Institution: University of Huddersfield (UOH)		
Unit of Assessment: 32: Art and Design: History, Practice and Theory		
Title of case study: Reducing Chemotherapy-induced Hair Loss through Innovative Design: Internationally Increasing Patient Access & Wellbeing and Facilitating Rapid Commercial Growth		
Period when the underpinning research was undertaken: 2008-2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Dr. Ertu Unver Prof. Mike Kagioglou	**Role(s):** Principal Enterprise Fellow Dean of Art, Design & Architecture	**Period(s) employed by submitting HEI:** 1999-Present 2013-2020
Period when the claimed impact occurred: 01.10.2015-31.12.2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Chemotherapy-induced hair loss is one of the most traumatic side effects of cancer treatment, its severe implications on patient wellbeing are well-documented. This research revolutionised the design and manufacturing process of the Paxman scalp cooling cap. The resulting award-wining product reduces/prevents hair loss during chemotherapy. Achieving regulatory approval internationally, the patented product became available in 54 countries between 2016-2020, dramatically increasing patient and clinical access to effective scalp cooling treatment, now reaching a minimum of 42,000 patients/annum. It was designed for a global market to meet the varying needs of patients and clinicians internationally, while enhancing cap-fit, treatment efficacy & patient experience. Global impacts on patient wellbeing have resulted and awareness has increased. Yorkshire SME, Paxman, are now the global leader in scalp cooling (80% market share) and able to supply an increasing number of the world's largest healthcare markets, promoting continued global growth with turnover quadrupling between 2015-2019 (£1.7M-£9.35M).

2. Underpinning research

Scalp cooling is a preventative treatment for chemotherapy-induced alopecia (CIA)/hair loss. Reducing scalp temperature limits scalp blood flow and drug delivery, minimising chemotherapy-induced damage to rapidly dividing hair follicle cells. The concept of scalp cooling has been recognised for >40 years but presented significant challenges for design and manufacture. Existing manual scalp cooling products included frozen gel/ice packs, which had limited effect due to lack of temperature control, poor-fit and patient discomfort. Machine-based scalp-cooling utilising continuous coolant-flow, provides a comfortable and successful treatment option, but patient access was severely limited primarily due to design and manufacturing constraints.

This case study describes the design, development, prototyping and manufacturing optimisation of the Paxman Scalp Cooling Cap. The research addressed the challenge of designing a highly effective and adaptable cooling-cap which met the varying requirements of patients and clinicians internationally, and the development of a novel mass-manufacturing method capable of producing the cap's complex geometry using CE/FDA approved biocompatible materials.

The research founded a strong collaboration between the University of Huddersfield's product design team, led by Dr E. Unver (1999-present, Principal Enterprise Fellow, editorial board member for "Design Journal") and SME Paxman Coolers Ltd. Paxman was initially formed as a spin-off from a beer-cooling company, in response to a family member suffering CIA. They installed their first prototype scalp-cooler in Huddersfield Royal Infirmary in 1997. Paxman saw steady growth and while the product innovatively addressed an unmet clinical need, design and manufacturing methods limited distribution and wider success, and scalp cooling remained an underutilized therapy. In 2012, an academic collaboration was established with Dr E. Unver, with his 3D design, additive manufacturing and mass customisation expertise providing the key to overcome these growth-limiting factors. Dr Unver's prior research provided a strong foundation for the novel integration of digital design and manufacturing technologies, which underpins this research. Dr Unver had previously created novel digital design and production methods by combining computer based generative systems with mass customisation and 3D printing technologies (2008) [3.1], supervising multiple PhD students and authoring articles in the field of mass customisation, additive manufacturing, 3D scanning, 3D simulations and rapid tooling.

Design challenge (2012-2014): The first stage of the research involved designing a single standard-size cap. A Design Thinking methodology was used to identify and integrate key design inputs, which included optimised scalp-fit (paramount to maximising treatment efficacy), uniform

coolant circulation, enhanced heat-conductivity and patient comfort, easy-to-use, simplified moulding and manufacture, and adherence to US/EU medical product approval processes. Anthropometric data and 3D laser scanning were used to create 3D heads for 3D CAD modelling [3.2] for concept generation. Multiple cap forms were investigated, the final concept involved creating a 3D folded silicone cap (Fig.1). Materials research identified medical-grade silicone sheet as the optimal material for its non-allergenic, antibacterial qualities and reliable wall thicknesses in the moulding process.

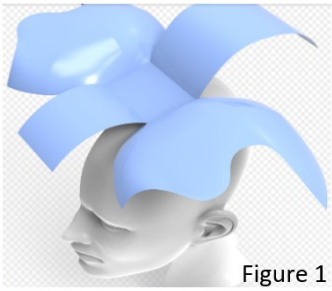
Figure 1

Production challenge (2015-2016): Traditional manufacturing technologies were unable to produce the complex geometry/forms required by the design parameters. **Tool Development:** Various technologies were investigated to create the tools required to produce the prototype. This included an international collaboration investigating the use of recyclable low-melting point alloy [3.3], but size limitations compromised this option. Ultimately, the research demonstrated the technical capability of 3D laser sintering as the optimal tool-production method and facilitated rapid generation of the tools, initially made from polyamides for prototyping [3.2] and later, alumide [3.4] for mass manufacture. The properties of the 3D printing materials were extensively evaluated in confidential manufacturing settings. Whilst both polyamides and alumide demonstrated appropriate thermal properties for silicone moulding at 100°C, alumide proved more durable in continued thermoforming cycles. Novel modelling methods were developed to achieve the required tolerances, surface quality, and define technical parameters.


Figure 2

Tooling development also involved designing a novel patented scalp-contact surface and cap channel design [3.5], in order to maximise scalp contact and heat exchange potential, while retaining adequate wall strength to contain the pressurised coolant.

Manufacturing-Method Development: The 3D-printed tools were then used to develop a revolutionary automated production method using twin-sheet silicone thermoforming, for the prototype (Fig. 2) and ultimately batch production, at a UK based silicone-manufacturer. This patented silicone manufacturing approach and system was a World-first [3.6].

Adaptation challenge (2017-2019): The novel combination of rapid-tooling and advanced manufacturing systems enabled affordable iterative design modifications, which were required to meet medical testing procedures and adapt to global markets, at significantly reduced tooling costs [3.4]. **Global adaptations:** Maximising scalp-cap-contact is essential to the success of scalp cooling treatment. Addressing global variations in head size and shape was a crucial step in generating an internationally successful treatment and product. Initially a product range based on Caucasian head shapes was developed, consisting of three cap sizes. Global variations in cranial anthropometry (head size/shape) were then evaluated to assess population head-shape variations, generating a 3D-scan database, ultimately leading to the mass production of a further 3 cap sizes/designs tailored to a more rounded, brachycephalic, Asian head size/shape.

The research was funded through an SME-led TSB grant (£55k allocation), then a KTP (2015–19, £181k), which was awarded "**Outstanding**" by Innovate UK.

3. References to the research.

Evidence of Quality: Publication in peer-reviewed outlets [3.1, 3.2, 3.3, 3.4] and international publication and granting of patents [3.5, 3.6]. References 3.2, 3.4, 3.5 & 3.6 are outputs of a KTP project (KTP9863, 2015-2019), rated Outstanding.

3.1 Unver, E., Atkinson, P., & Marshall, J. (2008) Automake Physics: Random Craft Production. *Computer-Aided Design & Applications*, *5(1-4), 58-65.* DOI: 10.3722/cadaps.2008.58-65. Peer-reviewed article developing novel digital design and production methods.

3.2 Unver, E., Sorbie, C., Silkstone, R., **Kagioglou, M.,** Paxman, R., Burke, P. (2016) Design & Development of a Medical Product Using 3D Technologies: Scalp cooling Cap Design Case Study. In: *Int. Conf.on Sustainable Smart Manufacturing (S2M), Oct 2016, Portugal.* DOI: 10.1201/9781315198101-13. Peer-reviewed conference paper. [can be supplied on request]

3.3 Durgun, I., Kus, A., **Unver, E.,** Jagger, B., Doruk, E. Findik, F. (2016) Experimental Investigation of Sheet Metal Forming Using a Recyclable Low Melting Point Alloy Tool. *Materials Testing Journal, 58(5), 475-480.* DOI: 10.3139/120.110871. Peer-reviewed article.

3.4 Unver, E., Binder, J., **Kagioglou, M.,** & Burke, P. (2020) An Approach of Rapid Tooling for Scalp cooling Cap Design. *Computer-Aided Design and Applications, 17(2), 337-347*. DOI: 10.14733/cadaps.2020.337-347. Peer-reviewed article on rapid-tooling for medical design.

3.5 Unver, E., Paxman, G. A. & Paxman, N. (2016) Patent: Heat Exchanger. WIPO WO/2016/046534 (152 states). **Granted in** UK:GB2530496B, Japan:JP6691108B2 and USA:US20170239082B2 **Published in** EU:EP3197407A1, China:CN107072808A. 3*Patent for cap scalp-contact surface novel design & manufacturing method.

3.6 Unver, E., Paxman, G. A. & Paxman, N. (2016) Patent: Heat Exchanger Cap. WIPO WO/2016/046535 (152 states). **Granted** UK:GB2528512B, EU:EP3197405B1 **Published in**, USA:US20170239083A1, Japan:JP2017529155A. 4*Patent cap design/manufacture method.

4. Details of the impact.

Hair loss/CIA is one of the most traumatic aspects of chemotherapy treatment, negatively impacting a patient's quality-of-life, psychological well-being, body image and social relationships. The fear of hair loss causes up to 8% of patients to consider declining potentially lifesaving, chemotherapy treatment (Marks et al. 2019). Overall incidence of CIA is 65% of chemotherapy patients with 65,000 UK patients and 3.12M worldwide affected annually.

This research has had global-reaching impacts, and was integral to International Regulatory Body Approval (2017-2019). The research has benefitted both patients and clinicians globally, significantly enhancing patient wellbeing, and internationally increasing patient and clinical access to effective scalp cooling treatment, since product launch in 2017. Furthermore, increased awareness has resulted, for the general public and clinical/research fields. Commercially, this research has facilitated SME Paxman to become the Global Leader in the scalp cooling field [a].

International regulatory approval: The patented, award-winning cap [b] was designed within the strict international regulatory framework producing a product suitable for a global market and facilitating successful regulatory approval internationally, including FDA (USA, 2017), Shonin (Japan, 2019), TFDA (Taiwan, 2017) and Brazil (Market Registration June 2019). Subsequent expanded regulatory approval (FDA 2018) further increased the number of patients able to benefit from Paxman scalp cooling, to include patients with solid tumours, as well as breast cancer.

Increased clinical/patient access & production: By revolutionising the design and cap manufacturing process, this research **increased production rates by 670%** and reduced production costs by 39% [a]. This has dramatically improved the company's capability to reach more clinics and patients globally, increasing the clinical availability and patient access to effective scalp cooling treatment. Designing the cap for a global market has **increased the treatment options** for patients internationally, even reaching clinics where no form of scalp cooling was previously offered [e,f]. Prof. M. Toi MD, Director of the Breast Cancer Unit, Kyoto University Hospital Japan, stated 'We started using Paxman Scalp Cooling caps at Kyoto University Hospital in 2016, prior to this we did not offer scalp cooling device treatment. We found that this method could prevent alopecia remarkably' [e]. The cap is now distributed to 54 countries, treating a minimum of 42,000 patients/year [a]. In the UK, Paxman now works with 98% of NHS and private hospitals [a]. Paxman have installed the highest number of scalp cooling systems/caps in the world with >3,500 systems in total, and >600 installed in the USA since 2017, reaching patients at 300 locations in 40 states [a] including the top five USA cancer centres (Honor Roll 2019-20). Until 2016, only manual caps were available to USA patients, which are not FDA-approved [c], the USA is now Paxman's largest market, with a growth rate of 700% in the 2-years post FDA approval [a].

The **revolutionary manufacturing approach** enabled the creation of innovative designs, which were previously impossible to manufacture. Pioneering the use of 3D printed tooling in silicone sheet moulding batch production, paved the way for mass manufacture. This low-cost printed tooling also enabled affordable design adaptations for regulatory approvals, expediting route-to-market, and **facilitated adaptations to address racial variations** in head sizes/shapes. The Japanese head shape is more brachycephalic (rounded) than that of Caucasians. A Japan-based clinical trial (The HOPE Study) initially utilised the Caucasian-fit cap for Asian patients but had reduced success rates, due to sub-optimal scalp-contact/fit. The manufacturing ability to rapidly/economically adapt the design to the more-rounded Asian head shape/size, significantly increased cap-fit for Asian patients [e]. These adaptations opened-the-door to the Japanese market, which is now Paxman's second largest market. This research enabled Paxman to mass-manufacture a range of 6 cap sizes, addressing racial head shape/size variations and meet the

needs of the global market [a]. Recently, Dr. S. Ohsumi MD, Chief of breast oncology, Shikoku Cancer Centre, Matsuyama, Japan, published clinical data which 'found that the efficacy of scalp cooling, with the Paxman Scalp Cooling System, during chemotherapy infusion for hair loss mitigation in Asian women is similar to that in Caucasian women' (Ohsumi et al. 2020) [f].

Enhancing patient wellbeing: The superior design of the cooling-cap reduces the incidence and severity of CIA/hair loss by enhancing thermo-conductivity and scalp-contact, ensuring optimal fit and even cooling. Dr J. Nangia MD, Director Breast Cancer Prevention Program, Baylor College of Medicine USA and PI on the SCALP clinical trial, observed 'This new cap design provides an enhanced fit which increases efficacy and hair retention rate' [c]. Recent analysis of patient self-reported hair loss indicated a 15%-20% **enhancement in treatment efficacy** compared to previous Paxman cap versions [d]. Furthermore, conformation to a greater variety of head shapes/sizes increased treatment efficacy by accounting for racial variations in skull morphology (see above). **Patient comfort** has been enhanced due to the superior design providing a more ergonomic fit, utilising a softer, flexible silicone enhancing patient tolerability [d]. Prof. M. Toi, HOPE Study researcher & Internationally renowned breast cancer clinician, observed 'Patient comfort is enhanced, less pressure applied on the chin strap, increasing the patient's tolerability of scalp cooling & desire to continue scalp cooling treatment' [e].

Figure 3 [d]

Highly significant impacts on patient wellbeing have resulted, quantified through an extensive user feedback analysis of >150 patients across 9 countries [d]. A significant impact was found in five key areas of wellbeing. Ninety-nine percent (**99%**) of patients, who used this scalp cooling cap, reported some impact on their emotional wellbeing, with 93% stating a very significant/ significant impact on emotional wellbeing in addition to social activities (84%), work activities (77%), relationships with family and friends (70%) and physical/sporting activities (60%) [d]. The sub-themes of the personal impact are summarised in Fig. 3 [d]. USA-based patients commented: 'It made me feel like I had control over something during a time when things felt completely out of control', 'I feel like scalp cooling let me keep my identity, rather than just being a cancer patient' and 'Scalp cooling was a way I could minimize the impact cancer has on my young children. It would be frightening to them if mom had no hair' [d]. Providing patients with an empowering choice and ability to retain a sense of control, encourages positive attitudes towards their overall treatment. **Patient confidentiality and work-loss:** Retaining hair during chemotherapy provides patients with increased confidentiality. Studies have shown that 40% to 85% of all cancer patients have quit working while undergoing treatment (Giligan et al. 2018). Removing the visual cues caused by CIA, increases patients' privacy and choice regarding who to inform about their treatment. Patients report feeling able to continue working, reducing the financial burden. A USA-based patient reported 'The ability to keep my treatment private at work was priceless' [d]. **Longer-term patient outcomes:** clinical research demonstrates that scalp cooling, using this cap, not only reduces hair loss but significantly improves post-treatment hair-regrowth and patient outcomes [e] (Bajpai et al. 2019).

Clinicians and clinical approach: From a Health Economics perspective, nursing time investment is reduced compared to manual scalp cooling methods [c,e], where frozen caps have to be repeatedly replaced at regular intervals during a single treatment session.

The cap supports a patient-centric approach and the increasing importance placed on supportive care, aligning with the shift in clinical understanding, that the patient should be at the heart of the care pathway, not only treating the cancer but supporting the patient holistically. The Chairman of the Department of Breast Medical Oncology at The University of Texas MD Anderson Cancer Center said 'This is another step forward in making cancer therapy more personalized and putting the patients in the driver's seat as we create more options and pathways for our patients' [i-3.2].

Along with their presence, Paxman's influence in the US has grown significantly. In a major step towards making scalp cooling more available in the US, through Paxman's support the National Comprehensive Cancer Network® (NCCN) updated the **Clinical Practice Guidelines** in oncology for breast (V1.2019) and ovarian cancer (V1.2020) to include scalp cooling as a Category 2A recommendation [g]. Increasing access to effective scalp cooling provides the potential to reduce the 8% patients refusing chemotherapy due to hair loss fears, enhancing survival chances. **Increased awareness**: Increased cap production and patient/clinical access have been

fundamental to an international awareness-building movement. Awareness of increased access to scalp cooling treatment has been raised by news articles spanning five continents regarding this cap and it's associated clinical trails/FDA/launch, including high circulation outlets such as The New York Times [i-1.1]. High profile personalities, including BBC presenter, the late Rachel Bland, documented her chemotherapy and Paxman scalp cooling cap experience in her blog with 42k twitter followers and BBC podcast 'YouMeBigC' [g]. Accompanying Paxman's growth has been a rebranding and launch of the 'Changing the Face of Cancer' [i-2.1] and 'Clinical Pioneer Programme' [i-2.2] to internationally increase awareness and tackle cancer stereotypes. Public awareness of scalp cooling has increased from an estimated 9% to 25% [i-2.1]. Clinicians in USA and India have presented/demonstrated the cap in online videos, reaching out to potential patients [i-1.2]. Clinical awareness has also increased with international scalp cooling research dissemination by leading clinicians, including ESMO 2019 (European Society for Medical Oncology: 25k participants), where research utilising the Paxman cap was presented by three separate teams from Italy, Ireland and India [i-3.3]. Dr. Unver's team and Paxman have presented the cap extensively at conferences/exhibitions including Medtech 2015 & 2016 (>6k attendees) and Arab Health 2019 & 2016 (>100k attendees annually).

Commercial impact: The development of this product, globally recognised as the premier scalp cooling device, has had significant impacts for SME Paxman. The CEO of Paxman stated 'The collaboration has been highly successful and has been an integral element to our company's recent growth and success. We now dominate the market with an 80% share. Turnover has increased from £1.7M in 2015 to £9.35M in 2019, with a 47% increase between 2018-2019' [a,j]. This growth is primarily due to expansion into 54 international markets with 80% of revenues now generated from overseas sales. 'The US now represents our largest market. Growth rate in US was 700% for 2017-2018, with US turnover increasing from £0.225M (2017) to £1.58M (2018)', 'Paxman was listed on Nasdaq First North Growth Market in 2017, share value has increased by 466% (Q2-2017 to Q3-2019)' [a]. UK-based employee numbers have increased by >300% since 2012 [a] and Paxman continue to grow as they launch into new international markets [j].

Fundamental to this growth has been the ability to mass-manufacture caps and reduced production-costs, which enabled the **adoption of a new business model** optimised for international markets [a]. The new business model, now implemented in two of the World's largest healthcare markets, the US and Japan, 'is based on a single-patient-use cooling cap, which was not achievable prior to this research. Unlike our historical capital equipment sales business model, this pay-per-cap approach provides the company with a reoccurring-revenue-stream and ultimately a sustainable business future' [a]. A US subsidiary company was established in 2018 to meet the demands of the growing US market. Two joint patents providing IP protection for the cap design and manufacturing method, have been granted in the UK [3.6] and Japan [3.5], and published in USA, Europe and China. The economic impact of the research benefits British Industry, as both service provider and manufacturer.

In 2019, this successful collaboration led to the establishment of the **World's First Scalp Cooling Research Centre** [i-3.3]. Based at UoH, it unites a multidisciplinary team from the School of Art, Design and Architecture and the School of Applied Sciences, with a £1M commercial investment.

5. Sources to corroborate the impact

a. Testimonial Letter from **CEO of Paxman Coolers Ltd**, with Installation Country List.
b. Awards List Doc, inc.: Times Higher Education Awards 2017: Most Innovative Contribution to Business-University Collaboration (Shortlist), Medilink: Partnership with Academia 2016 (Winner).
c. Testimonial Letter from **Dr. Julie Nangia**, Baylor College of Medicine, TX, USA.
d. Confidential Technical Report: Comprehensive Analysis of Paxman Scalp Cooling Patient Feedback 2021 and associated raw data set. See Report Section 3.2.3- 3.3.3.
e. Testimonial Letter from **Prof. Masakazu Toi**, Kyoto University Hospital, Japan.
f. Testimonial Letter from **Dr Shozo Ohsumi**, Shikoku Cancer Centre, Japan.
g. NCCN Guidelines Update: Document with timeline, links and Paxman NCCN Request Letters.
h. BBC Podcast 'You, Me and the Big C', 05/04/2018, 'About the Body' guest Claire Paxman https://www.bbc.co.uk/programmes/p0639d7n [00:45 scalp cooling, 01:10:00 mentions research]
i. Awareness Raising Document inc: 1.1) News Coverage from 5 Continents inc: **New York Times**, **Hindu Times**. 1.2) Clinical Videos: USA, India. 3) Clinical/ Research Awareness
j. Paxman Financial Reports: Year-End Report 2019, Interim Financial Reports