomes for patients, allow us to design novel clinical trial approaches and run simulated clinical trials with historical data, and gather counterfactual data to inform regulator discussions. In addition, PUSH has developed a prospective treatment study of sirolimus to capture real-world data and practical usage data regarding mTOR inhibitors, established ongoing discussions with regulatory agencies in the US and Europe to inform the regulatory process for novel and repurposed drugs in EHE and other ultra rare cancers, and developed novel clinical trial endpoints and response criteria in EHE that best represents outcomes and symptom assessments that are meaningful to patients. In addition, PUSH is helping to evaluate serum biomarkers in EHE that can help us understand a person's disease and how well our treatments are working and is engaging with the broader sarcoma community to support novel clinical trial ideas to ensure that individual efforts are connected to the EHE community and benefit from all of the data, infrastructure, science, and opportunities that have been developed and organized by this effort.

Overall, we still have so much work to do, but I am so hopeful that these efforts will continue to grow and rapidly accelerate progress for EHE patients and set the paradigm of how to approach and cure ultra rare cancers around the world. None of this would be possible without the direction, passion, commitment, and presence of EHE patient advocacy groups and our patients and their caregivers. Together we are making a difference!

William Tap, MD

We want to thank Dr Tap for taking the time to write the Foreword for our annual report. We are very grateful indeed. We also want to thank him for the time, energy, compassion and care that he gives to EHE patients and the EHE cause. It is wonderful to know that people like you are fighting this horrible disease along side us. Thank you.

01 Patient Support and Advocacy

The Charity's Patient Support and Advocacy (PS&A) programme is one of our core areas of activity and lies at the heart of everything we strive to achieve. In this section, we hope we have been able to provide a sample of the inspiring work that is done to help promote awareness of EHE, support patients, and advocate for greater focus, support and funding for all EHE-related activities.

Review by Sally Baker, Trustee and EHE patient

Patient support

Patient support and engagement is one of the most important parts of our PS&A programme, allowing us to keep patients updated on the latest EHE developments, help them where they are facing challenges of whatever nature, and encourage and promote support for all our activities. Some of these engagement activities are summarised below.

Our EHE community continues to grow

One of the most common accolades the EHE Group receives from clinicians, researchers, regulators, donors and other stakeholders, concerns our EHE patient community that has been established globally, and who contribute so much to patient support, to research and to fundraising. Much of this comes from the community's EHE Support Group page on Facebook, established in 2013, which at the end of 2023 had more than 2,600 members, representing patients and their support groups from nearly 80 countries.

It was this same community that in 2015 established the EHE foundations and charities in the USA, Australia and the UK, to act as the focal points for fundraising and EHE-specific research. Canada and Italy have followed more recently, while other countries have established EHE patient networks. Now, as we look back, we can see how much our EHE community has achieved in building awareness and knowledge about EHE, in driving an active and very successful fundraising programme, and in advancing a growing international collaborative EHE research programme. This has only been possible due to the support of our global EHE family, and is why maintaining engagement with them is so important.

Everyday engagement

The foundation of all our patient engagement activities is the support provided by the patient community itself, through both local and global EHE social media platforms, allowing the patient body to share experiences and provide valuable information on a range of topics. As EHE has both variable presentation and course, having access to others with similar disease presentation and facing similar challenges is hugely important and comforting for those involved. It is both humbling and inspiring to see first-hand the depth of compassion and selfless provision of support that our community members provide to each other, and the strength and comfort they gain from this interaction.

Patient-targeted communications

We communicate directly with our patient and support community through different forms. Every quarter, the Charity produces **The Pledge,** the quarterly newsletter of the EHE Group, with a summary of the Group's global activities, We hope that this provides all our supporters with an inspiring summary of all that is taking place to help defeat EHE. Copies of all the 2023 editions are shown on the inside back cover of this report.

The EHE Group also organises periodic informal videoconferences with its members to update them on key initiates. In 2023, the EHE Foundation held its 'Science Saturday' event at which Hugh Leonard, Chair of Trustees for the Charity, and Denise Robinson, Director of Research of The EHE Foundation in the US, updated participants on the global EHE research programme. This was a well-attended event with participants finding the presentation both informative and inspiring.

01 Patient Support and Advocacy - continued

The largest of the EHE Foundation's patient-engagement events is EHE360, the EHE Foundation's annual patient conference. This event brings together patients, advocates, clinicians and researchers in an online environment where updates and information are provided on a range of topics. More than 200 people from 21 different countries attended the conference. EHE researchers presenting their latest findings are hugely popular, as are presentations on a wide range of different treatment options. The highlight for many is the 'Ask-the-expert' panel session at the end, where participants can post questions that are discussed by leading experts in the field. Hugh Leonard was delighted to be one of the featured speakers where he presented the preliminary analysis of the EHE Group sirolimus survey, as described later in this report.

European initiatives

The Charity is also seeking to establish a pan-European patient network, building off the foundation of the pan-European prospective observational registry being coordinated in Milan and funded by the Charity. This registry was formally launched slightly later than hoped in late 2023 (see Research section of this report) with the result that the Charity's European patient engagement was also delayed. We hope that this initiative will now be launched in 2024. In the meantime, any opportunities were taken through 2023 to engage with different European patient representatives, either as individuals or as country-specific patient groups.

Hugh Leonard was delighted, for example, to have the chance to meet with Dora Balda in London. Dora is from Greece and her daughter has EHE. Hugh and Dora had a brilliant two hours talking about all things EHE and plan to meet again in the future. For Hugh the meeting also amplified both the need for, and the benefits that could flow from, the establishment of a coordinated European patient group.

In September, Hugh also travelled to Milan to participate in the Charity -organised research discussions with the research team at the Istituto Nazionale dei Tumori in Milan, Italy. This also gave Hugh the opportunity to meet with the newest of the EHE global foundations, *EHE ITALIA Associazione Non Solo LAURA ODV*. Hugh and Andrei Ivanescu, President of EHE Italia, discussed their ongoing collaboration including their joint desire to establish the European patient network.

Remembering absent friends

At this point we also want to remember all those members of our patient community who contributed so much but who sadly left us far too early. They are a major part of the reason why we all spend so much time and energy working to find new treatments and a cure for EHE. We owe that to all those who are no longer with us.

EHE awareness opportunities

The Charity is always keen to engage with opportunities to talk about the disease, the research we are funding and the advances being made. Such opportunities often arise as part of a fundraising event, and two such opportunities arose early in the year.

Laptops and Lipstick quiz night

Kelly Denton is another of our global EHE community who is highly active and engaged in helping to deliver on all the objectives of the Charity. Her engagement with the EHE community, and in particular with the Charity, is driven by her daughter's EHE diagnosis.

It was thanks to Kelly's profile that a women's business network based in south London, Laptops and Lipstick, chose the EHERCC as their supported charity. As part of that support, Laptops and Lipstick organise an annual quiz night, which took place in late February.

It was an excellent night with a large turn-out. At the meal interval Hugh Leonard was able to explain what EHE is, and why it is so important that we continue to drive research into the disease. He was also able to thank them for their wonderful support.

The Hazel Peak Quiz Night No 2

Hazel Peak was a UK patient who was diagnosed with EHE in late 2021. Sadly Hazel had a very aggressive form of the disease and passed away very early in 2022. Her colleagues at Rolls Royce Submarines in Derby desperately wanted, however, to continue with their fundraising quiz night, which they had planned for her in March, and which was ultimately a great though understandably emotional success.

Roll forward one year and Hazel's colleagues decided they wanted to hold their second quiz night in her honour. Hugh Leonard was invited to attend the event, as he had the year before, and had the chance to speak to the guests about the research in the UK and Europe that their funds were helping to drive. People were genuinely interested and Hugh had the chance also to speak to some individually and answer their questions. And of course to thank them all for their brilliant ongoing support.

It is hard to overstate how useful and important these events are in helping to build awareness of EHE and to help achieve many of our core objectives. We want to join Hugh in thanking Kelly's supporters and Hazel's colleagues for all that they have done to help us fight EHE.

Advocacy

Our advocacy programme in 2023 has been focused on dealing with the challenges presented by an ultra-rare sarcoma like EHE. This has involved the Charity's participation, together with INT, Milan and the AntiCancer Fund, in two different but related initiatives. The first is seeking approval from the European Medicines Agency for the approval of the drug sirolimus for the treatment of EHE; the second is seeking to establish a new multi-party platform called PUSH to streamline drug approval for ultra-rare cancers.

Approval of sirolimus and our EHE patient survey

Sirolimus is a drug (marketed by Pfizer under the trade name Rapamune®) that belongs to a group of compounds known as mTOR inhibitors. The drug is approved for use as an immunosuppressant post organ-transplant. There is also now a substantial and growing body of evidence demonstrating the efficacy of this drug in the treatment of some forms of EHE. The challenge we face is that the 'label' for sirolimus, which effectively lists all approved uses of the drug, does not include the treatment of EHE.

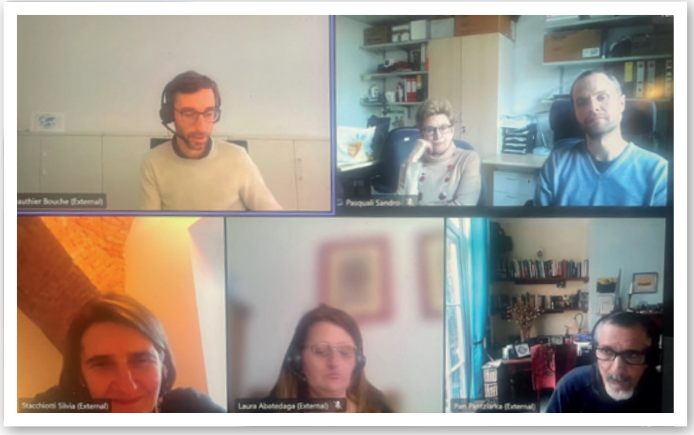
01 Patient Support and Advocacy - continued

The result of sirolimus not being formally approved for the treatment of EHE means that the drug can only be prescribed 'off-label'. For many patients, that is not an impediment to accessing the drug. But, if a patient's doctor will not or cannot prescribe off-label, or the health service will not pay for the drug, then an EHE patient may be denied access to this potentially important treatment.

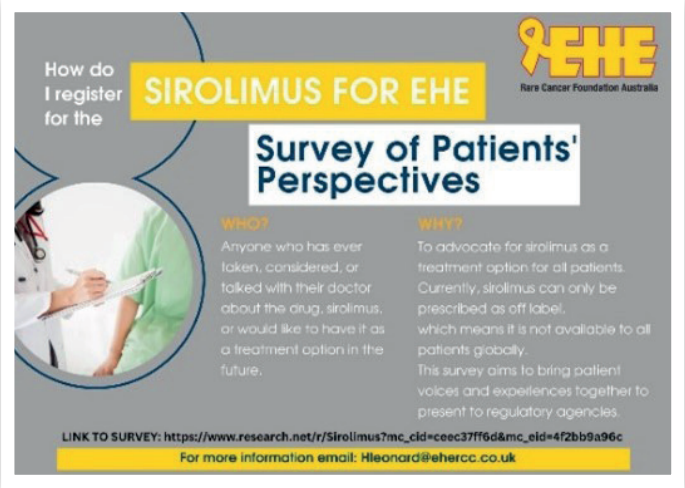
To counter this situation, there is now a worldwide focus on seeking approval for the treatment of EHE to be added to the sirolimus label, a process known as a 'label extension'. This process is currently most advanced in Europe at the European Medicines Agency (EMA).

To gain the label extension, an application must be filed with the EMA, under their established procedures. This requires a significant body of research and clinical trial data to be produced, collated and integrated, delivering results to demonstrate the efficacy of the drug to support the application. The challenge for ultra-rare diseases is that it is almost impossible to generate the standard package of data that regulators are used to, a fact recognised by regulators who in most cases are prepared to work with clinicians and patient advocacy groups to try and collate different but appropriate data to allow them to approve the label extension.

Prior to submitting the formal application, the EMA process allows the applicant to present its data for review and feedback, a process known as Scientific Advice. In compiling the information for the submission, Dr Stacchiotti's team, supported by the Anti-Cancer Fund in Europe and the Charity, undertook a worldwide search of published data involving sirolimus and EHE. This extensive data base was then reviewed and integrated into the submission document.



In addition to published data, the team were also very keen to include patient-curated data provided by the EHE Group. It was to provide this data that the EHE Group undertook its survey of patient perspectives and their experiences of treatment using sirolimus. The survey was directed at our global EHE community and was strongly supported by all the individual charities and foundations that make up the EHE group.



In total, 129 patients from around the globe participated in the survey that provided extremely useful real-world data that we believe supports the call for a label-extension. Key data from the patients' perspectives survey are summarised here, with the locations of participants shown on the map.

Of these 129 patients: 32 patients who had not undergone a liver transplant were taking or had taken sirolimus, for a range of different presentations of the disease; 21 patients had undergone liver transplant; and 76 had never taken sirolimus.

The distribution of different presentations is shown in Fig. 1. The predominance of liver/lung involvement (green bars) can be clearly seen with 67/129 (52%) of cases including this presentation. The most difficult cases with pleura involvement numbered only 6/129 (5%).

The median age (years) of all participants was 47.6 (range 14-81).

The distribution of both disease presentation and age of participants corresponds to disease descriptions from literature and demonstrates that the 129 participants provide an acceptable representation of the disease.

Participants were divided into three cohorts: (i) non-liver-transplant patients who are or have taken sirolimus; (ii) non-liver-transplant patients who have never taken sirolimus; and (iii) liver transplant patients.

The non-liver-transplant patients who are or have taken sirolimus numbered 32 of the 129 (25%) participants. Figure 2A shows the reasons for sirolimus treatment initiation. The most common reason was 'progressive disease'.

At the time the survey was undertaken 20 of the 32 participants were still on treatment with sirolimus. Figure 2B shows the duration that participants have or had been on the drug. These durations ranged from 'Less than 6 months' to 'More than 5 years; 21 participants had been on the drug for a year or longer; 5 had been on the drug for more than 5 years. Figure 2C shows the effect of the drug, with 20 participants experiencing stable disease and/or tumour shrinkage. Figure 2D shows the reason why 12 of the participants had discontinued taking sirolimus, with only 5 being directly attributed to the drug not working.

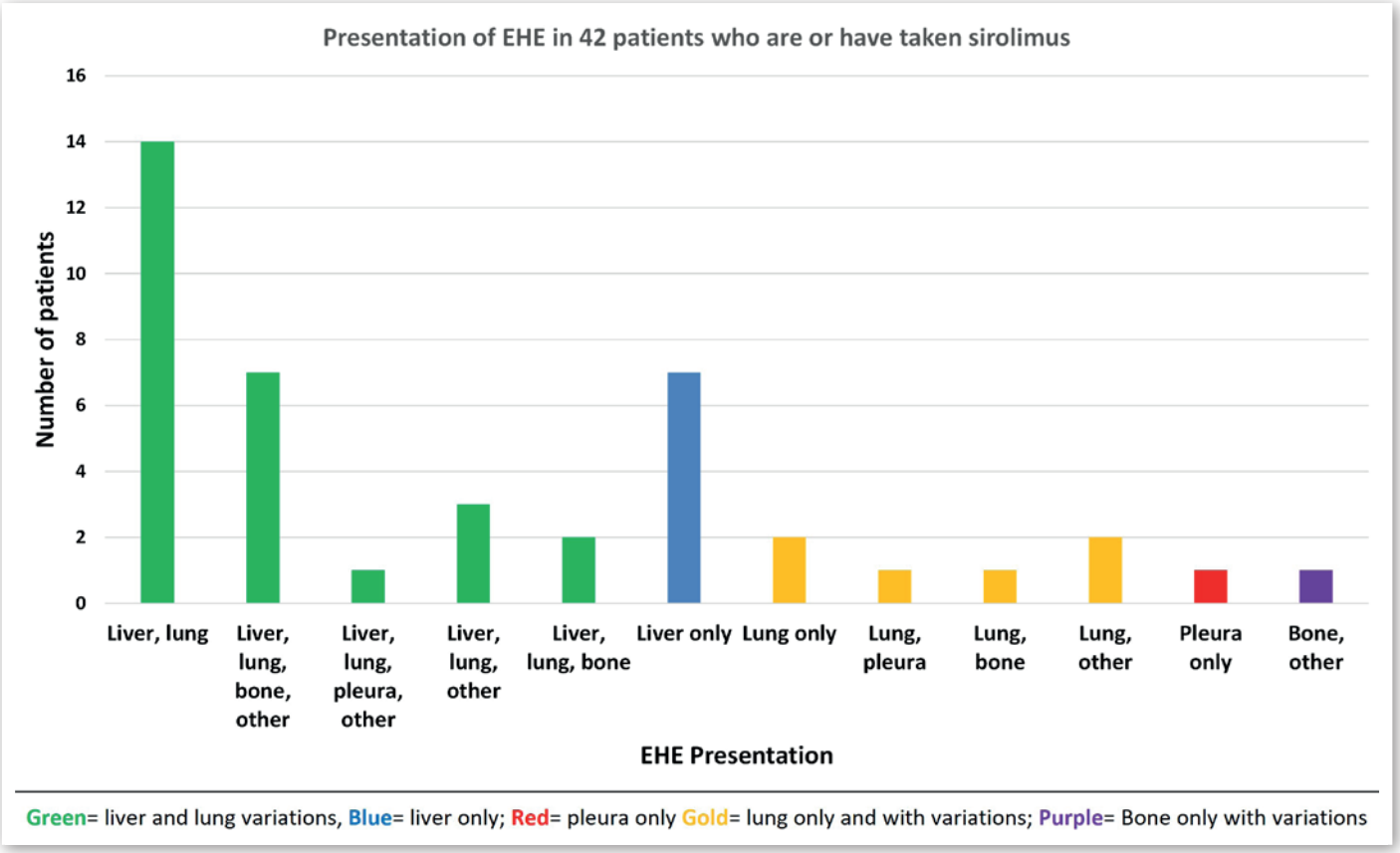


Figure 1

01 Patient Support and Advocacy - continued

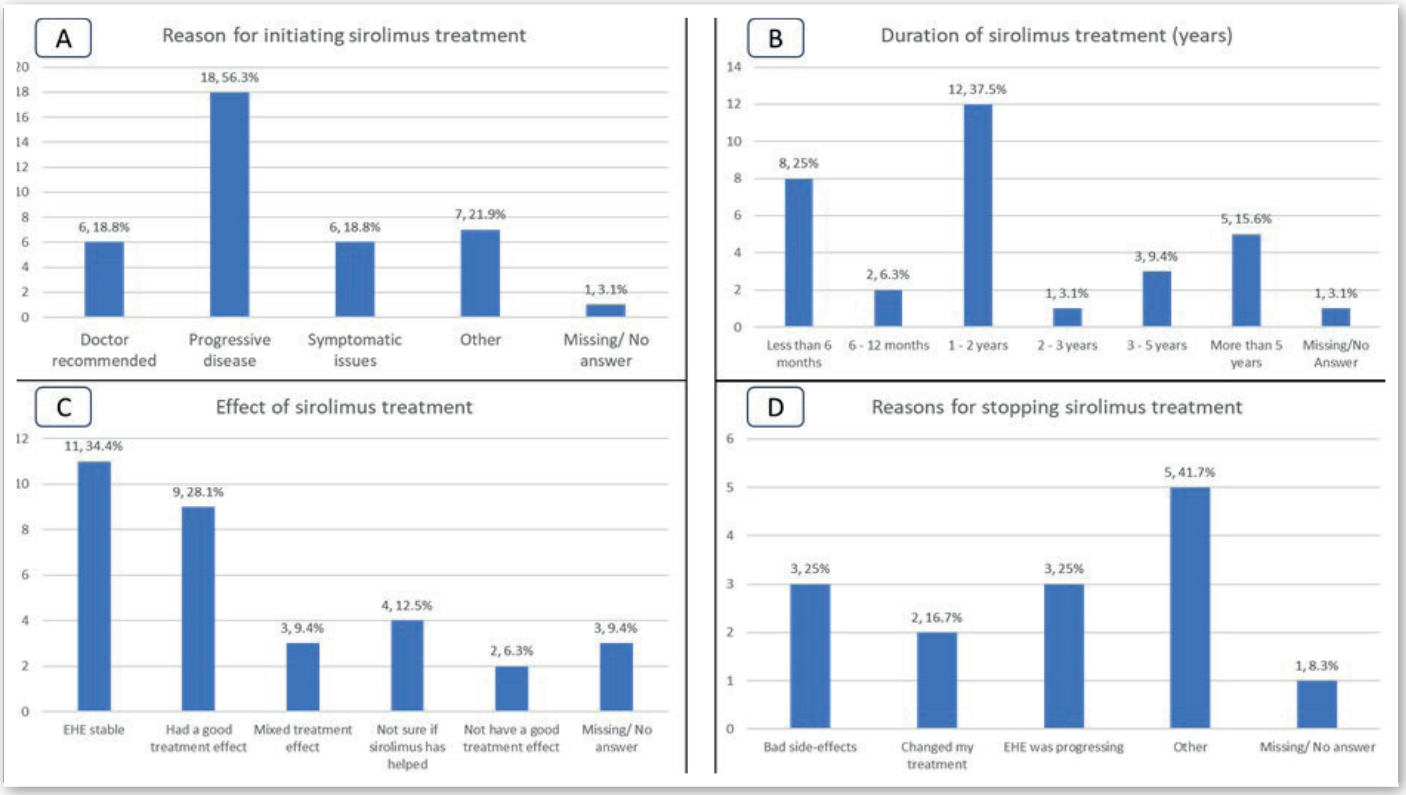


Figure 2 - Patient experiences of taking sirolimus. (A) Reasons for initiating sirolimus treatment. (B) Duration, in years, of sirolimus treatment. (C) Patient perspective on the effect of sirolimus treatment. (D) Reasons for cessation of sirolimus treatment.

The survey also explored the experiences and perspectives of non-liver-transplant patients who had never taken sirolimus. Of note was that of the 76 participants in this category, 32 confirmed that the drug was not available and a further 8 confirmed that it was but was not selected as it was only available off-label. In terms of actual discussions with their doctors, 45 participants confirmed that the drug had not been mentioned; a further 6 were told that it could not be used as it was not approved for EHE.

The survey concluded by asking participants to select how important it is to have sirolimus available to all EHE patients. Of the 129 participants, 87% placed availability of sirolimus to all patients as either 'hugely important' (76%) or 'very important' (11%), the two top categories of answer available. The importance was also mentioned in the following participants' comments:

"It is extremely important. I feel lost because I think in Portugal sirolimus wouldn't be approved for EHE treatment." (EHE patient)

"Although I do not know whether sirolimus would be an appropriate option in my case, I would think it is important to make it available to patients in every country - just in case!" (EHE patient)

"Critically important and potentially life-saving." (EHE patient)

The full results of this real-world data survey have now been published in the peer-reviewed journal Frontiers in Oncology, and can be found at:

https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2024.1367237/full

The full published results will also now be included in later Scientific Advice submissions to the EMA. These results are notably better than comparable results from any other drug approved generally for soft tissue sarcomas. We believe that these results coupled with the scientific information gathered by Dr Stacchiotti's team provide a very strong case for the approval of sirolimus.

CTOS 2023 and the PUSH Platform

In early November, Hugh Leonard, together with The EHE Foundation (US) Director of Research, Denise Robinson, attended the Connective Tissue Oncology Society (CTOS) 2023 Annual Meeting in Dublin, Ireland. Every year, physicians, scientists, and advocates from around the world come together to advance patient care and increase knowledge of connective tissue tumors (known as sarcomas) like EHE, where tumours form in the cells lining the blood vessels. CTOS is an important opportunity to engage and collaborate with sarcoma experts who are bringing novel ideas and experience together to improve the lives of sarcoma patients.

The week began with the Ultra-Rare Sarcoma Working Group (URSWG) meeting. EHE is considered an ultra-rare sarcoma, defined as affecting fewer than 1 person in every 1,000,000 people. Dr Silvia Stacchiotti led the meeting with Dr Bill Tap and colleagues, to discuss innovative approaches to conducting clinical trials in ultra-rare sarcomas.

The Charity and The EHE Foundation are working collaboratively with a team of clinicians, data experts, drug repurposing specialists and other patient advocacy groups to develop a clinical trial platform, PUSH (Pushing Ultra-rare Sarcoma towards Hope), to maximise the knowledge that can be gained from interacting with and treating every single patient affected by an ultra-rare sarcoma and to support developing new treatments to improve outcomes and quality of life. It is also hoped that by establishing such a platform, the costs of undertaking necessary trials and the risk of uncertainty of the regulatory process will both reduce significantly, resulting in greater appetite and engagement with industry.

Hugh Leonard is a member of the current PUSH Executive Committee, working to bring the PUSH concept to fruition.

Hugh and Denise also took the opportunity at CTOS to meet with the team that is spearheading the current discussions with the European Medicines Agency (EMA) regarding securing approval for an extension of the label of Pfizer's drug Rapamune® (sirolimus) for the treatment of EHE.

PUSH
PLATFORM

02
EHE Research

Study of the molecular and cellular features of EHE

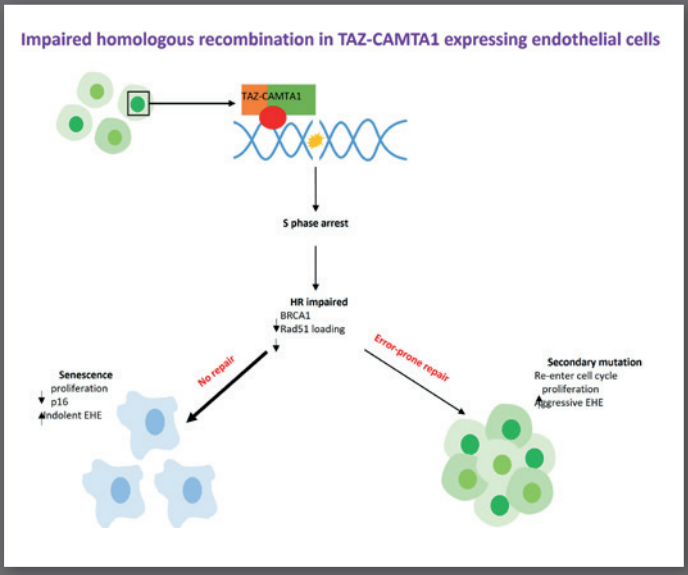
This four-year PhD project, under Dr Valerie Kouskoff at the University of Manchester, was funded by the Charity and was completed in early 2023. The research was then extended for a short period with a small grant awarded by The EHE Foundation under its annual grant cycle.

The aim of this project was to develop a model of EHE that could then be used to investigate various aspects of EHE biology. The model uses mouse embryonic stem cells, which are differentiated into endothelial cells. These are the cells that line blood vessels. The expression of TAZ-CAMTA1 (the fusion protein that drives EHE) is induced in these endothelial cells, allowing its function to be investigated in the type of cells where EHE tumours develop and grow. It was hoped that studies using this model would uncover previously unexplored mechanisms of EHE development, which may then lead to novel treatment options for EHE patients.

Investigations using this stem-cell-based model have revealed that TAZ-CAMTA1 expression causes a large amount of DNA damage in endothelial cells. DNA damage often occurs in cells, and is usually repaired without consequence by one of several DNA repair pathways. In endothelial cells expressing TAZ-CAMTA1, however, the large amount of DNA damage overwhelms these repair mechanisms, and often goes unrepaired. As a result, in many TAZ-CAMTA1-expressing cells, this causes cells to become arrested in the cell cycle, and then enter a state of senescence. This is a state in which the cells are dormant and cannot divide but also do not die. Senescent cells can accumulate in a tumour, and these results suggest that this could represent the indolent, or very slow-growing tumours many EHE patients develop.

The other consequence of overwhelming DNA damage is that a more error-prone pathway attempts to repair the damage. This leaves cells vulnerable to further genetic mutations occurring, which may then allow cells to bypass the barrier of senescence and induce uncontrollable proliferation. This could be the reason some EHE tumours suddenly become more aggressive and metastasise.
At the current time, this is the only theory that has been developed that explains the difference between indolent and aggressive EHE.

In 2023, during a short extension of the research programme, the research team were investigating if using drugs to inhibit some of the proteins involved in the onset of DNA damage or senescence-bypass could induce the death of TAZ-CAMTA1-expressing endothelial cells. Some of these inhibitors are already used or are in clinical trial for treating other types of cancer. The research looked at four different inhibitors, all targeting different aspects of DNA damage and seeing if these drugs could induce cell apoptosis in EHE cells. This was a small proof of concept, and while three of the drugs did not appear to have a measurable effect on EHE cells, one of the inhibitors produced more interesting results, both when used alone but also in combination with other inhibitors.
At the end of the year, the implications of these results were under review.



Review by Dr Oliver Pearce and Dr Kate Hooper, Trustees

Zebrafish modelling of EHE continues

In 2018, The Charity initiated research at the Bateson Centre at the University of Sheffield, to develop a zebrafish model of EHE. The Bateson Centre is one of the largest and oldest zebrafish facilities in Europe, and researchers there are experts in developing models of human diseases in zebrafish. Zebrafish are used because, if you are successful in creating the model you want, they are cheap and quick to produce. The embryos also develop outside the mother and are largely transparent, making it easy to see morphological changes as the fish develops.

The TAZ-CAMTA1 model

Creating a human model of a rare sarcoma is not simple in a zebrafish, and the team faced many early challenges in creating fish with EHE caused by the TAZ-CAMTA1 fusion protein. Early attempts, for example, demonstrated that the fusion protein was highly toxic to fish larvae, which did not survive. This required the team to introduce the EHE chromosomal translocation construct with a switch mechanism so that the TAZ-CAMTA1 could be 'turned on' once the fish had developed.

While several significant challenges were faced, the team in Sheffield continued to find solutions through extraordinary and painstaking attention to detail. At the start of 2023, the team, using a technology that analyses gene expression of all genes across the genome (RNAseq), initiated testing to see whether they could verify effects on other genes that are known to occur as a result of expression of the fusion gene in EHE, called the Seavey-set for EHE and the Cordenonsi-YAP signature set.

Testing for these effects in zebrafish requires some detailed analysis as some human genes have two equivalent genes in zebrafish due to their partial genome duplication during evolution. This resulted in the team using a 'tight set' containing only genes with a single equivalent in both human and zebrafish, and a 'broader set' which included genes which have two equivalents in zebrafish. Subsequent testing (see Fig. 1) showed significant enrichment of both sets in the upregulated genes, showing that the TAZ-CAMTA1 transgene (that part of the injected construct that is inserted into the fish's DNA) was having an effect consistent with expectations if it was working.

Testing for TAZ-CAMTA1 expression was also successful, but the team noted that the level of activated TAZ-CAMTA1 when 'switched on' was significantly lower than the level of the transgene control construct seen prior to switching. This was surprising as the analysis of downstream genes had shown a very convincing effect. Further work identified a number of possible causes for this reduced expression of TAZ-CAMTA1 associated with the TAZ-CAMTA1 construct. At the end of the year, the team had made modifications to the construct in new fish and hoped to be able to identify fish where the transgene had inserted successfully (called transmitters) by the end of the first quarter of 2024.

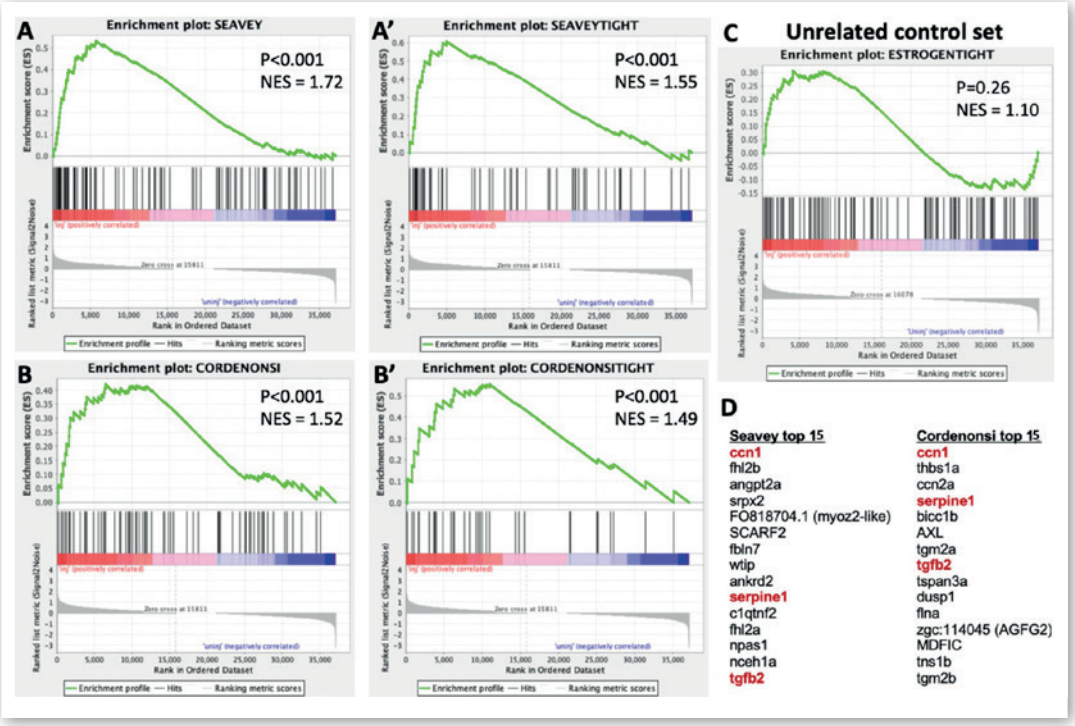


Fig 1 - GSEA analysis results (A,A') - Enrichment plots of both the 'broad' and the 'tight' Zebrafish-Seavey set. We expect that such genes (shown as black lines) will cluster to the left of the graph if there is TAZ-CAMTA1 activity, which can indeed be observed. The same can be seen for the 'broad' and 'tight' Zebrafish-Cordenonsi set. (C) Shows a control set (estrogen responsive genes) as an example of a negative result, black lines are not significantly clustered to the left. (D) List of 15 most responsive genes in each set, shared genes between the sets are in red.

02 EHE Research Continued

The YAP1-TFE3 model

Due to the ongoing difficulties creating zebrafish with a high level of TAZ-CAMTA1 expression, and following discussions with the Charity, it was agreed that the research team should also start to try and create an inducible YAP1-TFE3 line as a potential alternative to creating a TAZ-CAMTA1 EHE model in zebrafish. YAP1-TFE3 is considerably shorter than TAZ-CAMTA1 and may be easier to express at a high level. In addition, it will also be a valuable additional model of this different variant of EHE.

Despite the work on the TAZ-CAMTA1 model, there was still concern that expressing human genes in zebrafish may lead to difficulties in obtaining high expression levels. Therefore, the team decided to make a zebrafish equivalent of the YAP1-TFE3 gene rather than use the human genes as a starting point. This involved aligning the protein sequence of zebrafish YAP1 and TFE3 with their human equivalents and determining where, in the zebrafish sequence, the two genes should be joined. An attempt to amplify these pieces from cDNA failed. Further methods of creating a zebrafish equivalent of YAP1-TFE3 also experienced difficulties and it was therefore decided to synthesize the entire gene. This was done, and the resultant gene has now been cloned into a switchable construct, as was done for TAZ-CAMTA1. The full transformation construct has been injected into embryos and the team have confirmed that the construct can be switched on by co-injection with cre mRNA as shown in Fig. 2.

The team have now obtained the first transgenic embryos from this line and have started to raise larvae. Approximately 20 experimental fish and 20 control fish were raised. However, the team will be generating more in 2024.

The team will also be doing further experiments to establish if YAP1-TFE3 is a more 'potent' oncogene in fish than TAZ-CAMTA1. This has already started with the team co-injecting TAZ-CAMTA1 constructs or YAP1-TFE3 constructs, together with cre mRNA to activate the switches, and testing for levels of TAZ and YAP activity. This experiment suggested that YAP1-TFE3 is indeed more potent. In these experiments, embryos are mosaic, so only some cells in the embryo will have the oncogene expressing construct. It is therefore important to perform such comparisons on the real transgenic embryos that are now available for both TAZ-CAMTA1 and YAP1-TFE3. Once the team have embryos with the new modified TAZ-CAMTA1 construct, these can also be evaluated quickly for improvement of expression.

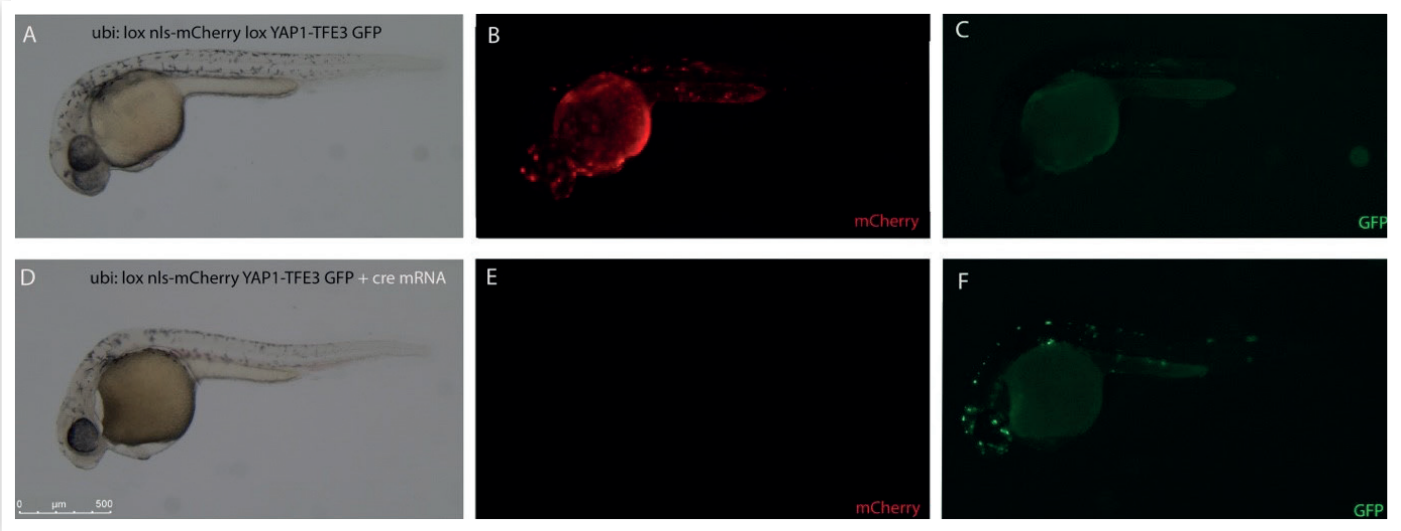
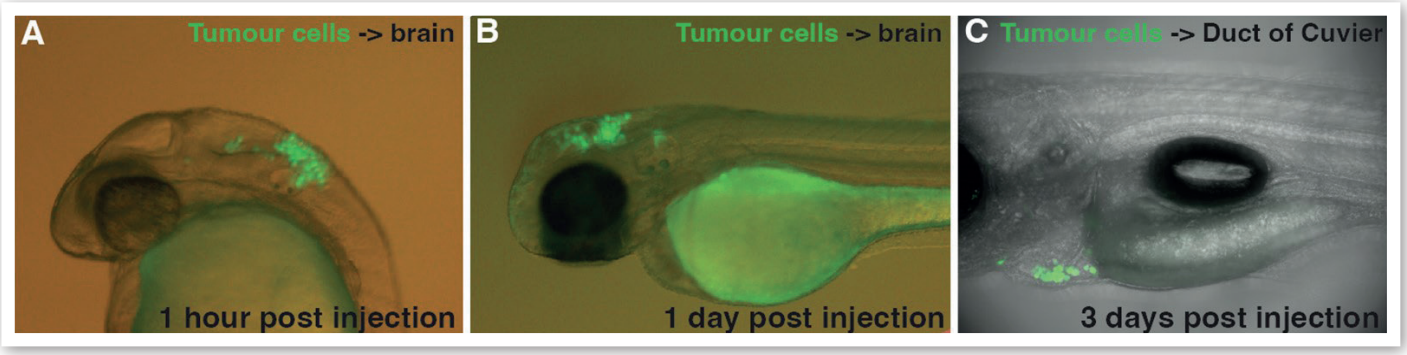


Fig 2 - Switch test for YAP-TFE3 construct - The embryo injected with the construct is shown (A), and verified by mosaic mCherry expression observed as expected (B), but no GFPNeon is visible showing the construct has not been induced (C). When cre mRNA is coinjected (D) mCherry expression is strongly reduced (E) and GFPNeon can be observed (F), showing that the switch is working.

Using xenotransplants; an alternative form of a zebrafish EHE model

Over the course of this project, it has become clear that getting zebrafish to develop EHE tumours remains difficult. If tumours continue to be low in frequency or are slow to develop, it may be difficult to exploit the zebrafish model. Therefore, following consultation with other researchers working with EHE models, the Sheffield team have contacted Dr Pasquali at the Istituto Nazionale dei Tumori (INT) in Milan in order to obtain EHE tumour cells from the EHE cell line developed by the INT research team. These cells can be transplanted into zebrafish larvae (xenotransplants) to study behaviour of these cell lines in a vertebrate *in vivo* environment. At year end the two institutes were initiating the procedures for this transfer.



(Example of a transplant of breast cancer cells is shown below (FvE, unpubl))

Forward focus

The team in Sheffield will be continuing their work on all fronts with the following key objectives:

1. In light of the development of mouse EHE models and human cell lines, a key priority is to initiate the establishment of xenotransplantation models (injecting human cells into fish embryos) as this will provide a different form of model. If successful it also exploits the transparency and size/cost advantage of the fish system most efficiently. Once the team have established good labelling procedures, transplantation sites, cell numbers, etc. and shown that the system can work, the Charity will discuss uses of this type of model with the Sheffield team and other EHE researchers.
2. The research team will continue to directly compare the activity of TAZ-CAMTA1, YAP1-TFE3; and modified versions of TAZ-CAMTA1, to check for comparative levels of YAP/TAZ activity. This will allow them to see whether these alternative approaches have solved the expression issues that have proved to be a significant difficulty in the original TAZ-CAMTA1 model fish. If the expression issue has been resolved, the Charity will need to discuss with the research team and other EHE researchers how such models can best be incorporated into the overall ongoing EHE research initiative.
3. The team will continue to monitor and bank their current zebrafish lines.

02 EHE Research Continued

The UK Biobank, The Royal Marsden Hospital, London

Access to biological samples is a critical component of EHE research initiatives. Tissue, fluid and blood samples provide researchers with critical access to actual EHE biological specimens that allow researchers to: investigate and understand the natural history and development of EHE; investigate new hypotheses; and develop and test both new and existing drugs to see if they will help combat the disease. The Charity was delighted therefore to fund the establishment of the UK National EHE Biobank at the Royal Marsden Hospital.

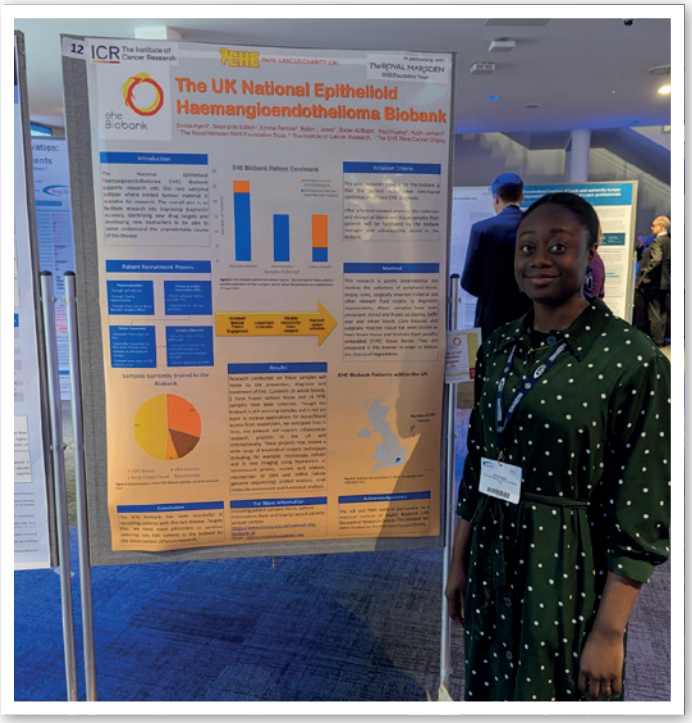
The role of the Biobank is to collate as many tissue, blood and fluid samples from EHE patients as possible. This is because there are only a tiny number of chances to capture EHE tumour and fluid samples each year, due to the extreme rarity of the disease. So all samples possible are captured and stored in the EHE Biobank to facilitate research into the disease.

The EHE Biobank has started well. Thirty nine patients have given consent for their tissue and fluids to be stored within the biobank. As this sarcoma arises in any area of the body, a range of tissue types have been captured and stored in the biobank, primarily consisting of biopsies of the lung, bone, liver and neck. A total of 27 blood samples, 24 archival Formalin-Fixed Paraffin-Embedded (FFPE) samples and 3 live tissue samples were collected in 2023.

The biobank team were also delighted to have the opportunity to present the biobank at the annual British Sarcoma Group (BSG) Conference on 22-23 March 2023. This was an excellent opportunity to promote the biobank because there were many sarcoma clinicians and professionals at the conference. Everyone that attended was able to learn about the EHE Biobank thanks to the excellent poster presented by the biobank team. The poster can be seen on page 2 of this report.

The Charity encourages all EHE patients to consider donating EHE tissue, fluid and blood samples to the EHE Biobank. The biobank team are hugely supportive and helpful and every sample is so important as they are so rare. Patients can contact the charity, visit our website or contact the Tissue Manager at the Royal Marsden Hospital if they have any questions or want to discuss any issues about the biobank.

ehe Biobank



Eniola Ayeni, Tissue Manager at the Sarcoma Unit, Royal Marsden Hospital at the. BSG conference

Significant EHE research focus continues at INT

The significant focus on EHE research, led by Dr Silvia Stacchiotti and Dr Nadi Zaffaroni at Istituto Nazionale dei Tumori (INT) in Milan continued through 2023. This programme focused on two main elements. The first involved INT's collaboration with the Royal Marsden Hospital and Institute of Cancer Research in London, a six-part multi-faceted research programme, including the establishment of a prospective EHE study and the identification of EHE biomarkers. The second is the setting up and ongoing administration of the world's first multi-centred prospective observational registry for EHE.

Multi-faceted research collaboration

The overall research program entitled *'Evaluation of Cytokines and Hormones as Biomarkers for EHE'* is a multi-centre collaborative project that is comprised of six key objectives. These objectives or projects can be summarised as follows:

Project 1: the identification and validation of novel circulating and tissue biomarkers (prognosticators and predictors of response to medical agents) to inform patient management as well as potential therapeutic targets;

Project 2: the development of patient-derived xenograft (PDX) models;

Project 3: the assessment of the activity of drugs relevant for the disease;

Project 4: the generation of PDX-derived cell lines to investigate the cellular and molecular determinants of drug activity and to be submitted to a CRISPR whole genome screen to identify new therapeutic targets;

Project 5: the dentification and evaluation of miRNAs;

Project 6: the description of the radiologic characteristics of EHE and their correlation with the clinical outcome.

This overall research programme is also supported and made feasible through the establishment of an observational study involving existing EHE patients at the Royal Marsden Hospital and INT in Milan. At year end the study had almost reached its initial target cohort of 50 patients, providing a material database and ongoing longitudinal blood samples from patients which have, for example, been instrumental in the biomarker arm of this research.

Updates of these different projects are provided below.

Project 1:
The assessment of circulating cytokines, hormones (and miRNAs), and ERα, Erβ and G-Protein-coupled Estrogen Receptor (GPER) expression etc and the identification of a novel biomarker for EHE;

Using a protein array able to simultaneously detect the expression of a hundred different cytokines in plasma samples of 15 EHE patients and 6 healthy individuals, a small panel of inflammatory cytokines was found to be differentially expressed. Among them we focused on Growth and Differentiation Factor-15 (GDF-15), a member of the TGF-β super-family, which has multiple roles in a wide variety of cellular processes. Using a specific ELISA assay, we looked at the concentration of circulating GDF-15 in a retrospective series of 23 EHE patients and observed a statistically significant association of GDF-15 levels with EHE aggressiveness. This result was confirmed in a second cohort of 21 EHE patients prospectively collected within the currently ongoing observational study.

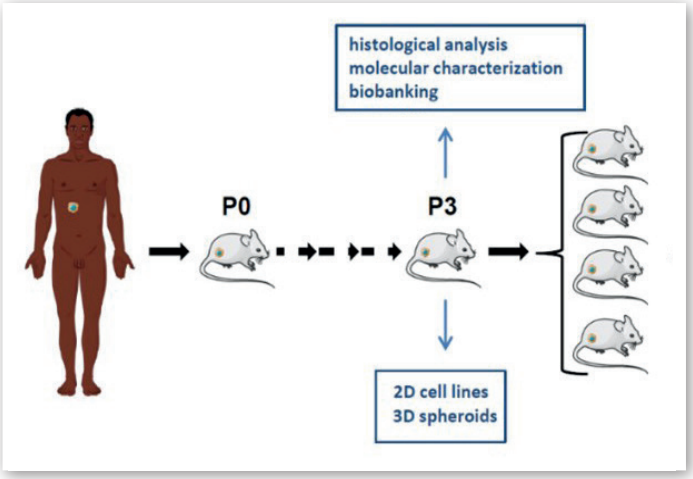
The assessment of circulating hormones and tissue expression of ERα, Erβ and GPER is ongoing.

The assessment of miRNAs is undertaken in Project 5.

02 EHE Research Continued

Project 2:
Development of additional PDX models;

Thus far only one fully established EHE PDX model has been developed, whose ability to reproduce the characteristics of the originating clinical tumor has been confirmed in terms of histo-morphology, presence of the *WWTR(TAZ)::CAMTA1,* overall transcriptomic profile (as detected by RNA-seq) and presence of *CDKN2A* homozygous deletion. A cell line was established following disaggregation of the EHE PDX.



Project 3:
Assessment of activity of drugs;

The PDX model was used to comparatively assess the activity of doxorubicin and sirolimus (at different doses). Doxorubicin showed almost negligible activity whereas sirolimus caused a dose-dependent tumor volume inhibition in treated mice and induced the down-regulation of mTOR signaling. The PDX is currently being used to assess the activity of inhibitors of the Hippo pathway, such as the TEAD family of transcription factors.

This PDX and the corresponding cell line were exploited to provide further evidence supporting the value of GDF-15 in EHE. GDF-15 was detected in the medium of the EHE cell line as well as in the blood of EHE PDX but not in healthy mice or in mice carrying another sarcoma type, confirming that the cytokine was released by the EHE. Interestingly, we found that sirolimus decreased the abundance of GDF-15 in our *in vitro* and *in vivo* EHE models.

Project 4:
Use of CRISPR in cell lines to help identify genes that confer drug resistance or sensitivity;

The EHE cell lines will soon be provided to Dr Paul Huang (ICR, London) in 2024 to start the CRISPR-based experiments.

Project 5:
Identification and evaluation of miRNAs

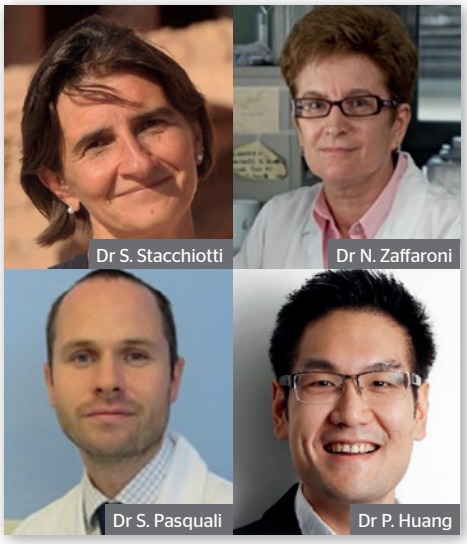
The expression profiling of plasmatic miRNAs has been initially carried out using the OpenArray Technology (which evaluate the expression of 754 different miRNAs) in the retrospective series of 23 EHE patients. Six miRNAs were found to be differentially expressed between patients with indolent and aggressive EHE. In order to evaluate the overall miRNome (global profile of expressed miRNAs), we repeated the analysis on both retrospective and prospective series of patients by miRNA-seq. The results are currently being analyzed by a dedicated bioinformatician.

Project 6:
Establishment and assessment of a radiological database.

The clinically-annotated radiologic scan collection on the study platform has been started. Response assessment is also collected by REDcap CRFs. The data analysis is planned after the end of the study.

The overall project is certainly producing some good results. The research team remain excited as they believe that within a few years, the data collected within this study will provide: (1) a better picture of the disease to inform decisions on how to treat patients with EHE and to define prognoses based on disease presentation; and (2) preclinical and clinical data to identify new treatment options and design better prospective clinical studies.

Dr Silvia Stacchiotti and Dr Nadia Zaffaroni are joint Principle Investigators (PIs) of the research taking place at INT; while Dr Paul Huang is PI for the ICR, London. Dr Sandro Pasquali is also a key member of the INT research team.

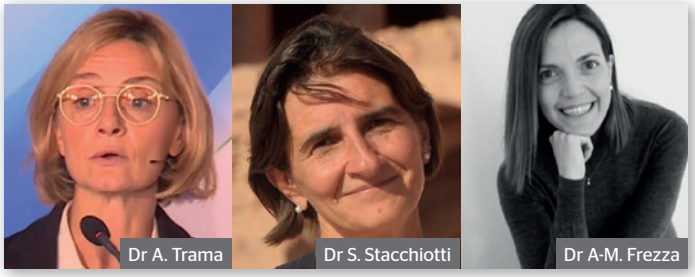


The EHE pan-European prospective observational registry

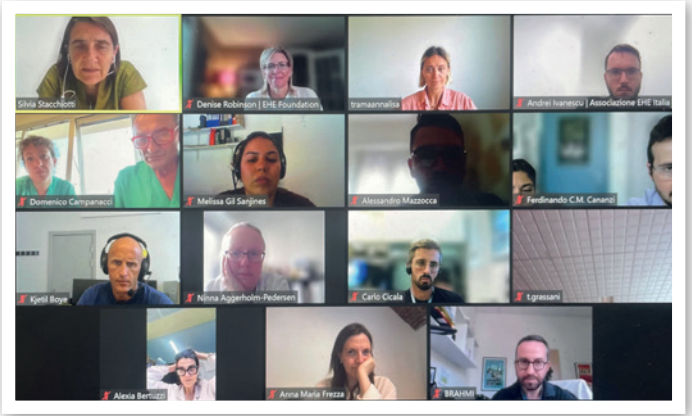
A cancer registry is an information system designed for the collection, storage, and management of data on persons with cancer. Registries for rare diseases such as EHE are very unusual as, to provide meaningful sets of data, patients from multiple centres need to be included. The need for pan-European registries for rare cancers was recognised by the European Reference Network in Rare Adult Solid Cancers (EURACAN). The STARTER project was therefore established on the basis that gathering data on rare cancers will support research, help to develop and/or improve clinical practice guidelines, support multidisciplinary discussion and consultations for patients with rare cancers, and ultimately improve quality of care across Europe. Setting up the STARTER project was also hugely important, as the project would define the registry model, set up the appropriate IT infrastructure, define and implement the legal and ethical framework, develop the registry governance, and initiate the first registries.

The Charity was therefore delighted when it was informed that EHE had been selected to be the first rare cancer within this important new data-gathering initiative, and immediately committed to funding the setting up of the first such prospective observational registry for the disease. The registry is being led and managed by Dr Annalisa Trama and the team at INT in Milan, Italy. The registry will be maintained within the European STARTER project and patients will be enrolled and data contributed by clinical providers at the participating hospitals/centres.

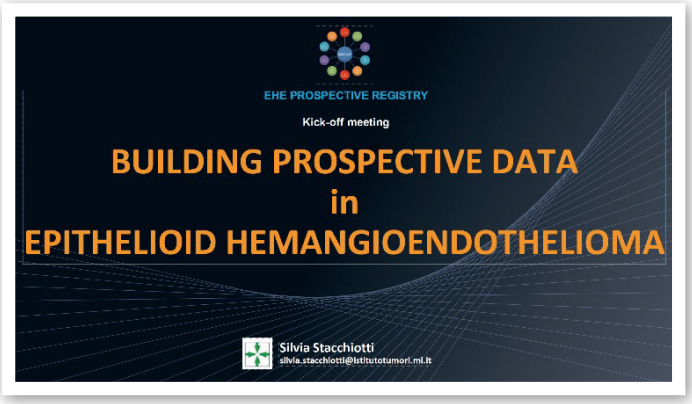
The EHE Registry project is being led by Dr Annalisa Trama and Dr Silvia Stacchiotti. Dr Anna-Maria Frezza is also a key member of the research team.



INT held the first briefing session of European hospitals that may be interested in joining the study in early 2023. A virtual zoom meeting was held during which Dr Stacchiotti, Dr Anna-Maria Frezza and Dr Annalisa Trama led a presentation of the study and invited expressions of interest. Subsequent interest levels were high and when the informal launch of the world's first ever multi-centre prospective registry for EHE took place at INT in September, a total of 21 hospitals had signed up.



There was understandably a lot of excitement as the INT team had been working hard over an extended period to develop the registry. This had not been easy due to the heterogenous nature of EHE, which presented a major challenge to all involved in creating the appropriate data capture infrastructure.



02 EHE Research Continued

Hugh Leonard was also thrilled to see the large number of institutes that had joined the project:

"Joining the project is not compulsory. Each institute that is eligible has to make its own decision as to whether to join the registry or not, so we were delighted to see that 21 hospitals had already joined the project. The registry team hope to add more hospitals in the future, including international centres who have expressed interest, but the immediate focus will be on getting the project up and running with the 21 initial participating institutions.

Capturing this data is so important as the design focuses on EHE, and over time the study will provide high-quality valuable data important for generating hypotheses and further interrogation of disease treatments. This was why we did not hesitate to provide funding to INT for the registry when we were approached."

The Charity congratulated the INT team for their dedication and hard work in getting the EHE prospective registry up and running, and are confident that this study will play an important part in the future development of the understanding and treatment of EHE.

Progress review

As part of its overall research management programme, the Charity coordinates periodic in-person reviews of progress. Such a review of the INT research was undertaken in September in Milan. The Charity invited Denise Robinson, Director of Research at The EHE Foundation in the US and Andrei Ivanescu, President of EHE Italia, to join the review process to maximise the sharing of information and the learning for the different EHE entities.

The meeting involved the whole INT research team as well as Dr Paul Huang from the Institute of Cancer Research, joint PI of the project. The team provided an excellent review of their work and a lively and robust discussion of the ongoing research was enjoyed by all.

Building an EHE research strategy

The meetings in Milan, involving the Charity, The EHE Foundation and EHE Italia, together with leading EHE clinicians and researchers, were a perfect opportunity to discuss the important issue of developing a broad and coherent EHE research strategy. Hugh Leonard explained:

"The EHE global community has done an extraordinary job of promoting research into EHE and getting an exciting portfolio of EHE research up and running. This of course has only been possible because of major donations and the amazing grassroots fundraising effort of so many in our global patient community and their supporters.

With continued successful fundraising, it is imperative that we develop a pro-active research agenda that prioritises areas where there are gaps in our knowledge, to bring forth critical data and advances in the development of treatments for EHE. This will also allow us to develop and promote a coherent multi-year research programme and associated budgets which we hope will in turn allow us to engage with larger sources of funding."

The goal is to produce a research strategy that will guide the EHE Group's research planning and help deliver the EHE Group's collective research goals, namely to find effective treatments for EHE. To date, we have funded amazing projects that have advanced knowledge in EHE; now is an appropriate time to assess the gaps in knowledge that need to be addressed in order to accelerate research that ultimately will improve the lives of people diagnosed and living with EHE.

These strategic discussions in Milan were the first in which the EHE Group had been able to engage with clinicians and researchers who are actively working with EHE, to seek their input and direction on an overall EHE research strategy. We could not be more grateful to Drs Stacchiotti, Frezza, Zaffaroni, Pasquali (all INT) and Huang (ICR) for giving us a whole afternoon to discuss and review our EHE research objectives. The debate was once again lively and excellent suggestions and observations were provided. We are now moving forward with further engagement with clinicians planned in 2024.

But it is not just the opinions of clinicians and researchers that the EHE Group want to hear. It is so important that we engage with our global patient community and also seek their input to this research process. The patients' view is very powerful when collectively voiced, and there is no group more vested in achieving positive outcomes than the global EHE community. We will ensure that they are involved as we move forward with this initiative.

Drs Stacchiotti, Zaffaroni, Pasquali, Huang and Frezza discussing an overall EHE research programme with Hugh Leonard, Denise Robinson and Andrei Ivanescu in Milan.

EHE Global Patient Registry is growing

The Charity was delighted at the end of the year to see the excellent early progress with regard to the EHE Global Patient Registry that was established and is administered by The EHE Foundation in the USA. More than 200 people representing 19 countries had joined the EHE Global Patient Registry. This is a wonderful start, but we want and need many more to join the registry. It is hard to overstate the importance and benefit of every single patient contribution.

Denise Robinson, Director of Research at The EHE Foundation and PI for the registry, explained:

"The value and benefit of a registry is directly related to the number of patients that are included. So please, if you haven't already joined, we encourage YOU to please consider joining today! Go to https://eheregistry.iamrare.org/ to find out more and register to join. Your input will help doctors, researchers, and other patients know, for example, how many people have EHE that is like your disease. By collating and analysing this data your input may lead to break-through understanding of EHE. Please don't just leave it to others. Join the registry today."

The Charity is actively promoting the registry and hopes that doctors and hospitals involved with sarcoma will also encourage participation. The Charity is also ready to assist anybody who has any questions or concerns about the registry, and can be contacted through the Charity website.

03 Fundraising and Finance

2023 has been another good year for the Charity. Our supporters have once again organised their own fundraising events while also engaging enthusiastically in the two big events the Charity coordinates: the London Landmarks Half Marathon and the Ride London Essex 100 cycling sportive. This has been particularly important as most charities continue to experience reduced levels of donations due to the ongoing cost-of-living crisis. The simple fact is that there is less available money for donation to great causes, and so we could not be more grateful to our supporters who have continued to work hard to raise the funding we need to drive our EHE research.

An example of the excellent support we continue to enjoy was the fact that we equalled our record for the number of runners taking part in the London Landmarks Half Marathon. Putting out a team of 50 runners, was very exciting. We want to thank EHE patient, Paul Dean, and Ginger's Fitness owner Paul Preston for the marvellous work they did, each organising teams of close to 20 runners.

Although fundraising may be slightly more challenging now, we want to reassure everybody that there is no financial risk to our activities, and especially to our ongoing research. The Charity is run entirely by volunteers and so our Charity running costs are very small indeed. As for our ongoing research programmes, our Charity governance prohibits us from committing to research expenditure unless we already have the full amount we are committing to in our account and unallocated. So today we continue to hold in our Charity bank account sufficient funds to cover all future research that we have contracted for. This means that the new funds raised each year are available to support additional research, which is excellent and enables us to keep moving forward.

Review by Jeff Collins

The fundraisers

As in all previous years, the foundation of our fundraising is our wonderful patient community and their supporters and individual networks. We have already mentioned the excellent numbers of runners who took part in the London Landmarks Half Marathon. We also had a team of 17 riders who took on the Ride London Essex 100 mile cycling sportive in May, including Hugh, our Chair of Trustees, and his son Sam. Not only did these wonderful people either run or ride, but many organised fundraising events themselves to supplement their fundraising, including cake sales, mini raffles and quiz nights.

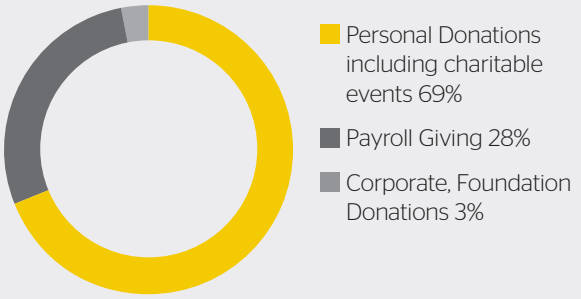
Fundraising is not just about the events coordinated by the Charity, however. The amazing sums we raise are the result of many small events and kind donations, regular monthly giving, employee matching, when available, etc. Every penny counts and there is no sum or donation that is too small to matter. In 2023 we saw Kelly Denton and Laptops and Lipstick organising their brilliant quiz night. The team at Rolls Royce Submarines in Derby organised their second annual quiz night in memory of their colleague, Hazel Peak. Hannah held an amazing concert at Pizza Express in support of her cousin who has EHE. Steph Scott and Adam Patrick organised an Easter Basket raffle. Mia Sallet ran 100 km over a month to raise funds in memory of her dear friend Isabelle, and David Thomas took on a 10k run to raise funds in memory of Janet Griffiths. We even had a Tyson Fury boxing glove to raffle. These are just examples of some of the brilliant events and activities that people organised to raise funds for EHE research, and for which we could not be more grateful.

Key objectives

In the 2023 calendar year our supporters raised a total of £53,400 for the Charity's key objectives. The sources of these funds are summarised on the pie chart.

During 2023, the Charity provided at total of £146,500 for EHE research. This sum comprised £109,900 in sole-funded projects at Manchester University (closing out our PhD on molecular and cellular features of EHE); Sheffield University (Zebrafish model); and INT/Royal Marsden Hospital/Institute of Cancer Research (UK national EHE biobanking and pan-European prospective registry of EHE patients); and £36,600 in projects jointly funded with The EHE Foundation (USA) at INT/Royal Marsden Hospital/Institute of Cancer Research (biomarkers, observational study of EHE patients).

Source of funds



Administration/business running costs

In 2023, we once again received the generous support of a single donor who funded 100% of our 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 2024.

The Charity received funding of £20,500 for its administration and business running costs account. During 2023, £25,100 of expenses had been incurred, which included an accrual of £1,200 for the independent examiner's fee. The remaining £23,900 funded fundraising events and support along with costs to update and improve the Charity's website and includes other administrative costs such as publishing and design costs and website maintenance.

"We are once again so grateful to our patient community, their supporters, and the corporate groups and foundations who supported us through the year. We are also grateful to all those who helped us and volunteered so that we could keep our Charity running costs as low as possible. I also want to thank all the companies and service providers who have supported us with their services, often provided at no cost or reduced cost.

We predicted in 2022 that 2023 and years beyond may continue to be financially challenging, and that outlook has not changed. Our Charity governance requires us to ensure that we already hold the funds for any funding commitments we enter into for exactly this type of situation, with the result that the Charity can maintain its robust financial position. We will also continue to manage all funds with the utmost care to ensure that we get the maximum benefit from every pound that our supporters have so generously donated."

Jeff Collins

Wonderful support for EHE in 2023

The following pages highlight some of the amazing events that raised funds for the Charity in 2023.

Laptops & Lipstick in action

'Laptops & Lipstick' is a business networking group for women that meets in Beckenham, Kent. In late 2021 the group choose EHERCC as its charity to support in 2022, thanks to the introduction provided by Kelly Denton, who lives in the area and whose teenage daughter has EHE. Kelly was delighted to then hear that the Charity's membership of the group was being extended for a further year, and in February 2023 they held their second annual Quiz Night to raise funds for EHE research.

The Quiz Night packed out the pub. Kelly and the Laptops & Lipstick group had also collected some wonderful raffle prizes which added to the fundraising. Kelly explained:

"Last night my local community all came together for a quiz night in support of EHE research. Amazingly, we raised over £2000. Hugh Leonard made a guest appearance and gave a fantastic speech explaining why these kind of fundraisers are so important. It was truly overwhelming to see how many people care."

Hugh was also hugely grateful:

"It was lovely to meet Kelly's family, their supporters, and some of the Laptops & Lipstick members, who have been brilliant. I was able to personally thank them for their ongoing support and explain more about EHE. With EHE being a predominantly female cancer, I think it is wonderful when we have a female-focused group that wants to help and support our work. It was also a very noisy and vibrant evening with the pub packed. I also had a wonderful opportunity over the meal period to tell them about the Charity, EHE and the work we do."

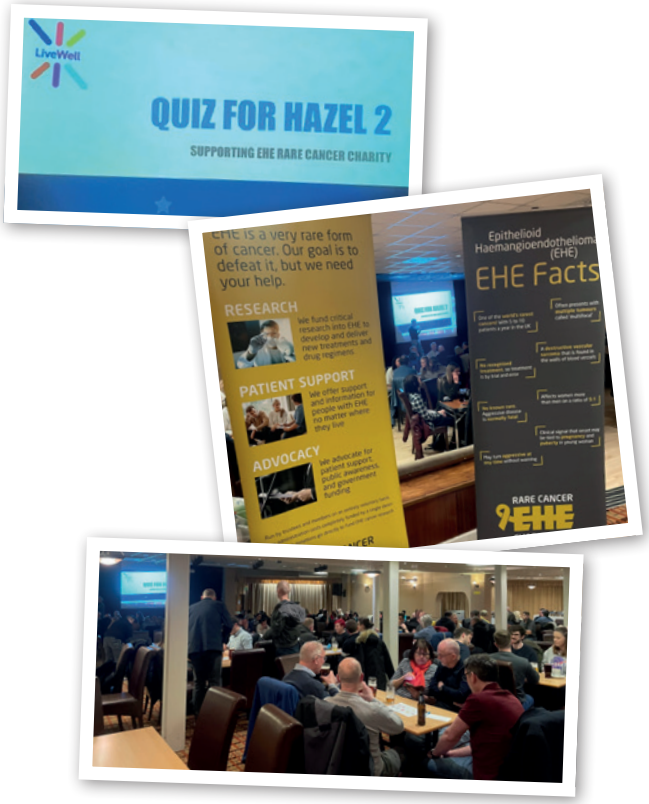
We want to congratulate Kelly and Laptops & Lipstick for organising such a positive event, and join Kelly and Hugh in thanking them for their ongoing support. We are also delighted to be able to share some photos of the evening.

Hazel remembered

At the start of 2022 the EHE UK patient community lost the lovely Hazel Peak. Her colleagues at Rolls Royce Submarines in Derby in the UK were understandably shattered. But they continued with their planned quiz night which Hugh Leonard from the Charity had the honour to attend. As the anniversary of Hazel leaving us approached, those same lovely colleagues decided that they wanted to continue to support the Charity, in memory of Hazel. Hugh explained:

"Hazel's wonderful colleagues decided that they wanted to repeat the process and so organised the 'Quiz for Hazel 2' in her memory. I was able to be there again and this time talked about our ongoing research, which their donations from 2022 had helped fund. Hazel's family attended also, which was lovely. It was certainly an emotional evening."

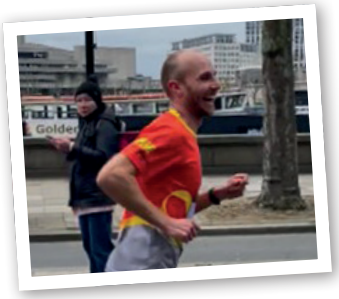
The event raised more than £3,000 for EHE research, thanks to the great organisation and the unbelievable generosity of all who took part. This sum was also matched by a kind donor, taking the total raised to more than £6,000. We could not be more grateful to Hazel's colleagues and Rolls Royce Submarines for all they have done.



2023 London Landmarks Half Marathon

The 2023 London Landmarks Half Marathon (LLHM) took place in April, and the Charity had a team of 50 people running for us, both to spread awareness of EHE and to raise critically needed research funding. Sally Baker, an EHE patient and Trustee of the Charity commented:

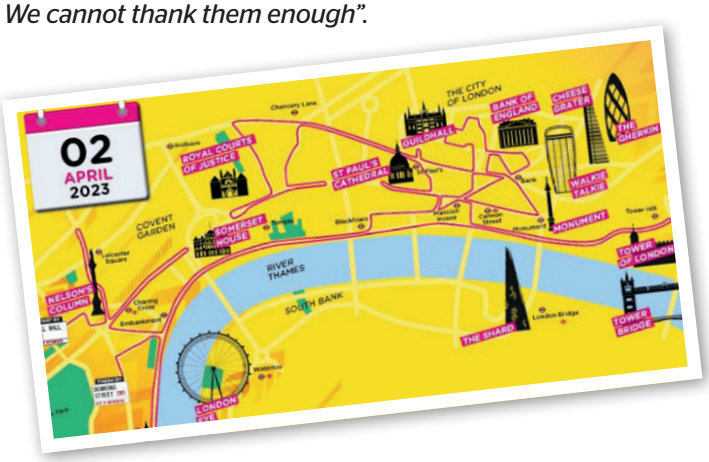
"We had two teams of 19 within our 50 runners. Paul Dean, a fellow EHE patient, had a team of 19 runners, and Ginger's Fitness, an outdoor fitness group from south London run by Paul Preston, also had 19 runners, supporting Kelly and her daughter, also an EHE patient. The other 12 who made up our 50 were all running in support of UK patients."



It was a fantastic day, not too hot, and the rain stayed away. Paul Dean was the star of the show, running the course in an extraordinary 1 hour and 21 minutes. Amazingly, Paul was disappointed as he had set his heart on finishing under 1 hour 20 minutes.

Each year the Charity sets up a cheer station on the course and this becomes a focal point for people who want to come and watch. Hugh Leonard loves the spirit of the event:

"I find it inspiring to see so many people running for so many fantastic causes. And having 50 of those runners representing our EHE global community is really special. We cannot thank them enough".



03 Fundraising and Finance Continued

LLHM pre-race fundraising

Some of those taking party in the 2023 LLHM were organising events in the build up to the race, using the half marathon as a catalyst for fundraising.

Paul Dean's brilliant supporters are one group that have organised a pre-race fundraising event, as Paul explained:

"Just a few days before the run, at the end of March, Lucy Calrow organised a pre-run EHE quiz and bingo night which Simon and Lesley Calrow hosted at the Fordhouses Cricket Club to raise funds for EHE research. Around 100 people took part and raised £520 for EHE research. It reminded me once again that I have some truly awesome support, but to be honest, I never ever forget that!"

Paul provided us with these great photos of the night. We want to join Paul in thanking everybody who took part and of course all those who ran.

An Easter Basket

Adam Patrick ran the LLHM with Jessica Rawdon and Adam and Jayne Sausby-Gallimore in memory of their dear friend Allana Parker, who many of our EHE family knew well. They decided to boost fundraising by raffling an Easter chocolate basket. We thought that was a great idea. We also loved Adam bringing his gorgeous new arrival to the race – the smallest ever person to wear a Charity running shirt!

Ginger's Fitness including cakes

Ginger's Fitness is an outdoor fitness group based in south London, who also had a team of runners participating in the LLHM in support of Kelly Denton, whose teenage daughter has EHE. As part of their campaign the group organised a cake sale in their local park on a Sunday. Paul Preston who runs Ginger's Fitness explained:

"We held the cake sale in the park immediately after our Ginger's Fitness class to boost our fundraising for the LLHM. Nineteen of the Ginger's Fitness community are running for the EHE Rare Cancer Charity. Cakes were available from 9.30 am. We had soft drinks, coffee, prosecco and bucks fizz all available for a donation of the person's choice. We asked people to tell their friends and family and to bring lots of cash to donate. It was great fun and we raised over £700 from this one event which was wonderful."

Paul wanted to say a huge thank you to Anja Workman, from Anja's Gingerbread, for baking so many brilliant cakes and gingerbread men for the sale. We loved the EHE gingerbread men runners.

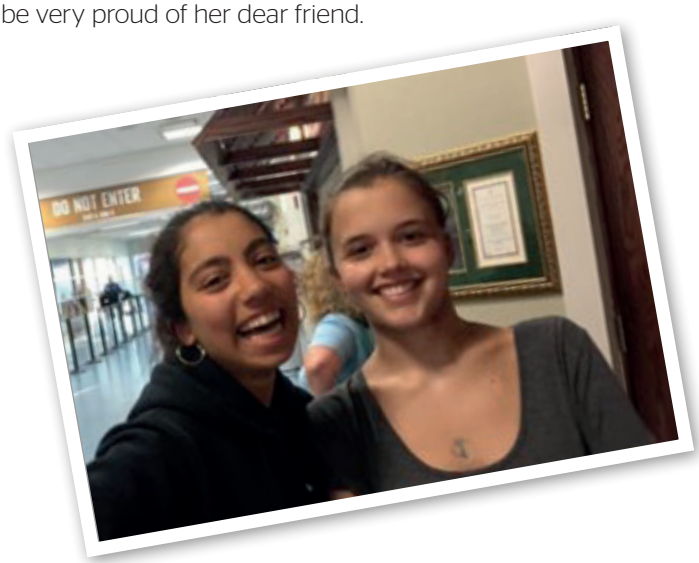
We want to thank everybody in Paul Dean's team, in Ginger's Fitness's team, Adam and all the other runners and supporters for their brilliant efforts.

Mia ran 100 km for her 'Zaza'

When Mia Sallet lost her dear friend Isabelle to EHE in February 2018 she, like Isabelle's family, was utterly devastated. Below are her words:

"Hello everyone. I will be running 100km in a month in memory of my best friend Isabelle, gone too soon. My Zaza, my Isabelle, I still think of you every day, more than once a day,. I miss you just as much as the day you left us, and will always have a hole in my heart, a deep sadness that will stay with me forever. I am doing this for you, for all the wonderful years we spent together, and all the memories I hold on to so so tight, it was too short. I hope you'll be proud, because quite frankly, running is not my favourite sport in the world, except maybe in 6ème with the cross country ;)! I have been wanting to do something in your memory, and to celebrate you for a long time. Thank you to Andy, for asking me to run the Asics 10k with him, which will be part of my 100km challenge within a month. You've been gone 5 years, and it feels like yesterday. I am doing this for you, for your family, for all those who love and miss you and for EHE. Miss you forever mon Isabelle, this is for you. Mia".

Mia ran her 100km in memory of Isabelle who will be very proud of her dear friend.



03 Fundraising and Finance Continued

100 miles cycled for EHE research

Each year the Charity secures a small number of places in the Ride London Essex 100 cycling sportive, where participants cycle 100 miles on closed and empty roads. The event starts in central London and goes north east out into Essex before returning to London to finish on the iconic Tower Bridge.

Why do people ride 100 miles? Simply to raise funds for one of a huge number of fantastic causes, all of which are desperate for funding. This year the Charity had 20 places in the event and had a great turn out. Hugh Leonard, Chair of Trustees of the Charity, took part again together with his son Sam, all in support of Sally Baker, Hugh's wife and Sam's mother, an EHE patient and Trustee of the Charity.

Sam Leonard said:

"Wow, that was fantastic but very very tiring! The last 10 miles coming back into London were very hard indeed with a series of flyovers to get over. But it was definitely worth it as we have been able to raise a lot of funding for EHE research."

Paul Dean was again the star for the EHE team, as he was in the LLHM. On his bike, Paul completed the course in 4hrs 48 mins, averaging more than 20 miles an hour over the whole ride. Unbelievable.

We want to congratulate all the riders for their brilliant performance and for helping to raise such badly needed funding for EHE research.

Throwing punches at EHE!

Many of our EHE global community use a boxing glove or clenched fist emoji when they post about their fight with EHE. Personalising the disease gives it a targetable characteristic. So we all smiled when Kelly Denton posted news of her latest fundraising idea:

"Hey Guys, believe it or not I have a signed Tyson Fury boxing glove which I am going to raffle for EHE, so please buy a ticket if you can."

There was certainly a lot of interest because there will always be excitement when such an iconic item becomes available from a current reigning world heavy weight boxing champion. Kelly was certainly not disappointed with the final result:

"Amazingly Tyson's glove helped me raise more than £500 for EHE research! Let's hope that money helps towards hitting EHE harder than a Tyson Fury punch!"

A stunning evening

Kelly Denton's family have been brilliant supporters of the EHE cause ever since her daughter was diagnosed with EHE. So we were not surprised when one of her relatives, Hannah, held a small and intimate concert in central London one Sunday night to raise funds for the Charity and for EHE research. Hannah had previously participated in and done very well on The Voice, a prime time music talent show, so those present were not surprised to be blown away by her phenomenal voice. Hannah was brilliantly supported by two other young singers, as well as her husband and brother, both talented musicians.

It was also great as there were four EHE patients present on the night, Sally Baker, Kim Alexander-Bird, Michaela Murphy, and Kelly's daughter. All agreed that is was lovely to be able to meet one another and their respective partners.

Hugh Leonard also had the chance to say a few words about EHE and the Charity at the start of the concert. At the end of the night Hannah had raised more than £1,000, an amazing achievement.

We want to thank Kelly and Hannah for organising this great event. Our community motto is ***Just Live,*** something that those present on the night very definitely lived up to.

Darren Thomas runs in memory of Janet

We always find it moving to see people taking on a fundraising event in memory of somebody who has lost their life to EHE. In September, Colin Griffiths posted news of Darren Thomas's Swansea Bay 10k run in memory of Colin's wife, Janet, who passed away at the end of 2022.

"As many of you know, Jan lost her brave fight with EHE Cancer in December 2022. In January 2023, 6 of our fittest lads (Dai, Darren, Scott, Stephen, Colin and Simon) started training for the Swansea Bay 10k to raise funds and awareness for this rare cancer. Unfortunately over the training period, injuries led to 5 having to drop out leaving just 1 - well done Darren! Darren will be taking part in the Swansea Bay 10k on Sunday 17th September to raise funds and awareness for The EHE Rare Cancer Charity UK. We as a family are greatly appreciative and if you would also like to support Darren and provide much needed funds for this charity please use their Just Giving page."

Darren raised nearly £1,000 for EHE research. We want to congratulate Darren for this fantastic effort. We are sure that Janet was watching and willing him on.

EHE Rare Cancer Charity UK

Financial Accounts for 2023

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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 2023.

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: 22 October 2024

EHE Rare Cancer Charity (UK)
Statement of Financial Activities
for the period ended 31 December 2023

	Notes	Unrestricted funds £	Restricted funds £	**Total 2023 £**	Total 2022 £
Incoming resources:					
Donations	2	53,387	20,450	**73,837**	106,559
Total incoming resources		**53,387**	**20,450**	**73,837**	106,559
Resources expended:					
Costs of generating donations		1,326	9,142	**10,468**	2,374
Charitable activities		146,463	-	**146,463**	155,199
Governance costs		-	1,200	**1,200**	1,200
Other administrative costs		72	14,767	**14,839**	4,9487
Total resources expended	3	**147,861**	**25,109**	**172,970**	163,721
Net surplus for the year		**(94,474)**	**(4,659)**	**(99,133)**	(57,162)
Transfer between funds		**-**	**-**	**-**	-
Balance brought forward		262,209	8,680	**270,889**	328,051
Funds carried forward	8	**167,735**	**4,021**	**171,756**	270,889

Funds carried forward for 2023 £171,756

EHE Rare Cancer Charity (UK)
Balance Sheet
as at 31 December 2023

	Notes	Unrestricted funds £	Restricted funds £	**Total 2023 £**	Total 2022 £
Current assets					
Debtors	5,9	128,246	-	**128,246**	212,171
Cash at bank and in hand		181,683	19,727	**201,410**	323,495
Total current assets		309,929	19,727	**329,656**	535,666
Creditors: amounts falling due within one year	6,9	(104,812)	(15,706)	**(120,518)**	(167,165)
Net current assets (liabilities)		**205,117**	**4,021**	**209,138**	368,501
Creditors: amounts falling due after one year	7,9	**(37,382)**	**-**	**(37,382)**	(97,612)
Net assets (liabilities)		**167,735**	**4,021**	**171,756**	270,889
Funds carried forward					
Unrestricted funds		167,735	-	**167,735**	262,209
Restricted funds		-	4,021	**4,021**	8,680
Total funds	8	**167,735**	**4,021**	**171,756**	270,889

The Charities Act 2011 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 21 October 2024 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 2023

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:

	2023 £	2022 £
Unrestricted funds:		
Personal donations including fundraising events	**50,949**	62,593
Corporate and Foundation donations	**2,438**	33,216
	53,387	95,809
Restricted funds:		
Administration fund	**20,450**	10,750
	20,450	10,750

3 Analysis of resources expended

	Unrestricted funds £	Restricted funds £	**Total 2023 £**	Total 2022 £
Costs of generating donations:				
Just giving fees	394	562	**956**	1,040
Fundraising event entry and other fundraising fees	-	8,580	**8,580**	-
Credit card and other processing fees	932	-	**932**	1,334
	1,326	**9,142**	**10,468**	2,374
Costs of charitable activities:				
University of Manchester PhD Study	4,314	-	**4,314**	33,001
Royal Marsden Biobank	19,719	-	**19,719**	16,450
Zebrafish Study University of Sheffield	58,097	-	**58,097**	55,198
Fondazione IRCCS and ICR Biomarkers	36,538	-	**36,538**	36,608
Fondazione Prospective Study	27,795	-	**27,795**	13,942
	146,463	**-**	**146,463**	155,199
Governance costs:				
Independent examiners' fee	-	1,200	**1,200**	1,200
	-	**1,200**	**1,200**	1,200
Other administrative costs:				
Design and publishing	-	4,675	**4,675**	2,683
Website maintenance	-	10,020	**10,020**	2,088
Bank fees	72	72	**144**	177
	72	**14,767**	**14,839**	*4,948*

Trustees' expenses

No expenses were incurred by Trustees during the period and reimbursed by the Charity (2022 – £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 2023

5 Debtors

	Unrestricted funds £	Restricted funds £	**Total 2023 £**	Total 2022 £
Prepayment to Royal Marsden	42,442	-	**42,442**	60,685
Prepayment to Fondazione IRCSS Istituto Nazionale Dei Tumori	52,654	-	**52,654**	118,526
Prepayment to the University of Sheffield	29,382	-	**29,382**	28,715
Other debtors	3,768	-	**3,768**	4,245
	128,246	**-**	**128,246**	212,171

Included within the debtors figures above are amounts of £97,612 (2021 – £25,055) due after more than one year.

6 Creditors: amounts falling due within one year

	Unrestricted funds £	Restricted funds £	**Total 2023 £**	Total 2022 £
University of Manchester	-	-	**-**	3,820
Royal Marsden	23,717	-	**23,717**	28,050
Fondazione IRCSS Istituto Nazionale Dei Tumori	51,457	-	**51,457**	95,433
University of Sheffield	29,382	-	**29,382**	28,715
Accrued independent examiners'	-	2,400	**2,400**	2,400
Other creditors	256	13,306	**13,562**	8,747
	104,812	**15,706**	**120,518**	167,165

7 Creditors: amounts falling due after one year

	Unrestricted funds £	Restricted funds £	**Total 2023 £**	Total 2022 £
Fondazione IRCSS Istituto Nazionale Dei Tumori	12,712	-	**12,712**	54,207
Royal Marsden	24,670	-	**24,670**	43,405
	37,382	**-**	**37,382**	97,612

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 and July 2021, a second and third phase of the project was agreed and in July 2022, 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 2021. The total cost of the project is £57,430 and commenced in July 2022. In 2022, £55,198 of payments were made and recorded as charitable activity cost (2021 – £26,483). The amounts committed to for 2023 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. In 2023, a final payment of £4,314 was made and recorded as charitable activity cost (2022 – payments of £29,181 and expense of £33,001). The project is now complete.

In March 2021, the Charity agreed to fund costs associated with the establishment and administration of an EHE Biobank and the provision of a Tissue Manager with the **Royal Marsden Cancer Charity and the Royal Marsden NHS Foundation Trust** with an estimated total cost of £85,150 over five years commencing in April 2021 (four years commencing April 2022 regarding the Tissue manager). In 2023, £27,567 of payments were made (2022 – £7,750) and £19,719 recorded as charitable activity cost (2022 – £16,450). The amounts committed to for future years have been included within Debtors and Creditors as appropriate.

In December 2020, the Charity contracted with **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 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 of the total costs. In 2023, payments of £12,928 were made and £10,731 was recorded as charitable activity cost (2022 – payments of £24,965 and £21,634 of charitable activity cost). The project concluded in 2023..

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 £117,396 with costs funded 50% by the Charity and 50% by the EHE Foundation in the United States. In 2023, payments of £37,401 were made and £29,247 was recorded as charitable activity cost (2022 – no payments were made and £14,975 was recorded as charitable activity cost). The remaining amounts payable by the Charity have been included in Debtors and Creditors as appropriate.

In December 2022, the Charity contracted with the **Fondazione IRCCS Istituto Nazionale Dei Tumori in Italy** to fund costs associated with a study aiming to provide a description of the population affected by EHE, giving an insight into the natural history of the disease and its variants, leading to the possible identification of clinical and biochemical prognostic and predictive factors. Total costs of the project are €91,500. In 2023, payments of £35,903 were made and £26,654 was recorded as charitable activity cost (2022 – no payments were made and £13,942 was recorded as charitable activity cost). The remaining amounts payable by the Charity have been included in Debtors and Creditors as appropriate.

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 Charity's activities and operations for the year ending 31st December 2023. 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 the Charity's charitable objects and its associated activities.

Signed this 22nd day of October, 2024

(signed) "Sally Baker"
Sally Baker Trustee

(signed) "Jeff Collins"
Jeff Collins Trustee

(signed) "Kate Hooper"
Kate Hooper Trustee

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

(signed) "Oliver Pearce"
Oliver Pearce 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:
Ms Sally Baker
Mr Jeffery Collins
Dr Katharine Hooper
Mr Hugh Leonard (Chair)
Dr Oliver Pearce

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 group's 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 the Charity.

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 and all editions of The Pledge

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

100% From well-managed forests FSC® C000000

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Cover images

Hugh Leonard visiting the Institute of Cancer Research in Sutton, Surrey. Back row, left to right: Hugh Leonard, Yuen Bun Tam. Front row, left to right: Nafia Guljar, Eniola Ayeni, Dr Paul Huang.

and

EHERCC runners before the London Landmarks Half Marathon.

EHE RARE CANCER CHARITY (UK)

England & Wales - Charity number 1162472

Accounts

Rare Cancer Charity UK

Annual Report and
Financial Statements 2022

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

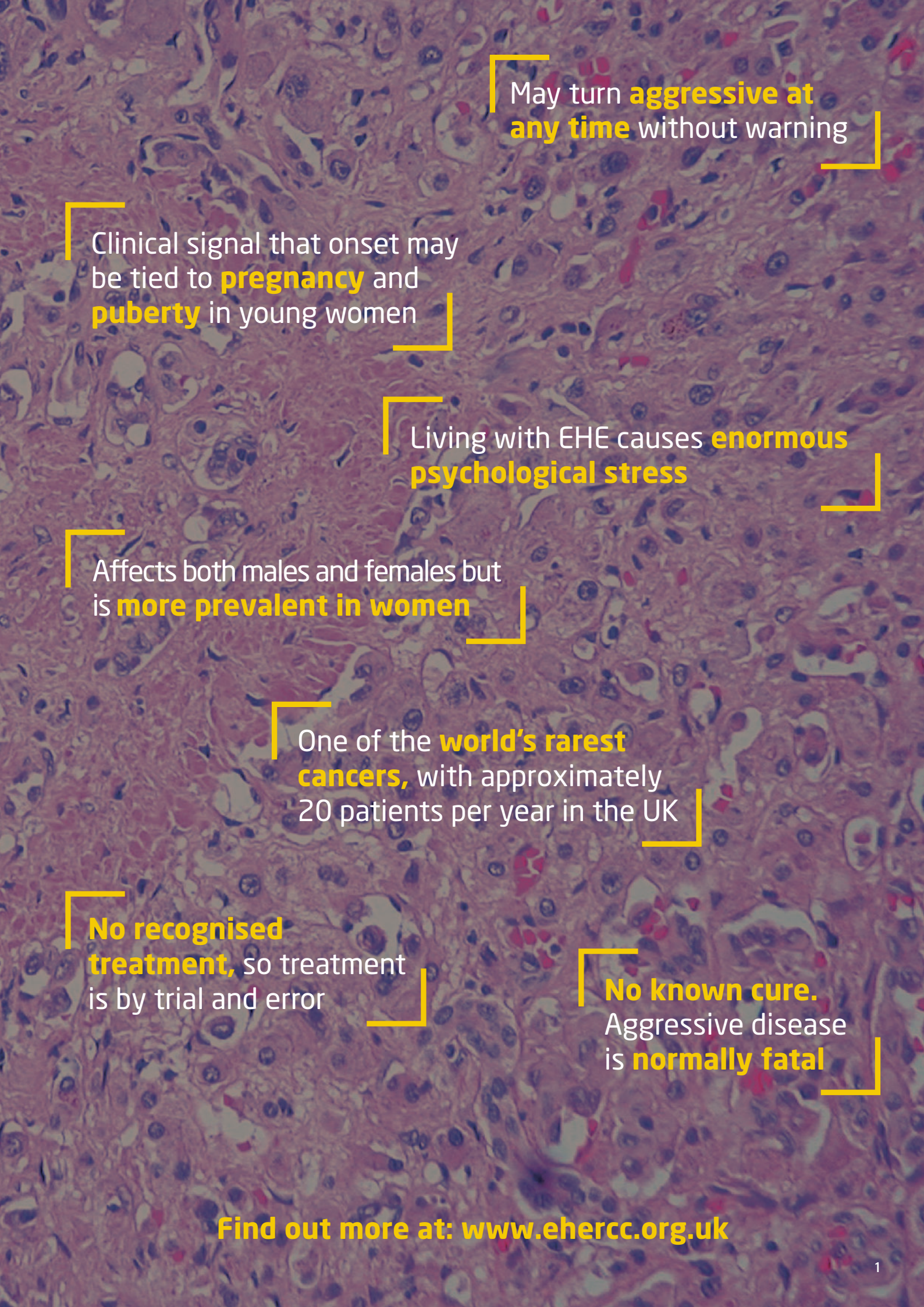
Can present as **indolent** (passive) or **aggressive**

Typically more aggressive in **young people**

Can re-present after long period with no disease

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

Tissue section of EHE involving a medium-sized blood vessel in the liver.



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 both males and females but is **more prevalent in women**

One of the **world's rarest cancers,** with approximately 20 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

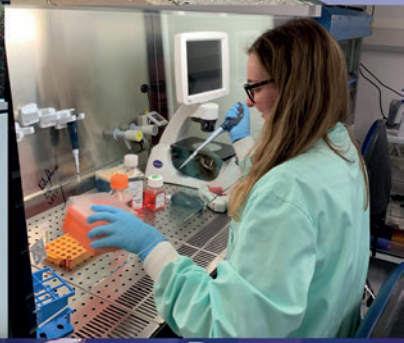
ESMO
Developing oncology practice resources
ESMO Booth - Hall 7, level 7.2

RARE CANCER
EHE
CHARITY (UK)
EHE is a very rare form of cancer.
Our goal is to defeat it, but we need your help!
Epithelioid Haemangioendothelioma (EHE)

RARE CANCER
EHE
CHARITY (UK)

PLEASE DISPOSE
THANK YOU
RARE CANCER
EHE
CHARITY (UK)

RARE CANCER
EHE
CHARITY (UK)
Funding critical rare cancer research

ICR The Institute of Cancer Research


EHE
pledge

EHE Rare Cancer Charity UK

Annual Report and Financial Statements 2022

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Message from the Trustees

The renewed energy and focus from our patient community seen in 2021, post-COVID, continued with record numbers of supporters wanting to run and cycle for the Charity in the London Landmarks Half Marathon and the RideLondon 100 cycling sportive, respectively.

The EHE research we are funding continued to produce positive results with our ongoing European collaboration expanding and the PhD we funded in Manchester coming to a successful conclusion. The international EHE research programme we support has also continued to grow and produce important results.

Our patient support and advocacy activities have also continued. Patient support and information sharing has been provided on a patient-to-patient basis through the group's global EHE Patient Support Facebook page. At the same time, every opportunity has been taken to engage with the general public, regulators, hospitals and other key stake holders to ensure that awareness of our EHE global community and the Charity continues to grow.

2022 also marked the start of a number of key initiatives to review the Charity's activities and structures with a view to strengthening our teams, recruiting volunteers, working with specialists, and engaging with key hospitals and research centres. All of this work is focused on further strengthening and expanding our operations so that we can support our patient community better, raise more funds, drive more research, and so bring forward the new drugs and treatments that are so badly needed to help those diagnosed with EHE.

As we prepare this annual summary of our activity and achievements, we are once again reminded that the activities we are proud to report have only been possible because of the extraordinary commitment of our patient community and their supporters. This is even more extraordinary when we recognise that EHE patient numbers will always be tiny due to the extreme rarity of the disease. That makes their achievements all the more amazing. As always, therefore, we want to recognise every single person who provided their support, in whatever form, to the Charity in 2022 by saying a simple but profound "Thank You"!

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

2022 was another year in which the Charity and our EHE patient community continued to engage with all stake holders to increase understanding and awareness of EHE. Speaking opportunities are particularly valuable and we were delighted when Hugh Leonard was invited to speak at the prestigious ESMO (European Society of Medical Oncology) Congress in Paris in September. Hugh joined Dr Silvia Stacchiotti and other panel participants in a session entitled *'Ultra-rare sarcoma: Navigating an endless sea'*.

Smaller speaking opportunities are also valuable. Kelly Denton spoke at fundraising events she organised in support of the Charity and her daughter who is an EHE patient. Hugh Leonard travelled to Derby in the UK to participate in, and to speak at, a major fundraising event held in memory of Hazel Peak by her colleagues at Rolls Royce.

Early in the year, as part of our ongoing patient support programme, the Charity participated in the second annual EHE360 Scientific Symposium and Global EHE Patient Conference. This event, coordinated by The EHE Foundation in the USA, is now established as a key component of our EHE global advocacy programme, and provides our patient community with opportunities to hear about exciting EHE research developments and to engage with clinical experts.

Collaboration is also a key feature of the Charity's advocacy initiatives. Global collaboration between the different national EHE foundations has continued to provide a common approach across international EHE programmes and initiatives. This included the start of an important programme to seek a label extension for a drug called sirolimus, which is producing positive results for patients but is not approved for treatment of EHE and is only available off-label.

Ensuring engagement with the UK EHE patient community is also a core objective. The UK EHE WhatsApp group has proved to be particularly successful in this area, although we also regularly communicate with our members through multiple social media and other communication routes. Through these communications we have been able to promote the UK EHE Biobank and have seen excellent patient engagement.

02
Research

The Charity continued to fund important EHE research projects through 2022, as well as signing a further research contract at the end of the year.

A key focus for our funded research has been the ongoing European collaboration involving Istituto Nazionale dei Tumori (INT), Milan, the Institute of Cancer Research (UK), and the Royal Marsden Hospital, London. This multi-faceted programme is researching a number of key aspects of EHE, including the identification and validation of novel circulating and tissue biomarkers, and the development of patient-derived xenograft (PDX) mouse models and subsequent cell lines.

The Charity is also helping to fund the establishment of the first ever EHE-dedicated, prospective observational registry, which involves both European and UK hospitals. This registry will be part of the European STARTER project, and is being built, managed and coordinated by a dedicated team also based at INT in Milan.

In the UK, our focus has been on the continued work we are funding at the Bateson Centre in Sheffield, where the team are seeking to generate a zebrafish model of EHE. This has required painstaking attention to detail as the team have faced and solved multiple challenges.

All technical work relating to the four-year PhD we have sponsored in Dr Valerie Kouskoff's laboratory at the University of Manchester was completed and at year end Emily Neil was finalising her PhD thesis. Dr Kouskoff was also successful in securing a further grant from the EHE Foundation to evaluate the effect of PARP inhibitors on EHE.

The National EHE Biobank, funded by the Charity and based at The Royal Marsden Hospital in London, continues to gather critical tissue and fluid samples. We are continuing to work with the Royal Marsden to promote awareness of the biobank with hospitals across the UK.

03
Fundraising

Fundraising is the life blood of all that we do at the Charity and in particular our ability to fund key research. As always, our fundraising is a combination of grass roots activity driven by our patient community and their supporters, and charity-driven fundraising.

The largest of our two charity-driven events is the London Landmarks Half Marathon. In 2022 we had the largest team yet taking part, with 42 runners registered for the run. We were particularly delighted that two runners from the USA flew over specifically to take part in the race, along with the usual great support and involvement of our UK members.

The RideLondon-Essex 100-mile-long cycling sportive was also well supported, with 20 riders taking on this major challenge. As Chair of Trustees, and having spent several years encouraging others to participate for the Charity, Hugh Leonard also wanted to take part and he rode in the event.

We were also thrilled in 2022 to learn that the Charity had been successful in securing a substantial grant from the Texel Foundation. This was the third time since inception that the Texel Foundation has supported the Charity and was the largest single donation received to date, for which we are hugely grateful.

Fundraising can be both inspiring and emotional when organised in memory of a loved one. Hugh Leonard attended the first annual Hazel Peak Quiz Night, organised by Hazel's colleagues at the Rolls Royce facilities in Derby. A walk-in coffee morning event, attended by friends and family, was held in Skegness in memory of Allana Parker who was an active volunteer for the Charity.

The Commando Boot Camp, comprising 25 women in Yate in the UK, completed their planned half marathon carrying a 70kg log. Running in support of their friend and EHE patient, Nicola Henderson, these women epitomise the extraordinary dedication and generosity of our supporters.

A number of other events were organised by groups or individuals through the year, including stalls at festivals, cake sales, coffee mornings, 100-mile walks and the sale of home-knitted headscarves.

All of these wonderful contributions, together with similar events in prior years, have combined to provide the amazing fundraising the Charity has enjoyed, and which allowed us to report in August that the total funds raised, since our inception, had exceeded £1 million.

More information about these and other events can be found in this report.

Objectives and Achievements for 2022

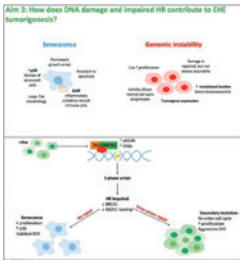
Every year we review our activities and achievement against the goals that we set for ourselves. We believe that this honest appraisal is important so that all our supporters and stakeholders can see how we are progressing. Below is the 2022 assessment; while on the opposite page you will see our objectives for 2023.

01 Patient Support and Advocacy

What we said we would do...	...and what we achieved
Review what is important to UK patients.	Patient engagement maintained through social media.
Launch UK biobank discussions with patient community.	Ongoing promotion of biobank continued successfully.
Progress regulatory discussion of IRE ablation.	Regulatory focus switched to repurposing (label-extension) of sirolimus for EHE.
Maintain sarcoma centre engagement	Communication maintained and copies of annual reports sent.
Re-launch pan-European patient engagement.	Pan-European engagement delayed awaiting start of pan-European patient registry.

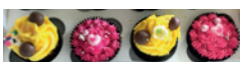
02 EHE Research

Engage and support existing projects.	Continued through the year.
Complete contracting of INT/ICR collaborative research projects.	Both projects contracted and initiated.
Evaluate new research, including immunotherapy.	Assisted with US grant cycle. Immunotherapy discussions initiated.
Continue to build/refine research coordination/strategy optimisation.	Ongoing, with close coordination with global EHE partners.
Initiate and coordinate review presentations.	First presentation held for Manchester PhD.



03 Fundraising and Finance

Support grassroots fundraising.	Continued to promote and support fundraising.
Revisit past fundraising post-COVID.	Past fundraising reviewed.
Initiate fundraising review.	Contracted with NOVA Fundraising for review.
Assess EU funding for EU projects.	Initiation on hold pending fundraising review.



Charity Organisation

Review additions to charity bodies.	Reviewed but no changes made
Relaunch voluntary support.	Delayed pending fundraising review.
Re-establish social media.	Initiated and ongoing.
Continue to assess charity activities.	Continually reviewed by Trustees.

Our Forward Focus for 2023

Because rare cancers are not rare to those who have them

01 Patient Support and Advocacy

- Continue sirolimus repurposing
- Assist patients with engagement with charity activities
- Launch new website
- Revitalise other social media
- Engage with European patient community

02 Research

- Support existing research
- Review and communicate results
- Engage with EHE partner foundations in research review
- Develop and promote coherent EHE research strategy
- Organise additional research review meetings

2023 AND BEYOND

03 Fundraising

- Support and encourage grassroots fundraising
- Coordinate key charity events (LLHM and RideLondon100)
- Continue to develop fundraising strategy with NOVA fundraising
- Coordinate review of research strategy and develop draft fundraising programme

Charity Organisation

- Consider appropriate support for research strategy
- Implement fundraising strategy
- Establish structures for European engagement
- Evaluate need for additional structures and personnel for the above

Foreword from the patient community

Jonathan Granek (Chair of EHE Rare Cancer Foundation Australia; Cancer Consumer Representative and Advocate; EHE Survivor and Research Subject; Husband, Father, Son, Brother, and Friend).

My story began back in 2009 when I was an active, fit and healthy 26 year old who incidentally injured his back. Subsequent scans showed a suspicious lesion in one of my vertebra with a fracture. This led to more scans, a biopsy and an inconclusive diagnosis with four pathologists who had never seen anything like it before. I was then referred to Australia's most experienced sarcoma unit at the Peter MacCallum Cancer Centre in Melbourne, and four months after the fracture, I had a confirmed diagnosis of stage 4 EHE. Being relatively asymptomatic I was prescribed a 'watch and wait' palliative treatment strategy. Intervention would only be necessary if my disease progressed.

Patients with ultra-rare cancers face huge challenges because so little is known about these diseases. The paucity of research, especially in more advanced and complex cases like mine, results in very limited treatment options being available and no established treatment regime that could cure me. The clinical advice at the time was that systemic therapies available would only have a limited effect before the tumours become resistant and that I would almost certainly experience a shortened life span.

In short, the outlook was not great, but I knew that other EHE patients lived in constant pain, barely making it through the day. I saw myself as lucky and was determined to remain positive and hopeful that I could live in relatively good health even though I had an ultra-rare cancer. I also decided that I needed far greater knowledge of rare cancers and EHE to give myself the best fighting chance of surviving this horrible cancer.

Jonathan Granek

Following diagnosis, I spent much of my spare time over the next 5 years building my health literacy. I wanted to understand what it meant to have a rare cancer, and what was needed to improve outcomes. I read scientific publications; networked with prominent cancer researchers and clinicians; and connected with other EHE patients across the globe. I spent time learning more about the health system, how cancer research is conducted and new treatments are developed. And I joined Australia's oldest research institute, the Walter and Eliza Hall Institute of Medical Research (WEHI), as a consumer representative consultant.

Cancer care is a monumental challenge

At the time of writing this, across the globe there are over 18M individuals being newly diagnosed with cancer annually and over 10M cancer deaths. By 2040, these diagnoses and deaths are expected to exceed 30M and 16M respectively. The impact is callosal.

While the number of deaths in the major common cancers have now decreased below that of population growth, the story is very different for patients diagnosed with one of the remaining 200+ rare and less common cancers. When we consider just rare cancers (those with an incidence of 6 per 100,000 cases or fewer) the outcomes are devastatingly poor, with the numbers of those newly diagnosed and dying outstripping population growth. Patients diagnosed today with rare cancers **have a very poor chance of survival,** almost entirely due to the **vacuum of research and development, and the funding to drive it.**

In addition to this research neglect, the management of rare cancers are more complex, requiring more people with less information available for decision-making. Complex multimodal tailored treatment approaches and multidisciplinary teams of experts are required to treat them. These factors have profound implications for health infrastructure and resources, imposing massive economic burden.

Understanding where Rare Cancers Fall Short and How to Bridge the Gap

Research is key! Without it, no new evidence-based information is generated to instigate change and improvements. Challenges exist in every aspect of the care and management of rare cancers, without exception, but two critical areas can be singled out.

The first is the development of early detection and diagnostics. As for nearly all diseases, the earlier they are detected the greater the chance of successfully dealing with them. The second is prognostics and the development of effective treatments, but to progress with these, patient data, disease information and research of fundamental biology are all required.

Support Groups as the Catalysts of Change

It became clear if the outcomes for rare cancers like EHE were to ever change for the better, these shortfalls would have to be addressed, and it needed to be organised, long-standing, far reaching and en-masse. In 2015, with the involvement of like-minded people also affected by EHE, I co-founded a registered not-for-profit charity called the EHE Rare Cancer Foundation Australia. Our sister Foundations in the US and UK were also founded that same year.

Today, we work in close partnership with each other, now with the additions of organisations in Canada and Italy too, and under the banner of the EHE Group. Together, we work to address the needs of people affected by EHE in over 75 countries across the globe, and support multiple research initiatives to bridge these gaps led by an impressive group of researchers and clinicians.

Our research initiatives to date for such a rare disease have been both world-first and world-class, but we are now at a pivotal juncture. The rate of progress is now very much in the hands of the growing international patient community who, by taking action and supporting multiple data-gathering initiatives. can meaningfully affect the necessary changes that will one day save lives. More than ever we must recognise that ***"alone we are rare, but together we are strong".***

01 Patient Support and Advocacy

At the core of the Charity's patient support and advocacy activities are two simple objectives, both centred on our patient community. The first is outward looking, spreading awareness of EHE and the impact that an EHE diagnosis has on patients. The second, which is inward looking, is to try and ensure that individual patients and the community as a whole are as well informed as possible regarding any aspects of the disease that are important to them.

Receiving a diagnosis of EHE, an incurable, ultra-rare cancer, is devastating for every patient. EHE patients not only have to live with this fact, but also the realisation that EHE can turn aggressive at any time, when the disease becomes very destructive. Yet doctors cannot provide any prognosis or prediction of when this will happen as they don't know what triggers this change.

So we take every opportunity to bring these facts to the attention of others. Although social media is an important component of any messaging, we continue to believe that there is nothing better than speaking to actual audiences, ultimately hoping that it will result in growing support from all key groups (clinicians, researchers, regulators, governments, funders, and the general public) for our different activities. Over time we hoped to build momentum and see an increase in awareness of EHE, and we are delighted that this has indeed been the case.

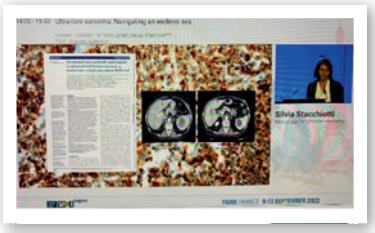
Our inward-looking support of EHE patients is largely provided by the patient community itself, through both local and global EHE social media platforms, allowing the patient body to share experiences and provide valuable information on a range of topics. With EHE having both variable presentation and course, having access to others with similar disease presentation and facing similar challenges is important and comforting for those involved.

Sharing information about the charity and its activities is also the objective of the EHE Group quarterly global newsletter, The Pledge, edited and produced here in the UK for the EHE Community worldwide. In addition, we share this Charity Annual Report with as many people as we can as part of our awareness and patient support programme. We encourage anybody who is reading this report to share it with others, and so help us in spreading the word. And if you would like additional copies please contact us.

Review by Sally Baker

"2022 has been another good year with regard to our patient support and advocacy activities. We have taken advantage of several important speaking opportunities. We were also able to involve, and engage with, the EHE patient community at the EHE360 Scientific Symposium and Global EHE Patient Conference. Regulatory engagement involved initiating processes both in the UK and Europe to secure approval for sirolimus to be used in treating EHE. These and other activities are outlined below."

The speaking highlight of the year was Hugh Leonard participating in a panel discussion at the ESMO 2022 Congress, together with sarcoma/EHE specialists including Dr Silvia Stacchiotti. The session was entitled *'Ultra-rare sarcoma: Navigating an endless sea'*. Hugh's presentation, entitled *'Advocating for patients with ultra-rare cancer'* addressed the challenges 'associated with ultra-rare cancers, and the importance of collaboration and partnership among patients, advocates, researchers, doctors, governments and pharma in the effort to find effective treatments for such rare diseases. Hugh took the opportunity to address particular areas of concern and how all parties together could help rare cancer patients.

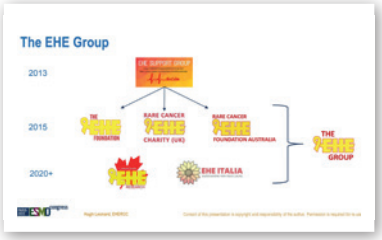


Several other opportunities to talk about EHE were taken. Hugh Leonard spoke at Rolls Royce Submarines in Derby during a fundraising event in memory of Hazel Peak. Kelly Denton spoke at several events organised in South London, including the quiz night organised by Laptops & Lipstick, a local business group for women who are supporting the charity and Kelly, whose daughter has EHE.

Laptops & Lipstick
The business group for women

Under our advocacy objective, we were also delighted to engage with Dr Silvia Stacchiotti and the European-based AntiCancer Fund on seeking approval for the use of the mTOR inhibitor, sirolimus, in the treatment of EHE. There is now a growing body of evidence that this drug is beneficial to patients with progressive EHE. The challenge, however, is that the drug is not formally approved for the treatment of EHE and is therefore only available 'off-label'. Having to be prescribed off-label means that for some patients the drug simply cannot be accessed (their doctor or hospital won't prescribe it) or cannot be afforded (available only at the patient's cost). We are therefore committed to addressing this inequality of access by securing the necessary approvals from the key regulatory bodies for use of the drug, with the relevant processes initiated at the end of the year.

Our engagement with, and support for, members of our patient community takes many forms, but the centre-piece of the year was the second annual EHE360 Scientific Symposium and Global EHE Patient Conference. This virtual event, organised by The EHE Foundation in the USA with input from the Charity and other EHE entities around the globe, provided the patient community with an update on key areas of research and clinical practice. Hugh Leonard was delighted to moderate and speak at a session focused on presenting and explaining the important ESMO paper *'Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts'* published in late 2021. The event closed with the very popular **"Ask the Expert"** panel session, where four clinical experts experienced with EHE responded to tabled questions about the disease and its treatment.



2022 also saw an expansion in our ongoing collaboration with the different global EHE foundations. Our collaboration within Europe is particularly important as we progress the development of the EHE Prospective Clinical Registry across Europe and the UK, and also seek to establish a pan-European EHE patient network.

Collaboration is also critical for the simple fact that ultra-rare diseases cannot afford to waste funding through poor communication, duplication of effort, or missed opportunity. We will therefore always remain focused on ensuring that all elements of global EHE activity are as coordinated and optimised as possible. We owe this to our patient community, but also to our supporters and donors who provide us with funding and rightly expect it to be appropriately managed.

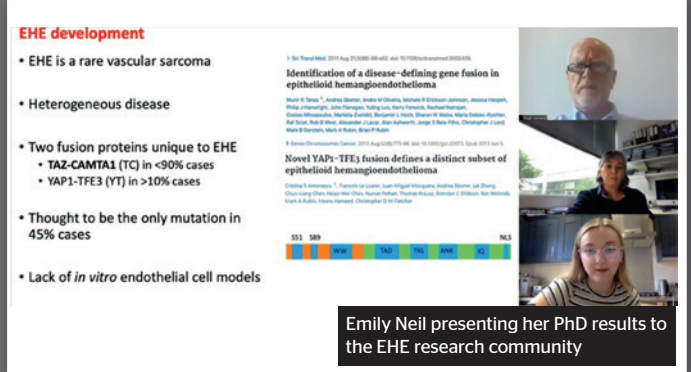
02
EHE Research

When the Charity was established in 2015, it was unclear how much interest there would be in EHE within the research community. We have been delighted therefore with the levels of engagement we have seen in the UK, Europe, north America and Australia since our inception. Here in the UK, all funds that we have received have either been spent or are allocated to research we have committed to, and which continues to produce exciting results.

We are also excited by the clear interest in both expanding our current projects and in establishing new research looking into different aspects of the disease. A continual challenge, of course, is raising the funds we need to drive that research, but we are confident that there is genuine appetite from established and respected centres of research to add to the ongoing global EHE research programme. That is why two of our core objectives for 2023 are to establish a clear strategic research framework for EHE and an associated fundraising strategy to support it.

While we are excited by the future potential and interest in EHE research, we are equally excited by the ongoing research we are currently funding. Summaries of these research programmes can be found on the following pages.

Hugh Leonard visiting the Institute of Cancer Research at the London Cancer Hub in Sutton



Emily Neil presenting her PhD results to the EHE research community

Review by Dr Oliver Pearce and Dr Kate Hooper

European collaboration

The Charity, together with the EHE Foundation (USA), is funding this major European collaboration involving the Istituto Nazionale dei Tumori (INT), in Milan, the Institute of Cancer Research (ICR) in London, and the Royal Marsden Hospital in London.

The overall research program entitled *'Evaluation of Cytokines and Hormones as Biomarkers for EHE'* was initiated at the end of 2020 and extended and expanded at the end of 2022. The resultant overall research comprises a number of different objectives or projects as follows:

i) the identification and validation of novel circulating and tissue biomarkers to inform patient management (prognosticators and predictors of response to medical agents) as well as potential therapeutic targets **(Project 1)**
ii) the development of patient-derived xenograft (PDX) models **(Project 2)**
iii) the assessment of the activity of drugs relevant for the disease **(Project 3)**
iv) the generation of PDX-derived cell lines to investigate the cellular and molecular determinants of drug activity and to be submitted to a CRISPR whole-genome screen to identify new therapeutic targets **(Project 4)**
v) the identification and evaluation of miRNAs **(Project 5)**
vi) the description of the radiologic characteristics of EHE and their correlation with the clinical outcome **(Project 6)**

Dr Silvia Stacchiotti, one of Europe's leading sarcoma clinicians, and Dr Nadia Zaffaroni, one of our leading sarcoma researchers, are joint Principle Investigators (PIs) of the project in Milan; Dr Paul Huang is the PI at the ICR in London.

Dr Silvia Stacchiotti

Dr Nadia Zaffaroni

Dr Paul Huang

Updates as at the end of 2022 of the above projects are provided below:

Project 1:
The assessment of circulating cytokines, hormones (and miRNAs), and ERα, Erβ and GPER expression and the identification of a novel biomarker for EHE.

Using a protein array able to simultaneously detect the expression of a hundred different cytokines in plasma samples of 15 EHE patients and healthy 6 individuals, a small panel of inflammatory cytokines was found to be differentially expressed. Among them the researchers focused on Growth and Differentiation Factor-15 (GDF-15), a member of the TGF-β super-family, which has multiple roles in a wide variety of cellular processes. Using a specific ELISA assay, they looked at the concentration of circulating GDF-15 in a retrospective series of 23 EHE patients and observed a statistically significant association of GDF-15 levels with EHE aggressiveness. This result was confirmed in a second cohort of 21 EHE patients prospectively collected within the currently ongoing observational study.

The assessment of circulating hormones and tissue expression of ERα, Erβ and GPER is ongoing.

The assessment of miRNAs is undertaken in Project 5.

Project 2:
Development of additional PDX models.

At the end of 2022, the team had fully established one EHE PDX model, whose ability to reproduce the characteristics of the originating clinical tumor had been confirmed in terms of histo-morphology, presence of the *WWTR(TAZ)::CAMTA1,* overall transcriptomic profile (as detected by RNA-seq) and presence of *CDKN2A* homozygous deletion. A cell line has also been established following disaggregation of the EHE PDX.

Project 3:
Assessment of activity of drugs.

The PDX model was used to comparatively assess the activity of doxorubicin and sirolimus (at different doses). Doxorubicin showed almost negligible activity whereas sirolimus caused a dose-dependent tumor volume inhibition in treated mice and induced the down-regulation of mTOR signaling. At year end the PDX was being used to assess the activity of inhibitors of the Hippo pathway, such as the TEAD family of transcription factors.

This PDX and the corresponding cell line were exploited to provide further evidence supporting the value of GDF-15 in EHE. GDF-15 was detected in the medium of the EHE cell line as well as in the blood of EHE PDX but not in healthy mice or in mice carrying another sarcoma type, confirming that the cytokine was released by the EHE. Interestingly, the team also found that sirolimus decreased the abundance of GDF-15 in their *in vitro* and *in vivo* EHE models.

Project 4:
Use of CRISPR in cell lines to help identify genes that confer drug resistance or sensitivity.

At the end of 2022 it was planned that the EHE cell lines would soon be provided to Dr Paul Huang (ICR, London) to start the CRISPR-based experiments.

02 EHE Research Continued

Project 5:
Identification and evaluation of miRNAs.

The expression profiling of plasmatic miRNAs was initially carried out using OpenArray Technology (which evaluated the expression of 754 different miRNAs) in the retrospective series of 23 EHE patients. Six miRNAs were found differentially expressed between patients with indolent and aggressive EHE. In order to evaluate the overall miRNAome (global profile of expressed miRNAs), the research team repeated the analysis on both retrospective and prospective series of patients using miRNA-seq. At the end of 2022 results were being analyzed by a dedicated bioinformatician.

Project 6:
Establishment and assessment of radiological data base.

The clinically-annotated radiologic scan collection on the study platform has been started. Response assessment is also collected by REDcap CRFs. The data analysis is planned to take place after the end of the study.

Canada joins the collaboration

We are delighted to see this research collaboration continuing to produce positive results. We were also excited when the project was materially expanded with Canada joining the collaboration, following the same programme. The Canadian arm of the project is centered at the Princess Margaret Hospital (PMH)/Mount Sinai Hospital in Toronto and is being led by Dr Albiruni Abdul Razak, Medical Oncologist at PMH.

Dr Albiruni Abdul Razak

EHE Prospective Observational Registry

A key challenge in understanding an ultra-rare disease such as EHE, with heterogeneous presentation, clinical course and variable response to the same treatment in different patients, is simply gathering patient data in a consistent and methodical manner to allow the disease to be studied and understanding to be gained. For ultra-rare diseases this is very difficult due to the lack of patient numbers in any one hospital, or indeed in any one country, leading to limited data and information being available.

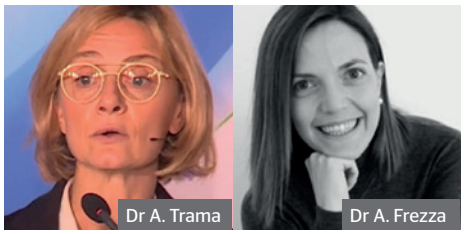
The Charity was therefore delighted when Dr Stacchiotti submitted a grant proposal to establish an EHE prospective observational registry to start to collect such data. Her proposal addressed the rarity and lack of patient numbers by making the registry pan-European, including the UK. The objective of the registry will be to collate data from participating hospitals across the European Union and the UK, providing key data and informational opportunities for clinicians and researchers who want to learn more about EHE, and support for those who suffer from it.

The original idea was to establish this as a stand-alone registry, centred at and managed from INT in Milan. However, early discussions in Milan led to the realisation that this registry could also be established within the STARTER (Starting an Adult Rare Tumour Registry) project, a new major initiative by EURACAN (The European Reference Network (ERN) on Rare Adult Solid Cancers) to establish registries for the ten recognised rare-cancer types across Europe. STARTER is also centred at INT in Milan, and is being led by Dr Annalisa Trama. The suggestion of using EHE as the first example of a sarcoma to be included in the registry was based on the core realisation that for such a rare disease, the establishment of a registry could be game-changing in terms of understanding and ultimately treating the disease.

The proposed study will aim to provide a description of the population affected by EHE, giving an insight into the natural history of the disease and its variants, leading to the possible identification of clinical and biochemical prognostic and predictive factors and answering some of the outstanding questions relating to the management and treatment of the disease.

1. Rare cancer of the connective tissue (sarcomas)
2. Rare cancer of the female genital organs and placenta
3. Rare cancer of the male genital organs, and of the urinary tract
4. Rare cancer of the neuroendocrine system
5. Rare cancer of the digestive tract
6. Rare cancer of the endocrine organs
7. Rare cancer of the head and neck
8. Rare cancer of the thorax
9. Rare cancer of the skin and eye melanoma
10. Rare cancer of the brain and spinal cord

Such an EHE registry will be the first of its type in the world, and offers a genuinely game-changing opportunity to the EHE community. The Charity was therefore delighted to help fund the three-year proposal with work starting in mid-2022. Agreeing and establishing the data collation protocol (CRF) for such a rare and heterogenous disease is itself a major challenge, but by the end of the year an appropriate CRF had been mapped out and the associated digital collection form had been generated and was being tested. The team, also led by Dr Trama and clinically assisted by Dr Anna Maria Frezza,

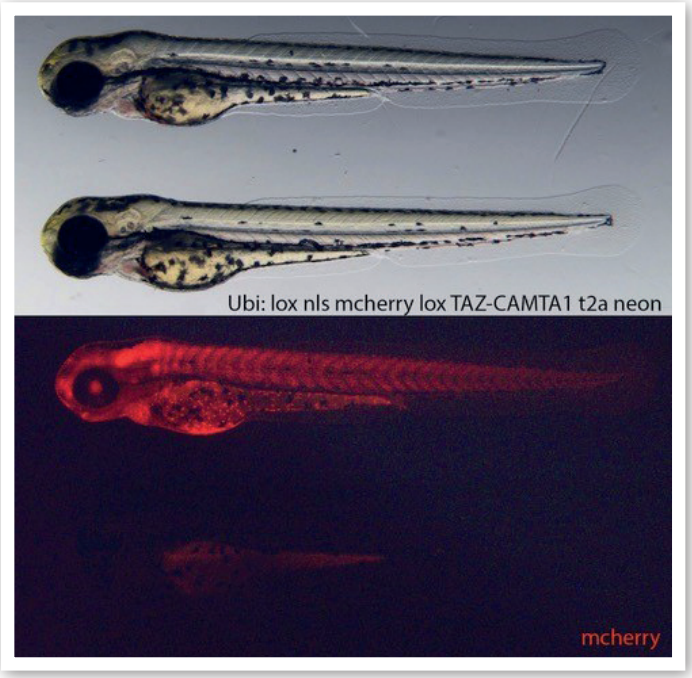


were hopeful that the testing process would be completed during the first half of 2023, allowing the enrolment of participating centres, and the introduction and launch of the project to be completed in the third quarter of the year.

EHE zebrafish model development

The objective of this project is to develop a zebrafish model of EHE. The basic components of the project were to develop a zebrafish line with the TAZ-CAMTA1 gene translocation construct present in endothelial cells, and a second zebrafish line with a switchable mechanism to activate the TAZ-CAMTA1 when required. By then crossing these two lines, it was hoped to generate fish with the TAZ-CAMTA1 construct that could be activated at different times in the development of the fish. The switchable mechanism was required as the TAZ-CAMTA1 fusion protein is highly toxic and lethal to the zebrafish at the embryonic stage.

Several key challenges have been faced, and at the end of 2021, although the team had developed a fish line with the TAZ-CAMTA1 switch mechanism in the endothelial cells, they had still not been able to get the TAZ-CAMTA1 gene translocation construct to present in the endothelial cells of zebrafish. So the EHERCC team were excited to receive reports from Dr Van Eeden in early 2022 that Eleanor Markham, the MPhil graduate undertaking the work, had identified two independent transmitters of their 'switchable' transgenic where TAZ-CAMTA1 can be driven by a new promoter, 'ubi'. Photographs clearly showed the 'detection marker' in red. This marker is attached to the construct and so everywhere you see red, the construct is present. It appears everywhere in the fish including, for the first time, in the endothelial cells.



Dr Van Eeden, PI of the project at the Bateson Centre at the University of Manchester, was delighted as the construct presence in endothelial cells meant that the team were

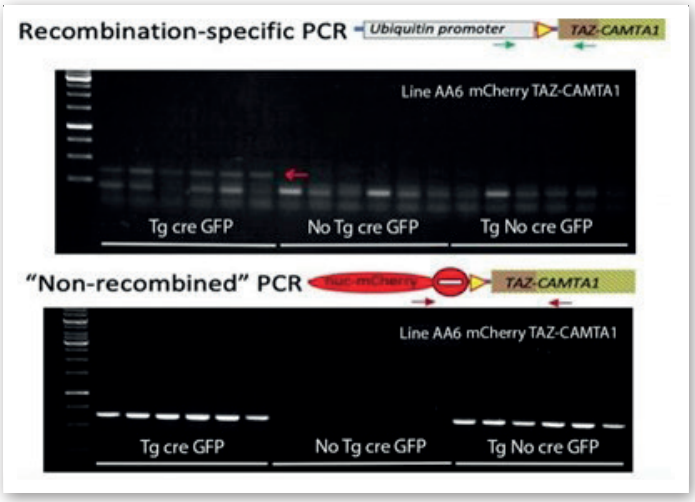
02 EHE Research Continued

potentially just one step away from being able to express the TAZ-CAMTA1 fusion protein in zebrafish. The team needed to ensure that the first few fish coming from the injected parents with the 'switchable' transgenic in the endothelial cells were used to establish a stock, before starting to test if the switch was working.

The next challenge was to create a different line that would allow switching in the endothelial cells. For this, a fish was required where the Cre protein is expressed in the endothelial cells. The team were able to obtain a construct that contained a version of the Cre protein that is tagged with GFP, a florescent green indicator, which would allow them to see directly if that Cre protein is expressed in the right place.

Eleanor was subsequently pleased to be able to report that they had successful developed a fish line transmitting the Cre protein as required, and attached a picture of the CreGFP switch transgenic that shows it is expressing the Cre protein in the blood vessels.

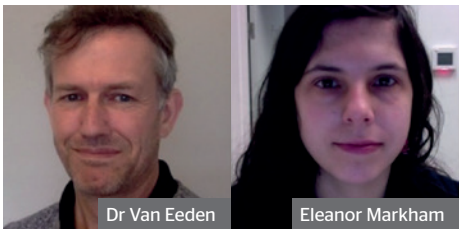
By the end of the year Eleanor had also been able to confirm that they had crossed both fish lines, namely the switchable TAZ-CAMTA (ubi:lox nls-mCherry lox TAZ-CAMTA1 fish (red) with the blood vessel switch line (fli1:cre GFP fish (green). The team had then undertaken PCR tests on resultant embryos that contain both constructs and could see that the switch was happening by analysing the genomes of these fish. The team were clear that this did not yet show that the TAZ-CAMTA fusion protein was being expressed, but it did show that the switch system was doing what it was supposed to do.



Early in 2023, the team planned to start using antibodies and qPCRs to see if the TAZ-CAMTA1 RNA, and protein were actually produced.

Eleanor will also be doing further tests with the fish to check if it is doing what it is supposed to do. At the same time they will also be working hard to identify fish with the required characteristics and so increase the number of fish available for experiments.

This has clearly been a challenging project, but we are hugely impressed by Eleanor's tenacity and her attention to detail as she has progressed through the painstaking work required to create an EHE zebrafish model.

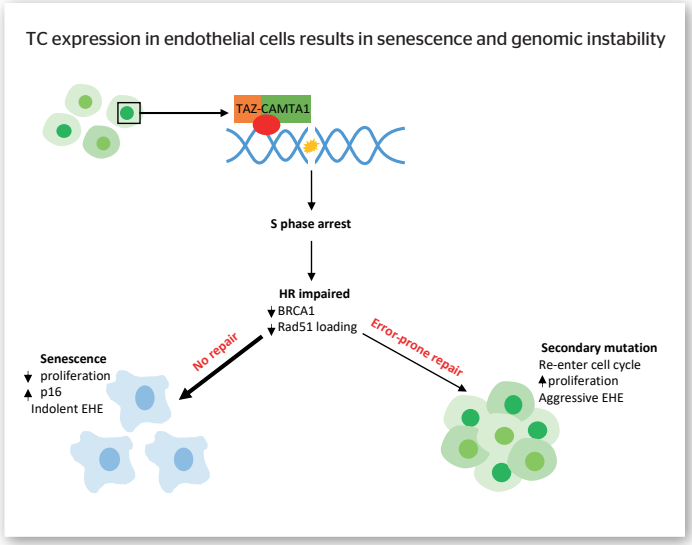


Manchester-based research

Emily Neil's PhD

2022 was the fourth and final year of our funding of the PhD being undertaken by Emily Neil in Dr Valerie Kouskoff's lab at the Division of Developmental Biology and Medicine, University of Manchester. Emily's work at the start of the year focused on confirming the results of some of her earlier experiments before starting to write up her thesis.

A key finding of Emily's work, reported in 2021, shows that EHE cells are captured in the S phase of the cell cycle. Her results also strongly suggested that these EHE cells captured in the cell cycle may ultimately become senescent, and may present as indolent disease. However, Emily also showed that homologous recombination (HR), the main DNA damage repair pathway in our cells, is impaired by the TAZ-CAMTA1 fusion protein. This in turn may lead to less reliable DNA repair mechanisms becoming active, with the resultant potential hypertranscription leading to secondary DNA mutations, some of which may allow the cells to avoid the S phase capture and so continue to proliferate. This is the first biological model we have seen that could explain the different levels of progression of EHE, from indolent to highly aggressive, and the unpredictable onset of more progressive disease from an initially indolent form.



Additional grant to test PARP Inhibitors

With the identification of DNA damage as an important component of EHE biology, and interesting preliminary results on testing Olaparib, Dr Kouskoff submitted an application to the EHE Foundation in answer to its 2022 call for grant proposals.

Dr Kouskoff's proposed research was titled 'Understanding and Exploiting the Genomic Instability Promoted by TAZ-CAMTA1'. The research goal was to understand further how TAZ-CAMTA1 interferes with the DNA damage response and whether this interference represents a therapeutic vulnerability that can be exploited. Dr Kouskoff proposed to test the druggability of the DNA damage response interference by TAZ-CAMTA1.

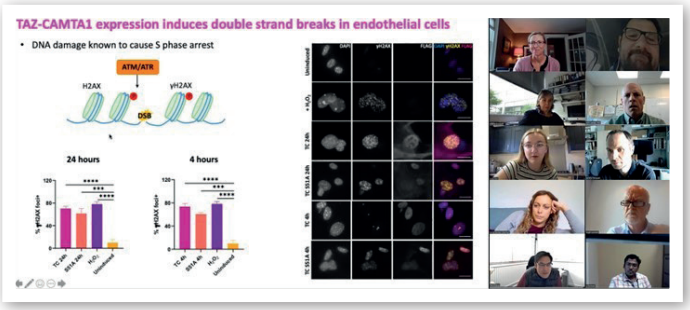
Dr Kouskoff was duly awarded a grant in late 2022 to fund this work, initially focusing on PARP inhibitors.

The final part of Emily's work was to therefore investigate whether PARP inhibitors are able to induce apoptosis (death) in TAZ-CAMTA1-expressing cells. PARP inhibitors, such as Olaparib, are commonly used to treat BRCA1-mutated cancers, where impairment of the HR DNA repair pathway causes genomic instability as error-prone pathways take over. Emily's assay revealed that TAZ-CAMTA1-expressing cells were more sensitive to Olaparib than TAZ-CAMTA1-negative cells and controls, as evidenced by a larger apoptotic population. This effect was particularly marked in the TAZ-CAMTA1-low populations, with TAZ-CAMTA1-high endothelial cells displaying a greater resistance to PARP inhibition. This may represent a mechanism by which cell death can be induced in these populations, with little effect on TAZ-CAMTA1-negative cells. This will require further experimentation to confirm. In 2023, Emily will be optimising a cell viability assay, which will allow calculation of the IC50 (half-maximal inhibitory concentration) of Olaparib in these cells, as well as allowing investigation of multiple drug concentrations and drug combinations at once.

02 EHE Research Continued

Sharing our research results

One of the challenges of research programmes is ensuring the results and knowledge gained is shared with other researchers to maximise the chance of success, minimise the chance of missing something important, and avoid unnecessary duplication. To help achieve this target, and as part of the obligations of the researchers who accept EHE Group funding, researchers are asked to periodically present their results to a group of fellow EHE researchers so that the group can discuss the results, encourage brainstorming in an energised and creative environment, and think about how to use the research and what follow-on research may be justified.



The first of these online presentations was held in mid-2022. Emily Neil from the Manchester team presented the results of her work. A core group of EHE researchers took part. These included John Lamar from Albany Medical College in New York, Munir Tanas from the University of Iowa, Sandro Pasquali from INT in Milan, Paul Huang from the ICR in London, and Ajay Pobbati from Dr Rubin's lab at the Cleveland Clinic. The EHE Rare Cancer Charity was also pleased to welcome Dr Sorrel Bickley, Director of Research, Policy and Support at Sarcoma UK, and Denise Robinson, Director of Research at The EHE Foundation' in the US. Although this was the first such review session. participants were delighted by the discussion and pooling of ideas at the end of the presentation.

Dialogue was ongoing at the end of the year concerning further work using the Manchester EHE stem cell model system.

Extending the sirolimus label

In late 2022, a group led by Dr Silvia Stacchiotti and comprising INT in Milan, the EHE Rare Cancer Charity UK, and the Brussels-based AntiCancer Fund, initiated a review process with the European Medicines Agency (EMA) seeking a label extension for the mTOR inhibitor 'sirolimus' so that this drug could be formally approved for the treatment of EHE in Europe. At the same time, the Charity and the AntiCancer Fund initiated a similar dialogue with the new NHS Drug Repurposing Programme in the UK

These initiatives are important because there is a growing body of compelling clinical evidence and experience demonstrating that sirolimus is having a noticeably positive effect for many EHE patients who have been prescribed the drug. Indeed, the drug is recognised as a potential first line treatment for EHE in the 2021 published ESMO paper *'Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts'.* Direct support for these label extension initiatives is being provided by doctors well known to our community through their participation, including Dr Silvia Stacchiotti from INT in Italy, Prof Robin Jones of the Royal Marsden in the UK, and Dr Bill Tap from Memorial Sloan Kettering in the USA.

Although some patients will be offered sirolimus 'off label', many will be denied access to the drug as it is not formally approved for EHE treatment and therefore their doctors and/or hospitals will not prescribe the drug. In addition, national health systems, funding entities and insurance companies may also refuse to fund the drug for the same reason, leaving patients with the option of funding themselves or not receiving this treatment. These circumstances result in a gross inequality of access across different countries in Europe, and even across different hospitals and health authorities within a single country.

An excerpt from the ESMO Consensus of Experts

"Among them, the highest clinical activity has been reported for mTOR inhibitors, with a progression-free survival (PFS) and overall survival in the range of 1 year and 2 years, respectively, and 10% of patients having even longer PFS. The panel agrees that these represent the preferred treatment options for patients with advanced and moderately progressive disease."

Dialogue and applications to the different regulatory bodies will continue in 2023, where the Charity will be fighting to achieve the appropriate label extensions and so secure access to this important drug for all EHE patients.

The importance of biobanking

The collecting of biological samples is critical for future research into any disease. With common cancers, tissue and fluid samples are abundant and collecting these samples is less important. For a disease as rare as EHE, however, banking biological samples is absolutely critical. With so few patients, and many of these not undergoing surgery, tissue samples in particular are ultra-rare. It is in fact hard to over-state how important tissue donation is for moving EHE research forward.

For these reasons the Charity funded the establishment of the National UK EHE Biobank at the Royal Marsden Hospital, and continues to fund the annual costs for collecting the samples. We also continue to promote the EHE Biobank through our patient community, and encourage all patients who have surgery coming up, including biopsies, to contact their primary care team or the Charity using the contact details below so that plans can be made to ensure their samples are captured and stored. The message is relative simple, but so important ... "Your tissue can help researchers learn more about EHE, and ultimately help deliver a cure for the disease. It really is that important."

If you have any questions regarding the National UK EHE Biobank, then here are some important contacts:

Contact the EHE Tissue Coordinator at the National UK EHE Biobank at the Royal Marsden Hospital, at rmh-tr.ehebiobank@nhs.net; or

Hugh Leonard at the EHE Rare Cancer Charity (UK) at hleonard@ehercc.co.uk

ehe Biobank

03 Fundraising and Finance

2022 started positively, with the stress of the COVID pandemic largely behind us, and the fundraising landscape again looking positive. Sadly this picture would change through the year as the Ukraine situation led to turmoil in the energy and financial markets, rising inflation, and a severe cost-of-living squeeze for everybody.

Despite this negative backdrop, the Charity enjoyed another positive year, largely due to the energy and enthusiasm of our members to continue to drive and support fundraising. Our patient community and their supporters have a huge, vested interest in seeing successful research deliver new treatments, and ultimately a cure for the disease. But as in the COVID crisis, we are also cognisant of the cost-of-living challenges now faced. We will therefore never take their inspiring enthusiasm, creativity and generosity for granted.

It was not just our individual members, their supporters and grassroots fundraising that led to such a positive year. We enjoyed record support for our London Landmarks Half Marathon event and the RideLondon-Essex 100 cycling sportive. We were also hugely grateful to the Texel Foundation for their award of the largest single grant we have ever received. Part of this unrestricted grant is now being used to allow us to engage with Fundraising experts as we seek to develop a broader fundraising strategy to drive a larger and more extensive research programme.

Review by Jeff Collins

At the end of 2021, we noted that we had seen a substantial recovery in fundraising post the COVID pandemic, and that the 2022 fundraising outlook was strong. I am pleased to be able to say that the enthusiasm of our supporters continued and we enjoyed great engagement from our patient community. That support ultimately enabled us to report in August that we had exceeded £1 million raised since our inception in 2015.

2022 was another positive year. Our grassroots fundraising was strong, with our patient community and their supporters again supporting the charity. We also saw record interest in our two major charity-organised events, where we had 42 runners in the London Landmarks Half Marathon, and 20 riders in the RideLondon-Essex 100 event.

The Boot Camp Commandos, a group of dedicated and motivated young women based in Yate ran a half marathon carrying a 70kg log, raising more than £7,000. Friends of Hazel Peake at Rolls Royce Submarines in Derby organised a major Quiz Night in memory of Hazel, and with donor-matching raised more than £10,000 for the charity.

Fundraising is of course not just about big events, as all fundraising, no matter what size, is so important. Kelly Denton coordinated several fundraising events. Wendy Cassidy organised a walk in coffee-and-chat morning in Skegness in memory of her sister, Allana Parker and raised more than £500. Jess Ralph ran in memory of her friend Al Mundy, who had passed away due to EHE, raising more than £1,000. Sue Dean, whose son Paul has EHE, set about knitting and selling headscarves for Christmas, and also raised well over £1,000 for charity. Kelly Davis meanwhile completed a 100 mile trek along the South Downs raising nearly £4,000 in support of her brother, Tyler.

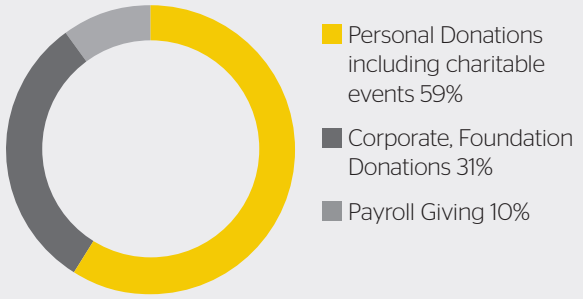
We were also delighted when the Texel Foundation awarded the Charity the largest single donation it has yet received. The £25,500 was granted as unrestricted funds, which also provides us with maximum flexibility to best serve the needs of the charity and our members. This was the third time that the Texel Foundation had donated funds to the Charity. We could not be more grateful to them for their fantastic support.

Key objectives

In the 2022 calendar year our supporters including the Texel Foundation raised a total of £95,800 for the charity's key objectives. The sources of these funds are summarised on the pie chart above.

During 2022 we provided funding of £155,200 for our UK research projects at the Universities of Manchester and Sheffield, funding for the EHE National Biobank and Tissue Manager at the Royal Marsden and funded (jointly with the US EHE Foundation) the collaborative research project between INT in Milan and the ICR in London.

Source of funds



Administration/business running costs

In 2022, 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 2023.

The charity received funding of £10,750 for its administration and business running costs account. During 2022, £6,600 of expenses had been incurred, which included an accrual of £1,200 for the independent examiner's fee. The remaining £4,150 related to fundraising events scheduled for 2023, with some funds remaining for future administration and business running costs.

The spend of £6,600 (excluding the £1,200 independent examiner's fee) included the fees associated with fundraising events conducted in 2022, and publishing costs, in addition to ongoing website maintenance.

"We are once again so grateful to our patient community, their supporters, and the corporate groups and foundations who supported us through the year. A particular and huge thanks must go to the Texel Foundation for their wonderful grant. We are also grateful to all those who helped us and volunteered so that we could keep our charity running costs as low as possible. I also want to thank all the companies and service providers who have supported us with their services, often provided at no or reduced cost.

Although 2022 has been another positive year, we must recognise that the current financial climate means that 2023 and years beyond may continue to be financially challenging, impacting our supporters and restricting their ability to donate funds, no matter how much they want to. We will therefore continue to ensure that we already hold the funds for any funding commitments we enter into. We will also continue to manage all funds with the utmost care to ensure that we get the maximum benefit from every pound that we have so generously received."

Jeff Collins

Wonderful support for EHE in 2022

The following pages highlight some of the amazing fundraising events that raised funds for EHERCC in 2022.

EHERCC fundraising passes £1 million

The Charity was delighted in August to announce that the total funds it had raised since its inception in 2015 had exceeded £1 million. Jeff Collins, Trustee of the Charity, commented:

"We are in reality a tiny charity with a tiny support base, due to the rarity of EHE, so it's pretty amazing that we have reached £1 million. To everybody who donated, ran, rode, swam, sold cakes, put on shows, quiz nights, race nights, rowed the Atlantic, sky dived, raffled, auctioned, and in any other way contributed to that total, including providing just encouragement and support, we just want to say a huge ***THANK YOU.****"*

But although we have been able to make a material contribution to global EHE research, we know that there is still a huge amount still to do. So while we thank all our supporters for all they have done in the past 7 years, we at the same time encourage them to plan for the next fundraiser. That second million needs to be raised!"

Texel Foundation grant awarded

The EHE Rare Cancer Charity were delighted to announce in June that they had received a grant award from the Texel Foundation, the philanthropic arm of the Texel Group. The Texel Foundation, established by the Texel Group in 2015, first supported us in that same year, shortly after the charity was started, providing the charity with its first corporate donation. The Foundation supported the Charity again in 2019 which was wonderful, and we were therefore delighted when at the start of 2022, we were invited to participate in their 2022 grant application round.

The application round was organised by Texel in compliance with IVAR's Open and Trusting Grant Making programme, promoting flexible funding, and designed to make the process of grant application easier, more open, and appropriate for those taking part, and to avoid unnecessary restrictions on the use of grants made. The application process was excellent as it was indeed very focused, with an initial short written application followed up by a meeting at which we were able to answer any questions that the Texel team had, and also describe in more detail what the charity was doing.

The Charity was then thrilled when we received the news that we had been successful in securing a grant award of £25,500. The focus of the grant application had been: (i) to allow the charity to increase participation in the pan-European EHE prospective study that is currently being finalised by the team at INT in Milan; and (ii) engagement with fundraising specialists.

The Texel Foundation grant is the largest single donation the Charity has yet received, and it is the largest donation from a corporate/foundation group. The funds will help us expand our activities and advance research into this terrible disease. The EHERCC could not be more grateful for this wonderful award. **Thank you Texel Foundation!**

London Landmarks Half Marathon – a brilliant day

The second quarter of 2022 started with the running of the London Landmarks Half Marathon. The EHE Rare Cancer Charity had 42 brilliant supporters who were all running for the charity and raising funds for EHE research. The Charity were also delighted when Denise Robinson, Director of Research at The EHE Foundation in the USA, and her close friend Ann Campbell, whose husband Steve passed away due to EHE, both flew over from America specifically to run and raise critical EHE funds for research.

We are so grateful to everybody who took part in the run for us. These people go out and train hard all through the winter to raise money for EHE research. They are awesome. We also want to thank Denise and Ann for flying over – that was very special. We loved having Ann here who was also running in memory of her husband, Steve, who died from EHE five years ago. It was a poignant reminder of why we are fighting so hard to beat this cancer.

The Charity team raised more than £17,500 for EHE research. We think that is a wonderful achievement and extend our thanks and congratulations to all who took part.

03 Fundraising and Finance Continued

Superwomen run half marathon for Nicola

Many people will run a half marathon to raise funds for charity, but very few will want to do that while taking it in turns to carry a 70kg (154lbs) log for the 13+ miles. But that is exactly what Nicola Henderson's friends did in late January in Yate in South Gloucestershire.

Running from Bristol to Chipping Sodbury under their slogan "Normal is Boring", the 25 women known as Commando Boot Camp, and trained and supported by fireman and ex-Marine Lee Ralph, smashed their initial target of £500 and raised a staggering more than £7,000 for EHE research.

Nicola, an inspiring patient who underwent a liver transplant due to her progressive EHE could not have been more grateful:

"So these are my friends... my lovely, crazy friends, who ran a half marathon for our cause; not only that, they are running with a 70kg (154lb) log!! The team are INCREDIBLE with a legend of a leader. I can never adequately express my gratitude to them for the amount of money and awareness raised for THE EHE RARE CANCER CHARITY UK!"

In memory of a very special woman

Wendy Cassidy wanted to celebrate the 50th birthday of her wonderful sister, Allana, who was diagnosed with progressive EHE in August 2018, and left us in 2020. This was a fundraising event that was very special for Wendy, but one she dearly wished was not necessary.

"My brilliant, wonderful, funny and simply gorgeous sister, "our Larney", left us far too early last year after her battle with an ultra-rare cancer called EHE. Allana would have been 50 on the 13th June, so I am organising an event the day after in remembrance of her, and to celebrate her 50th, because I know that is what she would want us to do."

Wendy's event, held in the Embassy Theatre Foyer in Skegness, gave those who knew Allana a chance to drop in and remember her and to share lovely stories about Allana. They also sold cakes, biscuits, tea and coffee to raise funds for EHE research, and set up a fundraising page so that people who could not make it were still able to contribute.

The event was a huge success, and many stories about Allana were indeed shared. Allana would have also been delighted and proud as Wendy raised more than £500 for EHE research on the day.

Vibrant Headbands to raise research funds

Over the past seven years we have seen a lot of different ways that people have found to raise funds for EHE research, but Sue Dean, Paul Dean's mother came up with a new product, working with friends in the Women's Institute. They decided to knit vibrant headbands for the winter which they are selling to raise funds for EHE research. Sue explained:

"With Christmas coming up and the icy cold winds forecast I thought why not put the headbands online so people can buy them. So I've set it up so that they are £10 each. With 80% of that going directly to The EHE Rare Cancer Charity UK and the other 20% covering the fees, postage and packaging. There are many colours just drop a message with the colour you'd like when you order!"

What a fantastic idea, and by the end of the year Sue and her team of helpers had sold an amazing 170 headbands. That's £1,360 for EHE research. Totally brilliant Sue. Huge thanks for such an inspired idea. We love them.

Running in memory of a dear colleague

Jess Ralph contacted the EHE Rare Cancer Charity in late September asking if we had any EHE running tops as she was running to raise funds for EHE research. The EHERCC are always delighted to provide running tops, both to support the runner, but also to spread further awareness of EHE. So we were thrilled that we did indeed have the right size top for Jess, for her run on 16th October.

Jess was running for her friend and colleague, Al Munday, who passed away in 2021 from EHE. Jess gathered donations when her friend passed away and then again in 2022 when it was his birthday. She wasn't able to do anything more at that time so had decided she'd run for the charity when she signed up for the Great South Run.

We were delighted when Jess posted news that she had made it around in one piece on the day and had raised more than £1,000 for EHE research, a tremendous result. Thank you Jess for your great support.

03 Fundraising and Finance Continued

EHERCC Team cycle 100 miles to raise funds for research

The EHERCC organises two larger scale fundraising events each year. The second of these is the 100 miles cycling sportive, that starts and finishes in London, and is called RideLondon. In previous years this event had taken place in the county of Surrey, south and west of London. This year, however, the event had moved to the county of Essex, north and east of the capital.

EHERCC had twenty riders in the event who collectively raised nearly £20,000 for EHE Research. Paul Dean, an EHE patient himself, completed the ride in just over 5 hours, an amazing achievement.

Hugh Leonard, Chair of Trustees, also took part.
"I have been encouraging people to take part in the London Landmarks Half Marathon and RideLondon events for the charity for 7 years now, and really felt it was time for me to take part. So I decided it had to be the RideLondon. It took me just over 7 hours, which I was very pleased with. It has been great training together as a group also, and of course we have raised a substantial sum for EHE research, which is wonderful".

"I will walk 100 miles..."

Kelly Davis's brother, who is on the front cover of this report, was diagnosed with EHE in early 2022. His diagnosis came "completely out of left field" as they say, and as for almost all of our members, was a shock. But also like nearly all of our other members, his family and friends are there to support him. Kelly decided she wanted to raise funds for EHE research and so we were delighted to see her post in August about her forthcoming campaign, an amazing 100-mile trek along the South Downs Way.

Then, on 13th September, Kelly posted news that they had completed the huge walk: *"So we made it! We completed the whole 100 Miles!!!! Back at home, slightly broken and completely drained, getting some well-deserved rest in! It's been a very challenging yet amazing journey for us! It's probably the hardest thing I've ever done in my life! The weather was against us, we had sun, wind, rain, hail and thunder storms! Literally didn't know what weather we were going to have thrown at us each day! It was so changeable! The terrain was a huge challenge! The hills and elevation were unreal most days! We were deliriously tired some days and so stiff from the day before. Each day seemed to roll into the next. A few days there was literally nothing to see, just following stony track after stony track, then climbing higher and higher! Relentless!! The last day at the Seven Sisters was by far the best day, what with the spectacular views. It was also the hardest with the elevation gain of 2,297ft."*

Kelly was super proud to be able to report that they had raised nearly £4,000 for The EHE Rare Cancer Charity to help fund EHE research. Kelly was rightly "over the moon" about their achievement and wanted to thank each and every person that had donated and had also helped with organisation or had supported them on their walk. We also want to say a huge thank you to Kelly and all her supporters for such a fantastic event.

Kelly is fundraising again

Like many of our members who are affected by EHE, Kelly has thrown herself into raising funds for the EHE Rare Cancer Charity in the UK as Kelly's teenage daughter is an EHE patient.

Kelly has organised large work events and evening quiz nights, but she also never misses a chance to run a small stall in a local fair or market place. At the Penge October Fest Festival Kelly ran a bottle raffle stall, raising £261 for EHE research. That's £261 we did not have the day before. Thank you Kelly. Your drive and energy is wonderful. We are so grateful. And as always Max, her dog, joined in!

In memory of Hazel Peake

It is always with mixed emotions that we publish news of fundraising events in memory of one of our EHE Warriors who is no longer with us in person. These events can however be very special indeed as people come together to celebrate the life of a loved one and dear friend. The quiz night held in Derby in memory of Hazel Peake was just such an event.

Hazel joined the EHE group in the UK in September 2021. She quickly became a regular voice in the UK WhatsApp group and maintained a real fighting spirit as she battled her aggressive EHE. Her branch of the Unite union supported the charity with a wonderful donation of £1,000, and Hazel was excited that her colleagues were also planning a quiz night for her early in 2022, to raise funds for EHE research.

Very sadly, Hazel's health deteriorated rapidly and she passed away in late January. Her colleagues, however, were determined to hold their quiz night to honour and celebrate their dear friend. And what a night it was. Organised by Paul Phillips, Lisa Neal and Katie Colbourne, a huge number of Hazel's friends and colleagues were there, together with Hazel's husband Andy and their daughter Emily.

The event, held at the Rolls Royce Leisure and Event Venue in Derby raised more than £10,000, thanks to the brilliant organisation and fantastic generosity of all who attended, and of all those who donated funds to the charity for EHE research. There was a lot of laughter, and just a few tears. But most of all there was a huge amount of love evident for a wonderful women.

We also want to say a huge thank you to Paul, Lisa and Katie, and to Rolls Royce who provided the facilities and the evening meal. That allowed all the funds raised on the night to go to EHE research, something we are sure Hazel would have greatly appreciated.

EHE Rare Cancer Charity UK

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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 2022.

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: 23 October 2023

EHE Rare Cancer Charity (UK)
Statement of Financial Activities
for the period ended 31 December 2022

	Notes	Unrestricted funds £	Restricted funds £	**Total 2022 £**	Total 2021 £
Incoming resources:					
Donations	2	95,809	10,750	**106,559**	100,926
Total incoming resources		**95,809**	**10,750**	**106,559**	100,926
Resources expended:					
Costs of generating donations		1,812	562	**2,374**	12,201
Charitable activities		155,199	-	**155,199**	134,264
Governance costs		-	1,200	**1,200**	1,200
Other administrative costs		72	4,876	**4,948**	5,117
Total resources expended	3	**157,083**	**6,638**	**163,721**	152,782
Net surplus for the year		**(61,274)**	**4,112**	**(57,162)**	(51,856)
Transfer between funds		**-**	**-**	**-**	-
Balance brought forward		323,483	4,568	**328,051**	379,906
Funds carried forward	8	**262,209**	**8,680**	**270,889**	328,050

Funds carried forward for 2022 £270,889

EHE Rare Cancer Charity (UK)
Balance Sheet
as at 31 December 2022

	Notes	Unrestricted funds £	Restricted funds £	**Total 2022 £**	Total 2021 £
Current assets					
Debtors	5,9	208,391	3,780	**212,171**	153,748
Cash at bank and in hand		307,448	16,047	**323,495**	311,379
Total current assets		515,839	19,827	**535,666**	465,127
Creditors: amounts falling due within one year	6,9	(156,018)	(11,147)	**(167,165)**	(112,022)
Net current assets (liabilities)		**359,821**	**8,680**	**368,501**	353,105
Creditors: amounts falling due after one year	7,9	**(97,612)**	**-**	**(97,612)**	(25,055)
Net assets (liabilities)		**262,209**	**8,680**	**270,889**	328,050
Funds carried forward					
Unrestricted funds		262,209	-	**262,209**	323,482
Restricted funds		-	8,680	**8,680**	4,568
Total funds	8	**262,209**	**8,680**	**270,889**	328,050

The Charities Act 2011 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 22 October 2023 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 2022

1 Accounting Policies

Basis of preparation: TThe 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:

	2022 £	2021 £
Unrestricted funds:		
Personal donations including fundraising events	**62,593**	76,125
Corporate and Foundation donations	**33,216**	3,901
	95,809	80,026
Restricted funds:		
Administration fund	**10,750**	20,900
	10,750	20,900

3 Analysis of resources expended

	Unrestricted funds £	Restricted funds £	**Total 2022 £**	Total 2021 £
Costs of generating donations:				
Just giving fees	478	562	**1,040**	1,101
Fundraising event entry and other fees	-	-	**-**	9,888
Credit card and other processing fees	1,334	-	**1,334**	1,212
	1,812	**562**	**2,374**	12,201
Costs of charitable activities:				
University of Manchester PhD Study	33,001	-	**33,001**	43,736
Royal Marsden Biobank	16,450	-	**16,450**	31,612
Zebrafish Study University of Sheffield	55,198	-	**55,198**	26,483
Fondazione IRCCS and ICR Biomarkers	36,608	-	**36,608**	32,433
Fondazione Prospective Study	13,942	-	**13,942**	-
	155,199	**-**	**155,199**	134,264
Governance costs:				
Independent examiners' fee	-	1,200	**1,200**	1,200
	-	**1,200**	**1,200**	1,200
Other administrative costs:				
Design and publishing	-	2,683	**2,683**	3,041
Website maintenance	-	2,088	**2,088**	1,883
Bank fees	72	105	**177**	193
	72	**4,876**	**4,948**	5,117

Trustees' expenses

No expenses were incurred by Trustees during the period and reimbursed by the Charity (2021 – £6,293).

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 2022

5 Debtors

	Unrestricted funds £	Restricted funds £	**Total 2022 £**	Total 2021 £
Prepayment to the University of Manchester	-	-	**-**	50,533
Prepayment to Royal Marsden	60,685	-	**60,685**	32,805
Prepayment to Fondazione IRCSS Istituto Nazionale Dei Tumori	118,526	-	**118,526**	31,477
Prepayment to the University of Sheffield	28,715	-	**28,715**	26,483
Other debtors	465	3,780	**4,245**	12,450
	208,391	**3,780**	**212,171**	153,748

Included within the debtors figures above are amounts of £97,612 (2021 – £25,055) due after more than one year.

6 Creditors: amounts falling due within one year

	Unrestricted funds £	Restricted funds £	**Total 2022 £**	Total 2021 £
University of Manchester	3,820	-	**3,820**	29,181
Royal Marsden	28,050	-	**28,050**	9,820
Fondazione IRCSS Istituto Nazionale Dei Tumori	95,433	-	**95,433**	37,005
University of Sheffield	2 28,715	-	**28,715**	26,483
Accrued independent examiners'	-	2,400	**2,400**	1,200
Other creditors	-	8,747	**8,747**	2,860
	156,018	**11,147**	**167,165**	112,022

7 Creditors: amounts falling due after one year

	Unrestricted funds £	Restricted funds £	**Total 2022 £**	Total 2021 £
Fondazione IRCSS Istituto Nazionale Dei Tumori	54,207	-	**54,207**	-
Royal Marsden	43,405	-	**43,405**	25,055
	97,612	**-**	**97,612**	25,055

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 and July 2021, a second and third phase of the project was agreed and in July 2022, 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 2021. The total cost of the project is £57,430 and commenced in July 2022. In 2022, £55,198 of payments were made and recorded as charitable activity cost (2021 – £26,483). The amounts committed to for 2023 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 2022, £29,181 of payments were made and £33,001 recorded as charitable activity cost (2021 – payments of £49,101 and expense of £43,736). The amounts committed to for 2023 have been included within Debtors and Creditors as appropriate.

In March 2021, the Charity agreed to fund costs associated with the establishment and administration of an EHE Biobank and the provision of a Tissue Manager with the **Royal Marsden Cancer Charity and the Royal Marsden NHS Foundation Trust** with an estimated total cost of £85,150 over five years commencing in April 2021 (four years commencing April 2022 regarding the Tissue manager). In 2022, £7,750 of payments were made (2021 – £3,875) and £16,450 recorded as charitable activity cost (2021 – £5,945). 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 (£101,797) 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 (£35,407) of the total costs. In 2022, payments of £24,965 were made and £21,634 was recorded as charitable activity cost (2021 – payments of £25,949 and £32,433 of charitable activity cost). The remaining amounts payable by the Charity have been included in Debtors and Creditors as appropriate.

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 £117,396 with costs funded 50% by the Charity and 50% by the EHE Foundation in the United States. In 2022, no payments were made and £14,975 was recorded as charitable activity cost (2021 – £nil). The remaining amounts payable by the Charity have been included in Debtors and Creditors as appropriate.

In December 2022, the Charity contracted with the **Fondazione IRCCS Istituto Nazionale Dei Tumori** in Italy to fund costs associated with a study aiming to provide a description of the population affected by EHE, giving an insight into the natural history of the disease and its variants, leading to the possible identification of clinical and biochemical prognostic and predictive factors. Total costs of the project are €91,500 (£80,995). In 2022, no payments were made and £13,942 was recorded as charitable activity cost (2021 – £nil). The remaining amounts payable by the Charity have been included in Debtors and Creditors as appropriate.

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 Charity's activities and operations for the year ending 31st December 2022. 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 25th day of October, 2023

(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
Dr Oliver Pearce
Ms Sally Baker

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 group's 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 the Charity.

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

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Cover images

EHE patient Tyler Davis participating in immunotherapy trial.

and

Some of the EHE RideLondon Essex team.

EHE RARE CANCER CHARITY (UK)

England & Wales - Charity number 1162472

Accounts

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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

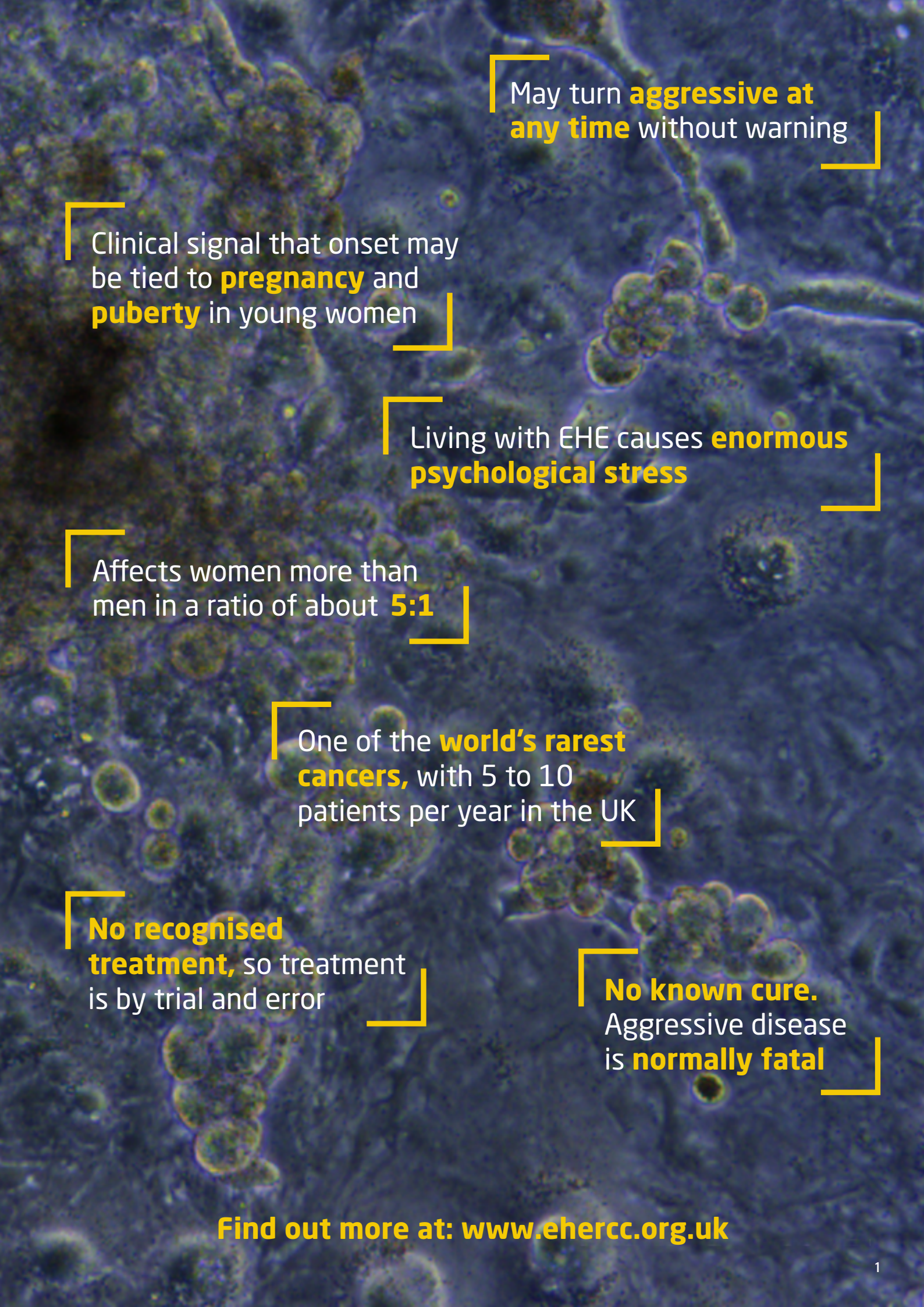
Can present as **indolent** (passive) or **aggressive**

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

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

EHE Rare Cancer Charity UK

Annual Report and Financial Statements 2021

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03 Fundraising and Finance	18
Wonderful support for EHE in 2021	20
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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. t 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 Instituto 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.

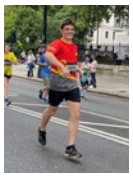
The charity once again ran its Giving Tuesday matched-funding campaign in November and secured matched funding for the more than £10,000 raised. The principal funds raised included a wonderful donation of £1,000 received from the Rolls-Royce Nuclear Power Branch of Unite, in Derby, in support of EHE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

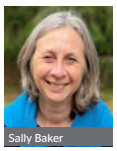
At the end of the year, the charity was also well advanced in its planning for its two big 2022 fundraising events, the London Landmarks Half Marathon (40 places) and the Ride-London-Essex 100 sportive (20 places). We look forward to 2022 being another great year.

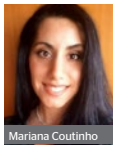
Objectives and Achievements for 2021

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.




Sally Baker


Mariana Coutinho

Silvia Stacchiotti

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 1980 - 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 to 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 moto 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.

EHE ITALIA
ASSOCIAZIONE NON SOLO LAURA

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.

EURORDIS
RARE DISEASES EUROPE

Sarcoma Patients EuroNet

European Cancer Patient Coalition

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 Instituto 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.

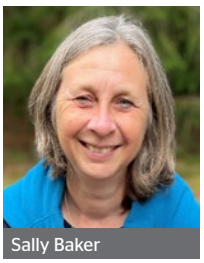
In addition to the consensus paper, the charity has agreed to fund the establishment of a European EHE prospective study which will also be coordinated by Dr Stacchiotti and her colleagues at INT, providing further engagement opportunities with the clinical community.

Charity organisation

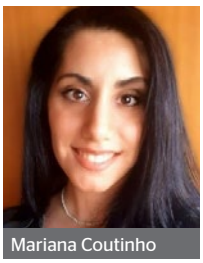
A key component of our patient support and advocacy work is to ensure that we continue to review and supplement the EHERCC with key personnel so that we have the resources to achieve our objectives. In 2021, a number of individuals joined the charity to continue this process of renewal and growth.

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.

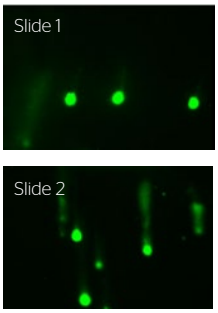
2. TC expression in endothelial cells results in downregulation of the endothelial phenotype
Phenotypically, TC-expressing endothelial cell populations show reduced tube-like formation. Data showed that TC causes transcriptional changes to genes involved in endothelial cell identity, and leads to reduced 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.

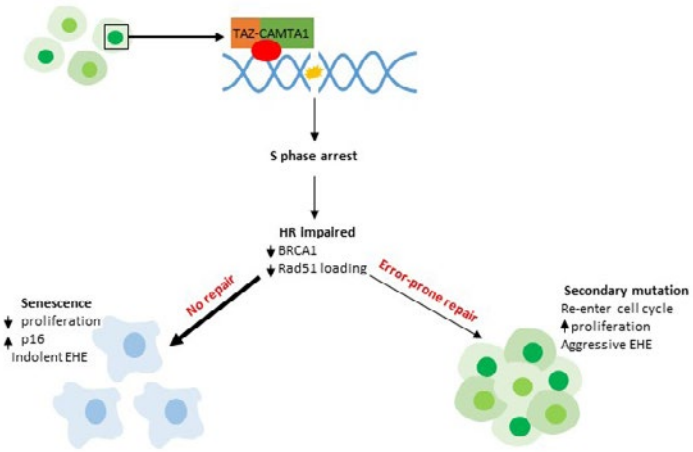
Emily then moved on to determine the p16 expression level in TC-expressing endothelial cells, as this protein is known to positively regulate senescence. Moreover the *Cdkn2a* gene, which encodes p16, is the most common secondary mutation to TC in EHE, and these tumours are often more aggressive. Interestingly, 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.

02 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-tried 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.

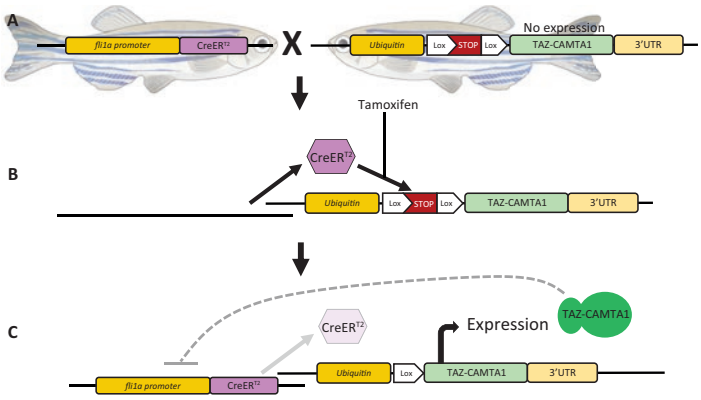


Fig: Strategy for driving TAZ-CAMTA1 in endothelial cells. Fish containing a fli1a-driven CreERT2 and a silenced TAZ-CAMTA1 expression construct are crossed together (A). The resulting larvae containing both constructs express an inactive form of Cre in the endothelial cells. When activated with tamoxifen 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

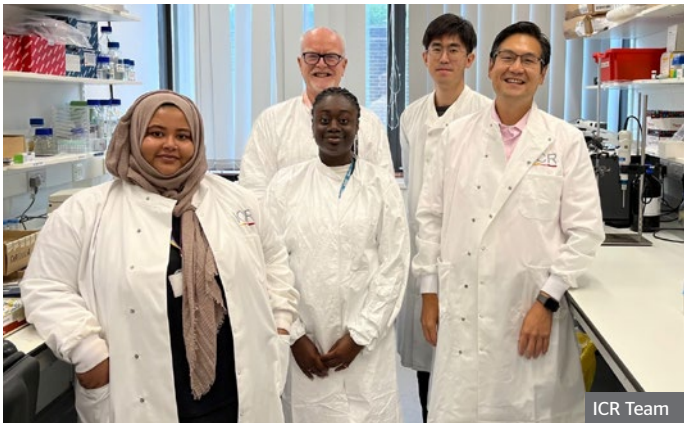
National UK EHE Biobank

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.

ehe Biobank

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



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 Instituto 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, Sirolimus, 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.

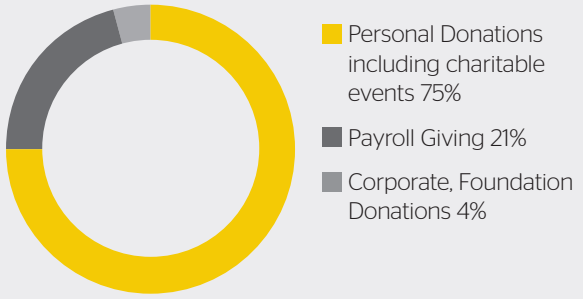
As always, fundraising events came in different shapes and sizes. The Bootcamp Commandos, a group of women based in Gloucestershire, used their major fitness training programme including the Three Peaks Challenge to raise over £7,000. Kelly Denton, mother of an EHE patient, organised multiple events 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 commited 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

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

Saving the loose change all adds up

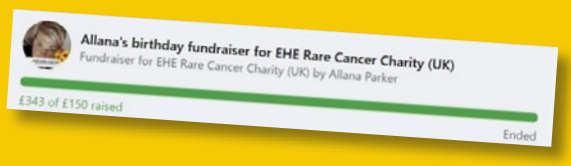
Fundraising is not always about mega events and huge sporting challenges. Sometimes it's about saving little and often. Hugh and his family decided to do this, following Jessie Hayman's Jessie Jars challenge, by putting their loose change most days in their own EHE jar at home. The last collection started 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.

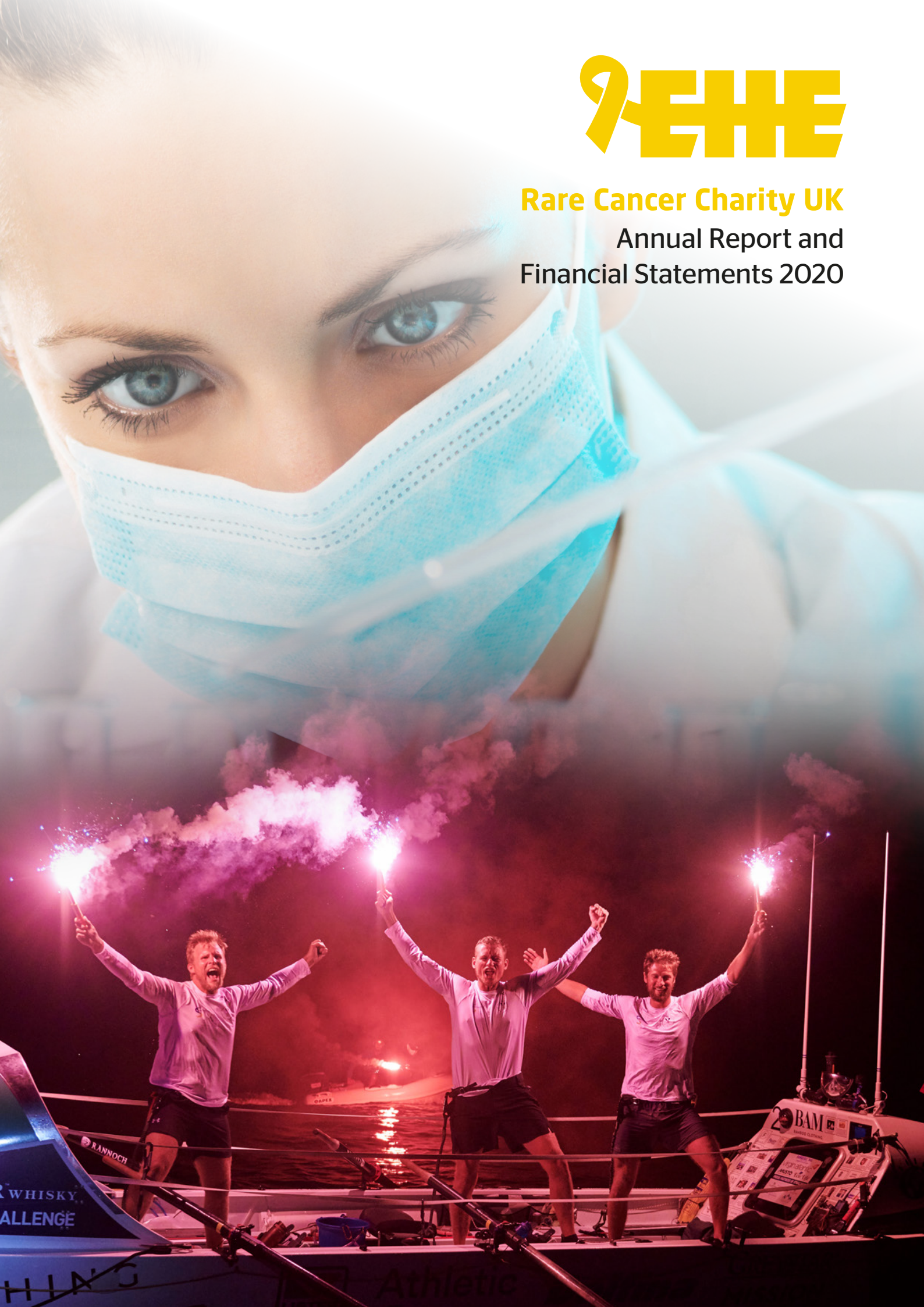
EHE RARE CANCER CHARITY (UK)

England & Wales - Charity number 1162472

Accounts

Rare Cancer Charity UK

Annual Report and Financial Statements 2020



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'

Flow cytometric slide investigating a role for mechanical signals in the regulation of TAZ-CAMTA1 activity: from Emily Neil, PhD student, Manchester University. PI: Dr Valerie Kouskoff.

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

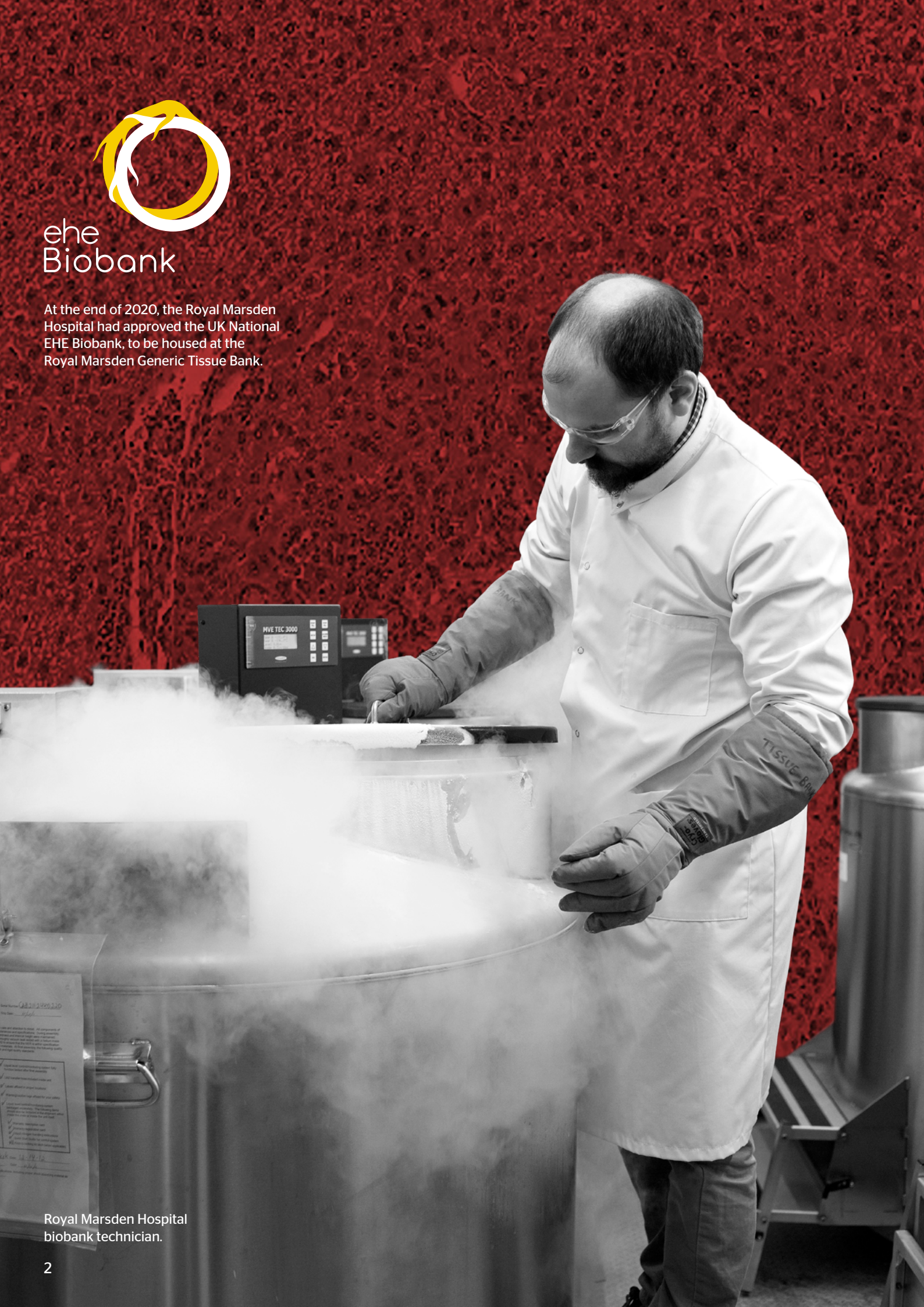
No recognised treatment, so treatment is by trial and error

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

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

ehe
Biobank

At the end of 2020, the Royal Marsden Hospital had approved the UK National EHE Biobank, to be housed at the Royal Marsden Generic Tissue Bank.



Royal Marsden Hospital biobank technician.

EHE Rare Cancer Charity UK

Annual Report and Financial Statements 2020

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Progress despite COVID-19

With the world battling a truly global pandemic, 2020 was an exceptionally difficult year at every level. Our members and worldwide patient community were all impacted yet, across the globe, they managed to weather the COVID storm with the same determination and spirit we witness on a daily basis, fortified by the extraordinary support accessed through our EHE social media platforms.

There were serious implications also for all our EHERCC activities. Research was largely suspended in the second and third quarters as lockdown took hold and research facilities were closed. Grassroots fundraising was impacted as many faced short-term uncertainty, while larger donors faced increased demand for their more limited funds. Major events such as the London Landmarks Half Marathon, in which we hoped to have 40 runners, were cancelled.

Faced with these circumstances, we chose not to prioritise fundraising as we felt this would be inappropriate and insensitive to the serious challenges that people were facing. We were confident that all our supporters would re-engage when some form of normality returned. We were delighted, therefore, when we did indeed see support for the charity's activities growing through the fourth quarter and into 2021.

In 2020, the fantastic support we always receive may have understandably reduced, but it never disappeared altogether. We hope it is clear, as you read through this report, that the enthusiasm and commitment to our activities was as strong as ever as we left 2020 behind. We cannot thank our supporters enough for all that they contributed through such a difficult year. We also are immensely grateful to the researchers and clinicians who have continued their work with EHE through 2020. Finally we want to say thank you to Liz Milligan, who resigned in March 2021, for all she contributed as a valued Trustee and colleague through 2020. To them all we want to say a huge

Thank you!

Left to right:
Hugh Leonard (Chair of Trustees),
Jeff Collins (Trustee),
Kate Hooper (Trustee),
Liz Milligan (Trustee, resigned 10.3.2021)
Dr Oliver Pearce (Trustee).

01
Patient Support and Advocacy

Patients with ultra-rare diseases like EHE often feel isolated at the best of times. Layer on top of that 2020 issues like social distancing, lockdown and the uncertainty of how COVID might affect your rare disease, and patients can feel overwhelmed. Our patient support activities, largely delivered through the global EHE Facebook patient support pages, have perhaps never been more needed than they were in 2020.

It was with this background that the support, advice and encouragement of our global community, shared through social media, was so important. This was especially true for our members who had undergone organ transplant, and faced exceptionally challenging isolation levels due to their suppressed immunity.
As always the support given was delivered tirelessly, by so many in our community, and provided with care, empathy and deep affection.

Of course, EHE does not stop during a global pandemic. Newly diagnosed patients still continued to engage with the charity through 2020. We are never pleased that new people have to embark on their own EHE journey, but we of course welcome them to our group, where we will always try to help answer any questions they may have, provide useful advice and information but perhaps most of all offer them support, encouragement and love within a group of fellow EHE patients.

Towards the end of the year, with the UK EHE community expanding, we decided that in addition to global social media, it was time to launch our own UK-focused EHE social media. Facebook, WhatsApp, Instagram and Twitter accounts were all launched. We hope that this will help foster an ever-stronger UK EHE community, together with delivering greater awareness and support for our work.

02
Research

Despite a COVID-related slowdown in research, our existing projects continued to deliver exciting results. At the same time, project expansions are under review, new research is being proposed and important infrastructure such as the UK National EHE Biobank is close to being finalised and going live. In short, COVID19 may have slowed us down for a short while but immediate and longer term EHE research possibilities are exciting.

The PhD we are funding at the University of Manchester, under Prof Valerie Kouskoff, has continued to shed light on how EHE is impacting the biology of endothelial cells.

The project team we are funding at the Bateson Centre at the University of Sheffield are continuing to attempt to develop an EHE zebrafish model. Led by Dr Fredericus Van Eeden, this work is proving to be challenging, with the TAZ-CAMTA1 construct still not expressing in the zebrafish endothelial cells. A full and broad review of progress and results with other experts in the field has led to the identification of several possible solutions to the current difficulties.

At the end of the year we had also seen good progress towards the start of two new projects. The first of these is the set up and start of the National EHE Biobank which will be centred at the Royal Marsden Hospital. This biobank will finally allow us to start to collate EHE tissue and fluid samples to support EHE research. At year end, ethics approval had been received and final operational approvals were being sought.

The second project is a collaboration between INT in Milan and the ICR in London. With Dr Silvia Stacchiotti and Prof Robin Jones acting as the respective Principal Investigators, this project is looking to identify possible cytokines and hormones as biomarkers of EHE, which in turn may provide an early sign of disease progression, helping clinicians decide on the appropriate treatment regimens.

At the end of 2020, we were also delighted to see ESMO coordinate a virtual consensus meeting, bringing together more than 90 multidisciplinary experts to collate, agree and document best practice for treating EHE.

03
Fundraising

2020 started with the great support we have always enjoyed, from our amazing EHE community, their supporters, and the general public. The second and third quarters were very different, however, as the COVID pandemic and social restrictions impacted every part of our society. Yet by the end of the year, the commitment to help raise funds for critical EHE research had reignited and was clearly growing as we moved into 2021.

The year started with the climax of Charlie Medwin's row across the Atlantic. This amazing 2,900 nautical mile adventure was completed when Charlie and his two team mates reached Antigua on 20th January. The row not only provided an excellent platform to raise EHE awareness over months of preparation and publicity, but also raised more than £25,000 for the charity, an amazing result.

With COVID hitting hard in the second quarter of the year, and with core events like the London Landmarks Half Marathon being cancelled, our fundraising focus was obviously impacted. We also made a policy decision not to push our supporters as we knew that many of them were facing their own challenges and significant uncertainty.

But the fourth quarter saw renewed interest in grassroots fundraising as many of our supporters began to reach out and re-engage with the charity. We therefore decided to run a matched-funds campaign over Giving Tuesday, with a single donor offering to match up to £10,000 in donations. With great support from many we were able to exceed that target and raised more than £20,000 for EHE research.

There are of course still COVID-related uncertainties ahead, so we will continue to undertake our fundraising activities with care and consideration for the current situation. However, the energy and renewed support we have seen suggests that many of our supporters are once again determined to assist in raising the funds we need to keep our exciting EHE research programme moving forward.

Objectives and 2020 Achievements

We believe it is important that we report openly and honestly how we did against the objectives that we set ourselves for the year, so that all those who support us can see how the charity is performing. On this page we have provided a summary of our achievements against our 2020 objectives. Of course, our 2020 objectives have been heavily affected by COVID19, and in some cases have therefore been rolled over into 2021.

	What we said we would do...	...and what we achieved
01 Patient Support and Advocacy	Promote National EHE Biobank and engage with patients.	Biobank delayed by COVID. Final approval awaited at year end.
	Promote international collaboration.	Regular EHE international group meetings held.
	Engage with European patients.	Deferred to 2021 due to COVID.
	Promote profile of EHERCC.	All UK sarcoma centres contacted.
	Increase engagement with UK patient community.	Zoom call held. New Exec Director engaging with volunteers. New social media accounts established.
02 EHE Research	Promote international collaboration including evaluating new proposals.	Largely deferred to 2021 due to COVID. Focus on supporting existing research during COVID.
	Assist with finalisation of UK National EHE Biobank.	Assisted with all required input. Final approval awaited at year end.
	Conclude PEACE project engagement and enrolment into biobank.	Deferred to 2021 due to COVID.
	Communicate research progress with patient community.	Achieved through Zoom call, The Pledge quarterly newsletter, and Facebook posts.
03 Fundraising and Finance	Support and encourage grassroots fundraising.	Adopted passive approach during COVID crisis.
	Complete fundraising strategy.	Abandoned due to COVID. We will re-assess once we see the post-COVID fundraising landscape.
	Develop strategy with RMH-ICR for funding of key biobank resource.	Deferred to 2021 due to COVID.
	Seek to secure fundraising expertise through voluntary sector.	Temporarily suspended as we wait to see post-COVID landscape.
Charity Organisation	Evaluate Board of Trustees expertise to support future growth.	Dr Oliver Pearce joined Board of Trustees.
	Engagement of an experienced charity professional.	Engaged Mike Rich as part-time Executive Director.
	Expansion of the Research and Medical Advisory Team.	Deferred to 2021 due to COVID.
	Review organization goals.	Deferred to 2021 due to COVID.

ehe Biobank

Dr Oliver Pearce

Mike Rich

Our Forward Focus for 2021

Because rare cancers are not rare to those who have them

Our forward focus continues to be on the four key areas that will deliver a robust, vibrant and dynamic charity creating real progress in the battle against EHE.

Objectives for 2021 and beyond are listed below. Several of these objectives are the same as those that we listed for 2020, due to their deferral because of the COVID19 pandemic.

01 Patient Support and Advocacy

- Promote UK National EHE Biobank and maximise patient engagement
- Join appropriate European patient umbrella groups and expand European patient and clinical/research engagement
- Engage with regulators concerning tissue management and EHE treatment approvals
- Maintain contact with sarcoma centres

02 Research

- Promote EHE research and international collaboration
- Assist with launch of UK National EHE Biobank
- Conclude PEACE project engagement and enrolment into biobank
- Support existing research projects
- Promote and evaluate new research initiatives

2021 AND BEYOND

03 Fundraising

- Support and encourage grassroots activity
- Review fundraising strategy post COVID, including recruiting volunteer fundraising professional
- Develop strategy for longer-term EHE biobank financing
- Assess possible European grant award to assist with European strategy

Charity Organisation

- Identify and invite patient representatives to join the Board of Trustees
- Continue to seek to expand Research and Medical Advisory Team
- Continue review of appropriate policies
- Review organization goals and conclude strategy and support required for success in post-COVID environment

Consensus paper

In spite of COVID19, which made the last two years a terrible time for all of us, in 2020 the EHE community reached the goal of building the first consensus document on the clinical management of EHE, in collaboration with the worldwide community of experts and patient representatives, including particularly the EHE Rare Cancer Charity UK (EHERCC).

This consensus paper is now published as an open access paper available to all doctors, researches, and patients and their caregivers who need it. We really hope that this document will help increase the knowledge of the disease, harmonizing the treatment of EHE patients all around the world, minimising misdiagnosis, mistreatment and discrimination, and will provide a strong foundation for the years ahead. Thank you to everyone who made this achievement possible!!!

Dr Silvia Stacchiotti is a medical oncologist, working in the Adult Mesenchymal and Rare Tumor Medical Treatment Unit, at the Fondazione IRCCS Istituto Nazionale Tumori (INT), Milan, Italy. She is involved in all institutional research activities on adult bone and soft tissue sarcomas (STS), with a specific focus on ultra-rare sarcomas, among which, in particular, EHE. Her research includes identification of new targets and new anticancer treatments for specific sarcoma types, studies on the immune-profile of sarcomas as well as on mechanisms of resistance to therapy and the development of preclinical models of sarcomas. She is the current president of the Italian sarcoma Group and collaborates with the Italian Network on Rare Tumors. She is the faculty coordinator of the Sarcoma track of the European Society for Medical Oncology (ESMO) and the subject editor of the ESMO guidelines committee for sarcoma and GIST. She is a member of the Board of Directors of the Connective Tissue Oncology Society (CTOS) and is the chair of the systemic therapy subcommittee of the EORTC Soft Tissue and Bone Sarcoma Group. She collaborates with several sarcoma Patients Advocacy Groups, among which in particular the EHE Rare Cancer Charity (UK) and The EHE Foundation in the USA, for both of whom she serves as a member of the respective medical advisory boards.

Foreword
Dr Silvia Stacchiotti

(Oncologist at The Instituto Nazionale dei Tumori (INT) in Milan, Italy)

In December 2020, we promoted a consensus meeting on this rare tumor under the umbrella of the European Society for Medical Oncology (ESMO), because guidelines for diagnosis and treatment were currently lacking and EHE patients are treated inconsistently across the world resulting in suboptimal outcomes.

Potential treatments include a number of loco-regional therapies, systemic agents, and also liver transplantation, but the degree of uncertainty in selecting the most appropriate approach remains high. Prior to the herein-presented consensus, the meeting was preceded by a comprehensive literature review and retrospective efforts to collect data on systemic treatments used to cure EHE patients, including sirolimus, and to identify prognostic factors. The consensus document is now signed by an international community of more than 80 sarcoma experts from several disciplines and from the major referral institutions in Europe, North America and Asia, with the contribution and the sponsorship of the Epithelioid Hemangioendothelioma foundations.

We do expect this paper to become the state of the art of diagnosis and treatment of EHE and the basis to build any future study. It will be disseminated by scientific networks and social media. A lay version for patients in many different languages will also be prepared. While EHE is indeed a rare tumor, we hope that this publication will help the EHE community and avoid the discrimination that patients with rare cancers often have to face. We do believe that this will help harmonise EHE management worldwide and ultimately benefit the most number of patients possible. In addition we do expect this report to be of great value in ongoing negotiations with the regulatory bodies (FDA, EMA and the like) about the process to develop and approve new agents for this disease. This is even more important since new compounds for treatment of EHE are now happily under development and new clinical studies are about to start.

In addition, the collaboration and support of the EHERCC and The EHE Foundation is making it possible to fund collaborative translational studies aimed at the identification of prognostic factors and mechanisms of disease progression, particularly including investigation into the role of inflammatory cytokines and hormones. 2020 has seen also the establishment of the first PDX model of EHE and of its corresponding cell line. This is of the highest importance in a rare disease, like EHE, in which it is so difficult to conduct clinical studies. New compounds and combinations can indeed be tried in the preclinical model and then translated into clinical studies once we see preliminary promising signs of anti-tumor activity. Indeed, this type of experiment is already under way.

Finally, a new platform to prospectively collect data on EHE patients is being considered and we hope will be established in Europe. This will be the basis for a prospective, international registry, fully dedicated to EHE, opening the way to a better understanding of the disease and its natural history.

All this would never, ever be possible without the strong and effective collaboration between EHE Patients and the experts, the exponential growth of which is probably the best news of 2020 and for the years to come.

Dr Stacchiotti

The EHE Rare Cancer Charity (UK) would like to thank Dr Stacchiotti, and her team at INT in Milan, for the wonderful support and care they provide for EHE patients globally. We are also very grateful for the time given by Dr Stacchiotti to write this foreword for our 2020 Annual Report.

01 Patient Support and Advocacy

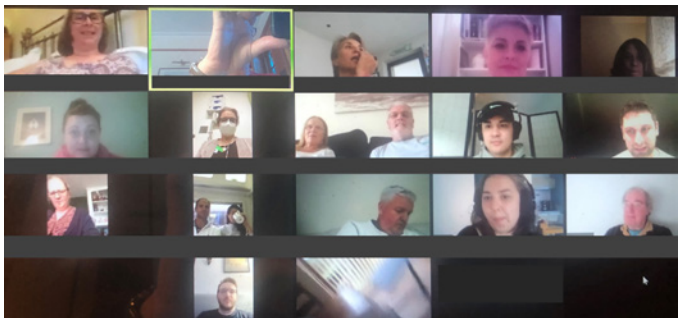
For many people, the social restrictions imposed by COVID19 on everyday life in 2020 came as a huge shock. People felt isolated and frightened, and many talked of the psychological stress they now faced. Indeed, our national media have rightly been shining a spotlight on the impact this is having on so many individuals. Yet for EHE patients, living with an ultra-rare cancer, these feelings of fear and isolation, and dealing with the relentless psychological stress of their diagnosis, are things they live with year in, year out, without any immediate hope of a treatment that will bring a swift and happy end to their situation. For all EHE patients, particularly those who have transplants or are undergoing treatments where their immune system is suppressed, the fear of how COVID19 may impact their EHE has added yet greater anxiety.

So 2020 proved to be a year in which the patient connectivity that our social media forums provide was even more valuable than ever before. Already established over the preceding six years, and with a global community involving more than 2000 people across more than 75 countries in the world, participants quickly engaged on all issues that concerned them about COVID and EHE. Questions were posted and responded to, and although answers were not available for all questions, the sharing of concerns and the discussion of the issues helped so many quickly come to terms with the pandemic. We once again must thank everybody that contributed to the forums for giving their time and energy and, through that, for the care and comfort they helped provide.

Review by Hugh Leonard

As outlined on the facing page, 2020 was an exceptional year for EHE patients across the globe. Yet the support that was provided tirelessly by so many people, many of them EHE patients themselves, was inspiring and wonderful to watch. This is particularly important for isolated patients who may be living in places with less developed medical care, and where feedback and information can be so important.

But the pandemic also had surprise benefits. One of these was the almost global acceptance and exposure to virtual meeting platforms, such as Zoom, Teams and Skype, to name just a few. With almost everybody becoming comfortable with these systems, the EHERCC was delighted to hold its first Zoom meeting in July. This proved to be a lively discussion with a lot of energy and ideas exchanged. We were also delighted to be able to introduce Mike Rich to the UK patient community. Mike has many years experience working in the charity sector and agreed to join us as Executive Director on a voluntary and part-time basis, bringing huge amounts of experience into the group.

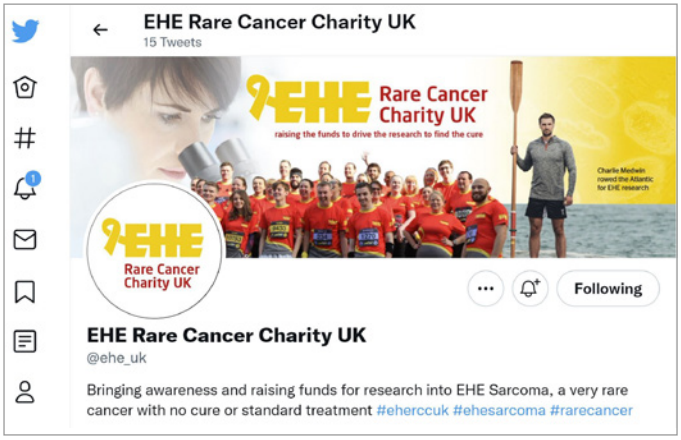


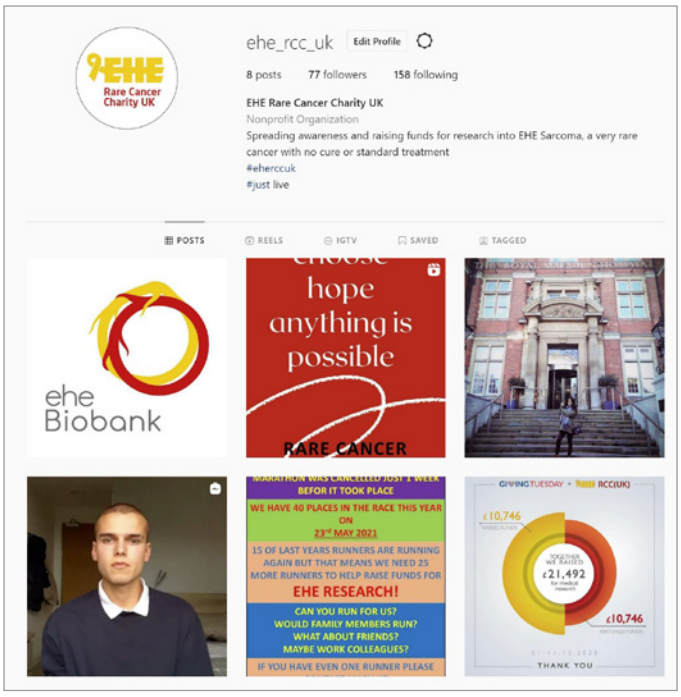
EHERCC Zoom call in July

One of the key issues agreed on this group call was the intent to establish volunteer groups to assist in key areas of the EHERCC's activity, including awareness, fundraising, and improved communications.

While the pandemic continued to create problems in areas such as fundraising and research, the EHERCC communications group, led by Allana Parker, were not the slightest bit curtailed in their thinking and foresight. Discussions with the UK patient community quickly identified that introducing UK-specific social media was not only sensible but that it was now necessary and something the UK patient community wanted.

The team set about building four new UK-focused EHE sites, on Facebook, Instagram, WhatsApp and Twitter. By the end of the year all four were successfully launched and are now active.





There have been some programmes casualties, however, to the COVID pandemic, and one of these has been the planned engagement and reach-out to the European community. Although the process did not progress far, we have completed our evaluation of the European-focused patient support groups we will apply to join in 2021, prior to beginning the process of creating a European EHE patient network. We are excited about this next phase of activity, hopefully allowing us to engage with, and support, an even larger group.

02
EHE Research

2020 was a strange year for research. The first quarter was unaffected by COVID, and yet, at the end of March, the national lockdown brought all projects to a standstill. The second quarter was lost almost completely, but the third quarter saw research labs reopening tentatively, with a more sustained return through the fourth quarter. At the end of the year we also began to receive enquires about new projects, and extensions of those we are already funding. This is very encouraging and leaves us once again excited about the future.

We have provided a summary of the main projects we are sponsoring on these pages, together with some thoughts and observations about the future. We hope that you will also find these exciting.

Project 1:
Developing an EHE zebrafish model

Over the past two years, a small team in Sheffield has been working hard, trying to generate an EHE zebrafish model. A zebrafish model would be a wonderful addition to EHE research as these fish are far cheaper and quicker to produce, and therefore far lower cost, than mice. However, the project has proved difficult with TAZ-CAMTA1 expression not presenting in endothelial cells. This was surprising as a parallel construct using GFP (green florescent protein) had been successfully introduced.

Dr Fredericus van Eeden, the Principal Investigator for the project, believes that a number of possible causes for this failure to achieve TAZ-CAMTA1 expression can be hypothesised. There could, for example, be sequence elements in the construct that lead to repression of expression. Codon optimisation was used to try and address this issue but does not change the sequence completely and although the team used two different approaches, it may not have "hit" the relevant bases. If the mechanism of this repression can be identified and understood, the team also hope that it might perhaps be therapeutically exploited in EHE tumours in humans. A detailed understanding of this mechanism is therefore warranted. In addition, understanding of the precise reasons may allow us to relieve this repression and gain epithelial expression. A new, four element, one-year project extension is under consideration.

The first approach will be to examine if there are sequence elements in the construct that prevent expression under control of the fli1a promoter that has been used.

The second approach has arisen following dialogue with Dr Valerie Kouskoff in Manchester who is also working on EHE. Importantly, Dr Kouskoff found that in embryonic stem cells the TAZ-CAMTA1 expression can lead to downregulation of endothelial markers including fli1 expression (the mammalian equivalent of fli1a). To provide the best model of the disease, the same promoter should be used as is actively driving TAZ-CAMTA1 in the human condition. In addition, the team will clone a similar element from the zebrafish and test both of these for driving expression in zebrafish and endothelial cells, initially using GFP as a reporter.

The third element of this year's work will address the issue faced with previous assays where the team only established that lines were not behaving as expected after creating a line, which takes a significant amount of time (3-4 months). It is clear from the team's previous attempts that TAZ-CAMTA1 requires more checks. Therefore, they will also do *in vitro* experiments before progressing with transgenesis in fish.

Review by Kate Hooper and Oliver Pearce

Assuming that the results of the first three elements are positive, the fourth element will be to apply these findings to hopefully create an EHE zebrafish model. Only when the team are convinced from their *in vivo* and *in vitro* experiments that the construct is working as expected, will they progress and raise transgenic lines.

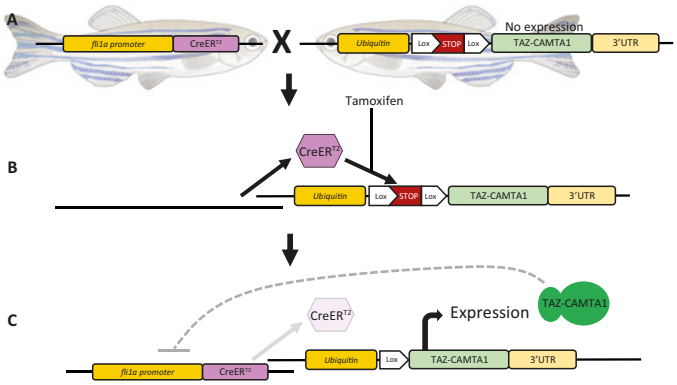


Fig: Strategy for driving TAZ-CAMTA1 in endothelial cells. Fish containing a fli1a driven CreERT2 and a silenced TAZ-CAMTA1 expression construct are crossed together (A), the resulting larvae containing both constructs express an inactive form of Cre in the endothelial cells -when activated with tamoxifen 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).

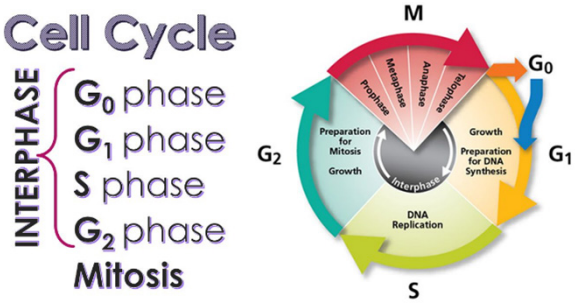
Project 2: Understanding the biology of how EHE affects endothelial cells

Despite university laboratories being completely shut down early in the year and then reopened, but with restricted access through a large part of the rest of the year, Emily Neal who is undertaking the EHE research PhD at the University of Manchester in Dr Valerie Kouskoff's laboratory, has been able to make good progress through the last quarter of the year.

Emily's PhD is seeking to show how EHE affects endothelial cells, and, in particular, to determine how TAZ-CAMTA1 activity and expression is regulated in endothelial cells. During the fourth quarter Emily was focused on three different approaches:

The first approach was to evaluate the transcriptomics of different endothelial cells. Transcriptomics is the identification of genes, using RNA sequencing, which are expressed during the transcription process in cells. This analysis was undertaken by inducing TAZ-CAMTA1 in endothelial cells at 10 days old. The cells were then separated into four different groups with different levels of TAZ-CAMTA1 expression. These are: (i) uninduced cells; (ii) cells with no TAZ-CAMTA1 expression; (iii) cells with low TAZ-CAMTA1 expression, and (iv) cells with high TAZ-CAMTA1. RNA sequencing will be used to identify the genes expressed, and the resultant differences for the four different groups of cells will be used to begin to understand what biological processes within the cell are altered as a result of TAZ-CAMTA1 expression. This final RNA sequencing is planned for the start of 2021.

The second approach was to use cell cycle analysis, as naturally-occurring TAZ is known to be involved in the cell cycle. The cell cycle is the name for the process by which our cells grow and proliferate, with different phases of the cycle given different names. The G1/G2 phases relate to cell growth periods. The S phase is the part of the cycle where the cell nucleus replicates and divides. The M phase is where the cells divide to produce two identical cells. The G0 phase is a sort of 'holding pen' where cells that have not yet fully synthesised their DNA are held until they are ready to move on to the S phase.



The objective of this part of the research is to see if TAZ-CAMTA1 affects the cell cycle. By analysing endothelial cells where TAZ-CAMTA1 was induced at 10 days, and then stained and analysed using flow cytometry, the number of cells in the different phases could be seen for different levels of TAZ-CAMTA1 expression. Early results have shown that in cells expressing TAZ-CAMTA1, a higher proportion are in the S phase than in cells with no TAZ-CAMTA1, but a lower proportion are in the G0/G1 phase. There was, however, no obvious difference in the proportions in the G2/M phases between all cell types. This suggests that TAZ-CAMTA1 expression increases the ability of cells to enter the S phase of the cell cycle. The question remains as to whether this leads to greater cell proliferation, or whether the cells remain arrested in the S phase, something that may be indicated by the lack of difference in cell proportions in the G2/M phases. Emily will be undertaking further research to try and answer these questions.

The third approach involves determining whether, in cells that are exposed to external mechanical stimuli, TAZ-CAMTA1 localisation and/or expression is affected. This is of interest as it is known that normally occurring (wild-type) TAZ is affected by such stimuli. This is also an interesting point because the mechanics within tumour tissue are quite different to surrounding non-tumour tissues.

The experiment took endothelial cells at 10 days old, induced TAZ-CAMTA1, and then introduced three different inhibitors of three proteins that are known to communicate mechanical stimuli to wild-type TAZ. The inhibitors used in these experiments are altering the internal cell cytoskeleton, so the current approach isn't actually altering the mechanics of the environment directly, but is replicating the effect that such mechanical stimuli might have on the target cells.

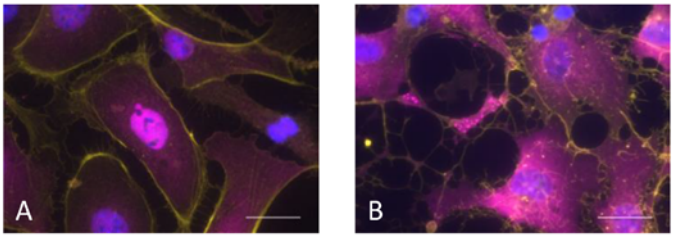
02 EHE Research Continued

The effect of these three inhibitors was then investigated by analysing where the TAZ-CAMTA1 appeared in the endothelial cells.

Early results showed that these inhibitors did have an effect on the TAZ-CAMTA1 expression. In one case the inhibitor seems to have reduced the overall number of cells expressing TAZ-CAMTA1. The other two inhibitors did not reduce the overall number of cells expressing TAZ-CAMTA1, but did seem to reduce the level of TAZ-CAMTA1 expression in those cells.

Finally, fluorescence microscopy techniques were used to visualise where the TAZ-CAMTA1 is situated within the endothelial cells. This revealed that TAZ-CAMTA1 was predominantly located in the nucleus of uninhibited endothelial cells. The addition of each of the inhibitors however increased TAZ-CAMTA1 presence within the cell cytoplasm, but did not completely remove it from the nuclei (see Fig 1). Taken together, this provides preliminary evidence that mechanical stimuli may have a role in TAZ-CAMTA1 regulation, resulting in its degradation and relocation into the cytoplasm.

Fig 1



Slide A shows endothelial control cells expressing TAZ-CAMTA1 but with no inhibitor treatement. The pink/purple areas show the location of TAZ-CAMTA1, almost exclusively in cell nuclei.
Slide B shows endothelial cells treated with inhibitor (blebbistatin). Again the pink/purple areas show the location of TAZ-CAMTA1 which is now predominantly present in the cell cytoplasm, but with some presence remaining in the nuclei.

All three of the approaches taken are delivering very interesting results about TAZ-CAMTA1 and its effects on the biology of endothelial cells. These of course are preliminary results, with further experiments required and planned to understand the implications to endothelial cells, and therefore EHE disease, and ways we may treat the disease. This will form the focus for 2021.

Project 3:
Launching the National EHE Biobank

In August 2019 the EHERCC initiated funding for the role of Tissue Manager at the Institute of Cancer Research in London. Managed by Dr Paul Huang, this new role, filled by Emma Perkins, was focused on developing the UK National EHE Biobank to capture and store samples from EHE patients for use in research.

As for many other projects, progress through 2020 was delayed by COVID19, but the EHERCC was delighted to be able to report at the end of the year that final ethics approval for the biobank had been received. Work was underway to complete all procedural approvals prior to the biobank going live in early 2021. When it does go live, participation in the biobank will be open to everybody in the UK, regardless of location, as this will be a national biobank, and will therefore allow patients to ask for their samples to be included wherever they live. Patients will be able to achieve this by either asking their hospital and doctors to enrol them and send the samples, or they will be able to enrol directly with the Royal Marsden team who will then contact the patient's hospital. Patients will just need to provide their consent. Patients will also be able to give blood samples at their local hospital and these will be sent to the Marsden.

The EHERCC is hoping that blood samples can be collected from participating patients every time they have a consultation. The biobank also want to collect samples from diagnostic biopsies, as well as from surgery to remove tumours during treatment. There may, in some cases, be other fluid samples that would be useful to collect. So even if patients are on 'wait-and-watch', there are important contributions that they can make.

The EHERCC wants to thank the Royal Marsden Hospital who have been instrumental in helping set the biobank up, and who will be managing and storing the samples at the Royal Marsden Generic Tissue Bank. We also want to thank the ICR for their involvement. We could not be more grateful for their brilliant support.

Project 4:
Identifying cytokines and hormones as possible biomarkers of EHE

The EHERCC was also delighted to be able to report that they had completed the signing of their first joint EHE project in Europe. This is an exciting project as it is the first time the EHERCC has signed a funding agreement with a European research facility. It is also the first collaborative research project the EHERCC has supported that involves a collaboration with three different organisations.

The European entity is The Instituto Nazionale dei Tumori (INT) in Milan, Italy. Researchers there will be collaborating with The Institute of Cancer Research (ICR) in London, UK. The third entity is Memorial Sloan Kettering (MSK) in New York, USA. The EHERCC funding, in combination with funding from the EHE Foundation in the USA, is for INT and the ICR only, as the MSK work is being funded by a private donation in the USA.

FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

ICR The Institute of Cancer Research

The project has two key objectives. The first is to assess: i) the profiles of circulating cytokines, hormones and micro-RNAs; and ii) hormone expression and activation of YAP/TAZ in tumour tissues; both as a function of the clinical course of the disease. To this end the analysis will be conducted on the whole study patient population compared to healthy controls, and by stratifying EHE patients who will enter the study in three subgroups according to disease behaviour (non-growing disease, slow-growing disease, highly aggressive disease with evidence of pleural effusion and systemic symptoms). The second objective is to identify and validate novel biomarkers to inform patient management (prognosticators and predictors of response to medical agents) as well as potential therapeutic targets.

Work on the actual research will start in early 2021. The EHERCC is thrilled to have three such prestigious institutions engaged in this important research. We look forward to providing further updates in our quarterly newsletter, The Pledge, and in our future annual reports.

ESMO (European Society of Medical Oncology) holds major EHE event

At the start of December, Dr Silvia Stacchiotti, based at INT in Milan, chaired a virtual ESMO meeting on the *"Development of the Consensus and Guidelines for EHE treatment"*. This is a standard ESMO procedure where disease experts are brought together to discuss all aspects of the disease with a view to agreeing the *"Consensus and Guidelines for EHE Treatment"*. Hugh Leonard from The EHERCC in the UK and Medha Deoras Sutliff and Jane Gutkovich from The EHE Foundation in the USA were invited to attend the meeting as patient representatives.

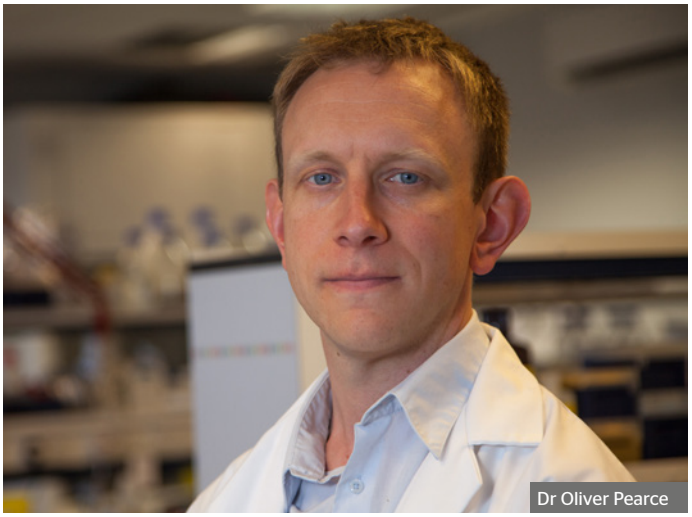
The 6-hour meeting involved 90 oncologists, surgeons, radiation oncologists, and palliative care specialists, mostly from Europe, but also included guest specialists from the USA, Japan, Canada, and India. The main body of the meeting consisted of an extraordinarily thorough discussion of all aspects of EHE management including proper diagnosis, prognosis, treatment of EHE in different organs, the role of systemic therapy, etc. Doctors developed a preliminary consensus on the proposed clinical approaches.

The edited draft will be circulated when ready for final comments, and the final draft will be submitted to the journal *"Annals of Oncology"* for publication.

We could not be more grateful to Dr Stacchiotti, ESMO, and all those who took part, for their time, dedication and the focus given to EHE in this amazing process. We look forward to seeing the final paper once approved.

Dr Oliver Pearce joins the charity

One of the key objectives of the charity in 2020 was to enhance the research understanding and capabilities of the Board of Trustees. The charity is therefore delighted to be able to confirm that Dr Oliver Pearce, Group Leader at the Barts Cancer Institute in London, joined the Board of Trustees during the third quarter of the year.


Dr Oliver Pearce

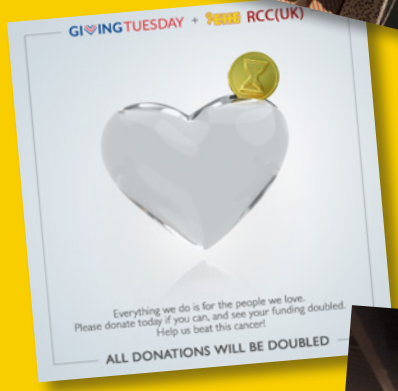
Dr Pearce's research group at Bart's is focused on the tumour microenvironment (TME); they are particularly interested in understanding the composition and function of the tumour extracellular matrix in immunosuppression. Dr Pearce brings state-of-the-art cancer research experience onto the Board of Trustees.

03 Fundraising and Finance

2020 was a significantly challenging year for all charities. The concept of group activities was no longer possible, bringing a temporary halt to the major fundraising events on the annual calendar. Even small and personal fundraising became very difficult. More importantly, many people faced significant uncertainty regarding their own, immediate future. Even the largest foundations were heavily affected, with their fundraising significantly reduced; meanwhile, for those still able to support important causes, demand for their limited funds became far greater.

In this environment, the Trustees recognised that it would be extremely difficult for our supporters to continue to fundraise, and that to continue to encourage them to do so was not therefore acceptable. We would of course encourage and assist anyone who chose to fundraise for us, but this would only be in cases of fundraising initiated by our supporters.

Of course EHE did not stop presenting or progressing in patients because of COVID19. EHE research therefore remains as critical today as it did before the COVID19 pandemic, and so fundraising to support that research will continue to be at the core of our activities. We were also confident that as soon as COVID19 restrictions began to ease, our wonderful supporters would re-engage. We were therefore delighted to see that re-engagement beginning as early as the fourth quarter of 2020. We leave the year therefore feeling very positive about 2021!



Review by Jeff Collins

2020 was a difficult year but, despite the challenges faced by everybody, fundraising continued, albeit at a lower level than previously enjoyed. We are also excited about the outlook for 2021 and will be working as hard as ever to assist and encourage our wonderful supporters.

Although significantly curtailed by COVID19, our wonderful supporters were still able to raise an amazing £53,100 in 2020. Their support and dedication was even more important in such difficult circumstances.

Good examples of the challenges faced were the cancellations of both the London Landmarks Half Marathon in late March, and the Prudential RideLondon100 event in July, both core events in our fundraising calendar. While the RideLondon100 event has in fact been permanently cancelled, the London Landmarks Half Marathon will restart in 2021, and we are delighted to already have 40 runners signed up.

We were also delighted to see Charlie Medwin and his colleagues safely complete the Talisker Whisky Atlantic Challenge at the start of the year, rowing more than 2,900 nautical miles to raise more than £25,000 for EHE research, partly in 2019 and partly in 2020.

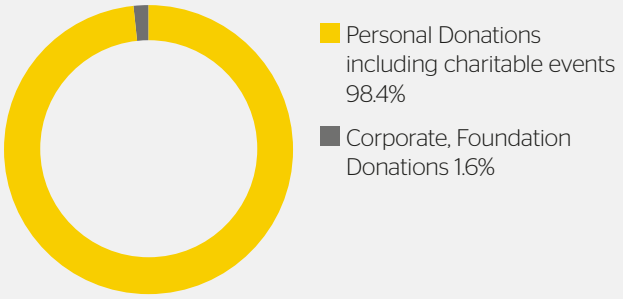
In 2020, we once again received the generous support of a single donor who funded 100% of the charity running costs. As in all previous years, we segregated these funds, donated for administration purposes, from those received from all other sources, which can therefore be allocated to fund our key objectives, and in particular, EHE research. It is the intention of the Trustees that the same will be true in 2021.

Key Objectives
In the 2020 calendar year our supporters raised a total of £51,900 for the charity's key objectives.

During 2020, our EHE research projects were suspended for a period in the second quarter, and operated on a restricted basis thereafter. Where possible, the research institutes worked with us to reduce and defer costs during these periods, for which we are very grateful. However, despite these delays, key projects were able to advance and our investments during the year of £118,400 continued to produce interesting results through the year. In addition, we were pleased to received final ethics approval for the National EHE Biobank, and sign agreements for combined biomarker research between INT in Milan and the ICR in London.

For existing multi-year research projects, the charity has recognised all funding obligations for future years (2021 and beyond). Details can be found in the notes to the financial accounts.

Source of funds



Administration/business running costs
The charity received funding of £1,200 for its administration and business running costs account. During 2020, £13,500 of expenses had been incurred, which included an accrual of £1,200 for the independent examiner's fee. The remaining £12,300 funded fundraising events scheduled for 2020, publications and other administrative costs and consulting fees to develop our fundraising strategy. The Charity had sufficient funding from prior year donations to meet these additional costs in excess of the current year donations.

"Despite the challenges faced in 2020 due to COVID19, we were pleased that our supporters were still able to assist us in raising important funding for critical EHE research. We also worked hard to ensure that costs were minimised and/or deferred in any areas where activity was curtailed during the year, including the research we are funding, and would like to thank all the associated institutes for their support in managing this difficult period. We were also pleased that our underlying policy of ensuring we do not expose the charity to funding commitments beyond our means meant that the challenges faced in 2020 did not at any time threaten any of our activities. This is a policy we will continue to follow. As in all previous years, the wonderful support the EHERCC receives comes in many different forms. I would once again like to take this opportunity to thank all the volunteers who have donated their time so generously, and to the companies and organisations who have provided their services at no or reduced costs. Special mention again goes to SFC Bennett Brookes who for the sixth year running have donated their bookkeeping services to the charity. Thank you."

Jeff Collins

Wonderful support for EHE in 2020

The following pages highlight the key fundraising events we were able to complete in 2020.

Rowing the Atlantic

Most people will have welcomed in 2020 with friends at a local party, or maybe with family at home, or even tucked up in bed asleep. Charlie Medwin, however, together with Lewis Matthews and Tom Whittle, welcomed the New Year sitting in a small boat in the middle of the Atlantic Ocean. Taking part in the Talisker Whisky Atlantic Challenge, under their team name All-Oar-Nothing, these three brave men were rowing in support of their respective charities. Charlie's chosen charity was the EHERCC, as his younger brother has EHE.

The All-Oar-Nothing team reached the finish line on 20th January after rowing more than 2,900 nautical miles. In the process, Charlie raised more than £25,000 for EHE research. We are so grateful for, and proud of, what these three fantastic men achieved.

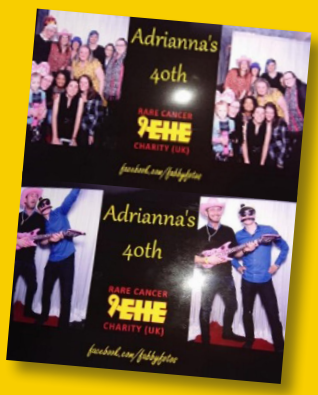
An amazing relay complete

It was on 1st January 2019 that Allana Parker posted news that her four wonderful friends, Natalie Ellis, Samantha Power, Ellen Cramoysan, and Sophie Kitchen, were embarking on a 400-day relay to raise funds for EHE research. These four very determined women each completed an amazing challenge over their 100-day section of the relay under the name EHERelayRaisers, all to help fund EHE research.

Their relay ended on 4th February 2020, and raised an amazing £4,424.49 which was presented to Hugh Leonard, Chair of Trustees, at their Masquerade Ball, held to celebrate the end of their relay. Allana thanked them for their wonderful support and noted that further donations had been promised. Indeed, when the final financial tally was posted by Allana on 19th February, the EHERelayRaisers total was confirmed at an extraordinary £4,964.49.

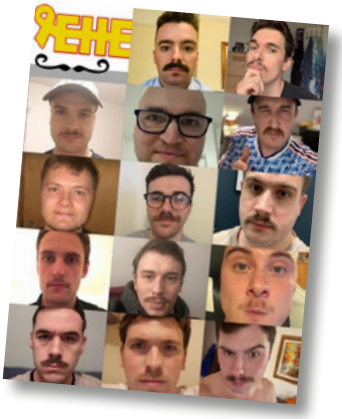
Partying the night away

On 15th February Adrianna Glennie decided to celebrate her 40th birthday with a party and gig at the Station Hotel in Stonehaven, Scotland. Adrianna wanted to raise money for two charities that are close to her heart. These are the EHE Rare Cancer Charity and Clan Cancer Support. It was a truly brilliant event with great music into the early hours of the morning.



Surprise for a mother

Tracey Betts shared news at the start of November of a huge surprise when, without telling her, her son Conor and 13 of his friends launched their campaign to grow moustaches through November in support of Tracey and EHE research.



Conor and his friends, with donations and gift aid, raised a staggering £3,031. That was doubled to more than £6,000 with our Giving Tuesday matched funding that included their campaign. Thank you so much guys! And here is the photographic proof of the moustaches grown!

What a night!

Allana Parker wanted to do something special to celebrate the end of the amazing EHERelayRaisers 400-day relay. As a group, these five women of boundless energy decided that holding a charity ball shortly thereafter was a great idea. And so, on 8th February, their EHE Masquerade Ball took place. And what a night it was. The event was spectacular with a wonderful setting, fantastic energy and amazing fun had by all who were there. The ballroom was spectacular, and there was also an amazing video backdrop featuring EHE patients from all over the globe, which ran continuously. And soon after the event Allana posted the wonderful news that the Ball and the relay together had raised an unbelievable £11,447.54!

EHE 2021 Wall Calendar

Our 2021 Wall Calendar initiative was started by Anna Wydro, to bring the EHE community together, but to also raise funds for EHE research. Using 12 photographs submitted by members of our worldwide EHE community, the final calendar looked spectacular. A total of 730 calendars were produced and distributed worldwide, to the UK, USA, Canada, Australia, Italy, Germany, Portugal, Finland, Poland, Greece, Ireland, Holland, Estonia, Hungary, and Belgium. Funds raised for EHE research totalled more than £6,300 or US$8,500. We thank and congratulate Anna on a great campaign, and Artur Rozwalak who, with Anna, provided the photographic and artistic input that made the calendars so special.

Donna and Amy raise more than £500

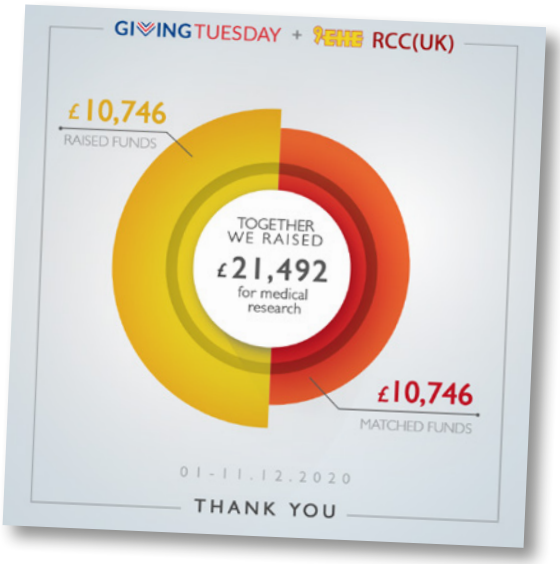
October saw two of Allana Parker's fantastic support network, Donna Watson and Amy Mills, complete their fundraising event for the EHE Rare Cancer Charity ". Donna explained:

"Last year was alcohol free for 1 month, and I raised £235! We would love to beat this. This year we are exercising before or after work for 31 consecutive days, biking, walking or running for 2 miles a day, a pretty big challenge for us as we haven't exercised for months."

So in early November, Allana was thrilled to be able to report that her friends had finished their challenge, raising £502 for EHERCC, topping the £235 they raised last October. *"I'm a very lucky person to have wonderful friends like these!"*

Giving Tuesday matched-funding a success

2020 was a tough year for charitable organisations across the globe, and the UK was no different. So we were delighted when, at the end of November, a kind benefactor offered to match all Giving Tuesday donations made to the EHERCC up to £10,000. We immediately brought this wonderful offer to the attention of all our supporters. Their generosity, including the donor agreeing that they would include Adrianna's gig in Stonehaven, and Connor's moustache growing buddies, meant that we reached our target, and secured £10,746 in matched funding. We of course send our sincere thanks to the donor who so generously provided the matched funding.



EHE Rare Cancer Charity UK

Financial Accounts for 2020

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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 2020.

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: 21 October 2021

EHE Rare Cancer Charity (UK)
Statement of Financial Activities
for the period ended 31 December 2020

	Notes	Unrestricted funds £	Restricted funds £	**Total 2020 £**	Total 2019 £
Incoming resources:					
Donations	2	51,867	1,200	**53,067**	158,445
Total incoming resources		**51,867**	**1,200**	**53,067**	158,445
Resources expended:					
Costs of generating donations		1,186	3,262	**4,448**	6,744
Charitable activities		118,365	-	**118,365**	115,653
Governance costs		-	1,200	**1,200**	1,200
Other administrative costs		99	9,011	**9,110**	7,148
Total resources expended	3	**119,650**	**13,473**	**133,123**	130,745
Net surplus for the year		**(67,783)**	**(12,273)**	**(80,056)**	27,700
Transfer between funds		-	-	-	-
Balance brought forward		447,339	12,623	**459,962**	432,262
Funds carried forward	8	**379,556**	**350**	**379,906**	459,962

Funds carried forward for 2020 £379,906

EHE Rare Cancer Charity (UK)
Balance Sheet
as at 31 December 2020

	Notes	Unrestricted funds £	Restricted funds £	**Total 2020 £**	Total 2019 £
Current assets					
Debtors	5,9	229,408	1,361	**230,769**	255,430
Cash at bank and in hand		321,937	3,049	**324,986**	413,852
Total current assets		**551,345**	**4,410**	**555,755**	669,282
Creditors: amounts falling due within one year	6,9	(108,688)	(4,060)	**(112,748)**	(105,371)
Net current assets (liabilities)		**442,657**	**350**	**443,007**	563,911
Creditors: amounts falling due after one year	7,9	**(63,101)**	**-**	**(63,101)**	(103,949)
Net assets (liabilities)		**379,556**	**350**	**379,906**	459,962
Funds carried forward					
Unrestricted funds		379,556	-	**379,556**	447,339
Restricted funds		-	350	**350**	12,623
Total funds	8	**379,556**	**350**	**379,906**	459,962

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 19 October 2021 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 2020

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:

	2020 £	2019 £
Unrestricted funds:		
Personal donations including fundraising events	**51,055**	88,098
Payroll Giving	**-**	8,813
Corporate and Foundation donations	**812**	38,848
	51,867	135,759
Restricted funds:		
Administration fund	**1,200**	22,686
	1,200	22,686

3 Analysis of resources expended

	Unrestricted funds £	Restricted funds £	**Total 2020 £**	Total 2019 £
Costs of generating donations:				
Just giving fees	425	562	**987**	1,580
Fundraising event entry and other fees	-	2,700	**2,700**	4,286
Credit card and other processing fees	761	-	**761**	878
	1,186	**3,262**	**4,448**	6,744
Costs of charitable activities:				
University of Manchester PhD Study	33,433	-	**33,433**	45,535
Royal Marsden Biobank	56,000	-	**56,000**	30,333
Zebrafish Study University of Sheffield	28,932	-	**28,932**	22,105
Contributions to Albany Medical College	-	-	**-**	15,789
Telluride Support	-	-	**-**	1,891
	118,365	**-**	**118,365**	115,653
Governance costs:				
Independent examiners' fee	-	1,200	**1,200**	1,200
	-	**1,200**	**1,200**	1,200
Other administrative costs:				
Design and publishing	-	3,810	**3,810**	4,193
Website maintenance	-	1,750	**1,750**	1,609
Other professional fees	-	3,348	**3,348**	1,116
Bank fees	99	103	**202**	230
	99	**9,011**	**9,110**	7,148

Trustees' expenses

No expenses were paid to Trustees during the period (2019 – £363).

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 2020

5 Debtors

	Unrestricted funds £	Restricted funds £	**Total 2020 £**	Total 2019 £
Prepayment to the University of Manchester	94,269	-	**94,269**	127,702
Prepayment to Royal Marsden	51,333	-	**51,333**	81,667
Prepayment to Fondazione IRCSS Istituto Nazionale Dei Tumori	67,840	-	**67,840**	-
Prepayment to the University of Sheffield	-	-	**-**	28,932
Other debtors	15,966	1,361	**17,327**	17,129
	229,408	**1,361**	**230,769**	255,430

Included within the debtors figures above are amounts of £63,101 (2019 - £103,949) due after more than one year.

6 Creditors: amounts falling due within one year

	Unrestricted funds £	Restricted funds £	**Total 2020 £**	Total 2019 £
University of Manchester	49,101	-	**49,101**	49,420
Royal Marsden	25,667		**25,667**	30,333
Fondazione IRCSS Istituto Nazionale Dei Tumori	33,920	-	**33,920**	-
University of Sheffield	-	-	**-**	21,699
Accrued independent examiners' fee	-	1,200	**1,200**	1,200
Other creditors	-	2,860	**2,860**	2,719
	108,688	**4,060**	**112,748**	105,371

7 Creditors: amounts falling due after one year

	Unrestricted funds £	Restricted funds £	**Total 2020 £**	Total 2019 £
University of Manchester	29,181	-	**29,181**	78,282
Fondazione IRCSS Istituto Nazionale Dei Tumori	33,920	-	**33,920**	-
Royal Marsden	-	-	**-**	25,667
	63,101	**-**	**63,101**	103,949

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. The first payment was made in 2019 and the second in 2020 as contracted. There are no further scheduled payments and the project came to a close in 2020 with total project expenses of £28,932 recorded in 2020 (2019 - £22,105).

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 2020, £49,420 of payments were made and recorded as charitable activity cost offset by £15,987 of amounts refunded as not spend during 2018 and 2019 (2019 – expense of £45,535). The amounts committed to for 2021 and 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 2020, the second payment of £56,000 was made and £56,000 recorded as charitable activity cost (2019 – payment of £56,000 and £30,333 as charitable activity cost). No further payments are required and remaining prepayments and expenditures have been included within Debtors and Creditors as appropriate, which will be recognized in the Statement of Financial Activities in 2021 when the expenditures to which they relate are incurred.

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 costs of the project is €115,000 (£104,020) 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 (£36,180) of the total costs. The remaining €75,000 (£67,840) payable by the Charity has been included in Debtors and Creditors as appropriate.

10 Subsequent events

During 2021, it was confirmed that amounts forwarded to the Sarcoma Alliance for Research through Collaboration (SARC) in 2020 to fund a biopsy of US$5,000 (£4,048) were not required and were therefore returned to the Charity in 2021. An amount of US$5,000 (£4,048) has therefore been recorded as a Debtor in 2020 (2019 - £Nil).

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 was made. As the commitment was not incurred as at the balance sheet date, no amounts have been recorded as liabilities in the 31 December 2020 financial statements.

In July 2021, the Charity contracted with the Bateson Centre at the University of Sheffield to fund a 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.

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 2020. 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, 2021

(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

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 10.3.2021)
Dr Oliver Pearce

Established in 2015.

One of three charities (UK, USA and Australia) working on EHE.

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.

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 SFC Bennett Brookes for providing bookkeeping services to EHERCC

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Cover images

Researcher in 2020 COVID pandemic

Charlie Medwin and friends complete their Atlantic row, raising more than £25,000 for EHE research