Development of a Hyperbaric Oxygen Therapy service to treat people with long COVID in a community pharmacy setting (Final Report)

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This final report provides an overview of the community-based HBOT study, for those with long COVID, funded by the Accelerate programme.

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Abstract

Background and rationale

Long COVID is an umbrella term used to describe a range of symptoms, particularly chronic fatigue, 'brain fog' and dyspnoea, which persist for weeks, months or even years after an initial, acute COVID-19 infection. It is estimated that up to 20% of people diagnosed with acute COVID-19 will go on to develop long COVID. The pathology is unclear and, as yet there are no effective treatment options. Emerging evidence indicates that hyperbaric oxygen therapy (HBOT) may help to improve many key long COVID symptoms, in the short term. This study aims to undertake a pilot evaluation of HBOT for people affected by long COVID; to explore changes in chronic fatigue, shortness of breath and quality of life with 4 weeks of HBOT at 14.4 atmosphere absolute.

Methods

A purposive sample from the long COVID Facebook group were recruited. Participants received 15-20 HBOT sessions using a single person chamber over a consecutive four-week period. Socio-demographic information, long COVID symptoms and date of infection was recorded using a bespoke questionnaire. Validated outcome measures including: Chalder Fatigue Scale, Dyspnoea-12 Questionnaire (high scores = worse symptoms) and EQ-5D-L (high scores = better health) were completed at baseline, at weekly intervals over the 4 weeks of HBOT therapy and at 4 weeks after completing therapy. Data was analysed using descriptive statistics using SPSS 27.

Five participants also took part in 2 separate, online focus groups to explore experiences of HBOT provision and subjective impact of therapy on long COVID symptoms. The focus groups were audio-recorded, transcribed verbatim and analysed thematically.

Results

Of the 10 participants recruited, 8 (7 females), age ranges from 26-35 to 56-65 years completed 4 weeks of HBOT. In the 6 people who had complete data, median (IQR) baseline v 4 week data was as follows: Fatigue 30 [28-32] v 22 [4-25], Dyspnoea 17 [6-22] v 4 [0-11], EQ-5D-L index 0.29 [0.07-0.49] v 0.60 [0.20-0.80] and EQ-5D-L VAS 40 [33-51] v 55 [49-73].

Participants reported a range of enduring, significance and fluctuating long COVID symptoms in the focus groups, including chronic fatigue, brain fog, joint pain and shortness of breath. Experiences of HBOT provision were positive but attending regular therapy sessions was often problematic, due to the ongoing challenges associated with long COVID. All reported a noticeable improvement in most of their bothersome symptoms and most participants also experienced a continued, gradual improvement in key symptoms in the 4 weeks since completing therapy.

Conclusion

HBOT has potential to improve symptoms in people with long COVID. Further controlled studies are urgently needed.

Impact

The use of HBOT to manage of long COVID symptoms may have an important impact on patients' symptoms and quality of life.

Background

Since its emergence in 2019, there have been over 630 million confirmed cases of SARS-CoV-2 virus (COVID-19), which have led to over 6.5 million deaths worldwide (World Health Organisation, 2022). However, since the mass vaccine rollout, many of the acute effects of the virus have been tempered and the number of COVID-19-related deaths have reduced significantly (Dyer, 2022). Nonetheless, there now is a growing interest in the longer term sequelae, following an acute infection, particularly as the impact on many of those affected, can be profound. It is estimated that up to 20% of people diagnosed with acute COVID-19 will go on to develop long term problems (Venkatesan, 2021).

Post-COVID-19 syndrome, or long-COVID (referred to as long-COVID hereafter), is defined by The National Institute for Health and Care Excellence (NICE, 2022) as signs and symptoms of the infection that continue for more than 12 weeks post-infection, with the absence of an alternative explanation. Long COVID is an umbrella term used to describe a wide range of enduring symptoms, such as chronic fatigue, cognitive dysfunction and/or dyspnoea, which persist for months or even years after an initial, acute COVID-19 infection.

The most recent Office for National Statistics (ONS, 2022) survey found that, as of October 1st 2022, 3.3% of the UK population (approx. 2.1 million people) were experiencing [self-reported] long COVID, lasting at least 12 weeks after initial infection. Of those with long COVID, around 1.1 million people self-reported symptoms lasting at least one year and 507,000 self-reported symptoms lasting at least two years (ONS, 2022). The most commonly reported symptoms are fatigue (70%), difficulties with concentration (45%), shortness of breath (42%) and muscle aches (42%) (ONS, 2022). While symptoms vary and often fluctuate, the long term effects of the illness can be debilitating and around 1.6 million people in the UK currently report that the condition ‘adversely affects their daily lives’ (ONS, 2022).

The precise aetiology of the condition is unclear but current theories include micro [blood] clots, inflammation, a ‘lingering virus’ and/or an ‘erratic immune system’. Consequently, there are, as yet, no effective treatment options. NICE (2022) predominantly recommends conservative management of key symptoms, including, where appropriate, lifestyle advice, such as pacing. However, anecdotal reports and emerging evidence indicate that hyperbaric oxygen therapy (HBOT) may help to improve many key long COVID symptoms, in the short term (Robbins et al., 2021, Bhaiyat et al., 2022).

HBOT involves the provision of high percentage oxygen, at a pressure greater than normal atmospheric pressure, within a chamber, by a trained operator. Sessions typically last 60-90 minutes and are usually provided daily (typically, with at least 2 consecutive ‘rest days’ per week) over several weeks (usually around 15-20 session are provided in a typical therapy block). Breathing in high percentage, pressurised oxygen can facilitate diffusion of

hyperoxygenated blood to the cells, which may generate an anti-inflammatory and/or anti-coagulant response that can promote tissue healing (Ortega et al., 2021). It can be provided safely, in a community setting, and is already widely used to treat carbon monoxide poising, decompression sickness and wound healing. However, despite the growing interest in the use of HBOT in long-COVID management, there is currently a significant lack of research in this area.

A rapid review of existing, relevant research was therefore undertaken to help inform this study. A key-word search strategy (using the following search terms; Post-COVID-19 syndrome, long-COVID and hyperbaric oxygen therapy (HBOT)) was developed and implemented over five online healthcare databases, including MEDLINE AND CINAHL. Only four relevant articles were obtained during the literature search, which illustrates the limited nature of the existing evidence base. All four studies are from high-income countries (e.g. UK and USA) (The World Bank, 2021). Three of the studies are cohort type designs with sample sizes ranging from 6 (Zant et al., 2022) to 73 participants (Zilberman-Itskovich et al., 2022), while the other is a case report (Bhaiyat et al., 2022). Table 1 provides an overview of all four studies:

Table 1. Summary of articles included in literature review

Title	Country	Lead author	Study Design	Aims	Intervention	Outcome measures
Hyperbaric Oxygen Treatment for Long Coronavirus Disease-19: A Case Report	UAE	Aisha M. Bhaiyat	Case report	To report the case of a patient with long post-covid syndrome treated successfully with HBOT.	Patient underwent 60 sessions of HBOT over 3 months.	Baseline evaluation of function using brain perfusion MRI, diffusion tensor imaging, computerised cognitive tests, and cardiopulmonary exercise test, and pulmonary function tests. Function measurements were remeasured 4 weeks after HBOT.
Hyperbaric Oxygen Therapy for the Treatment of Long COVID: Early Evaluation of a Highly	UK	Tim Robbins	Quasi-experimental cohort study	To evaluate the effect of HBOT on long-covid-related fatigue symptoms.	10 patients underwent 10 sessions of HBOT over 12 days.	Chalder fatigue scores and cognitive assessments performed at day 1 and 10.

Promising Intervention						
Hyperbaric Oxygen Therapy to Treat Lingering COVID-19 Symptoms	USA	Albert E Zant	Quasi-experimental cohort study	To record the effects of HBO_2 on COVID19 symptoms lingering longer than 30 days post clearance.	Six patients underwent HBOT over between 24 and 85 days.	Baseline assessments taken including the ImPACT concussion assessment, muscle and joint pain measurements, and the Borg dyspnoea measurement
Hyperbaric Oxygen Therapy Improves Neurocognitive Functions and Symptoms of Post-COVID Condition: Randomised Controlled Trial	Israel	Shani Zilberman-Itskovich	Randomised, placebo, double-blind trial	To evaluate the effects of HBOT on patients suffering from post-COVID-19 with ongoing symptoms 3 months after infection; a randomised, placebo, double-blind trial.	73 patients underwent 40 sessions of HBOT over 2 months.	Primary outcome: Cognitive assessments evaluated by the Mindstreams computerised cognitive testing battery. Secondary outcomes: Brain MRI for brain perfusion evaluation, SF-36 quality of life scores, PSQI sleep quality score, BSI-18 for psychological distress, BPI for pain intensity and impact. Also evaluated were sense of smell, and pulmonary function. Follow-up assessments were performed at baseline and 1-3 weeks after the last treatment session.

While the studies largely focused on slightly different outcome measures (often using different tools of data collection) they primarily focused on the impact of HBOT on pulmonary function, fatigue, cognitive function and/or pain. There were also significant variations in the provision and/or duration of HBOT and the review therefore has to be considered accordingly.

The effects of HBOT on pulmonary function was assessed by three studies (Zilberman-Itskovich et al., 2022, Zant et al., 2022, Bhaiyat et al., 2022). Two studies (Bhaiyat et al., 2022, Zant et al., 2022) reported an improvement in pulmonary function and dyspnoea scores, respectively, following HBOT. However, Zilberman-Itsokovich et al. (2022) found that there was no significant changes in pulmonary function post-treatment. All four studies also explored the impact of HBOT on fatigue/energy levels and, while different methods of

measurement were used, all reported improvements in fatigue and/or energy levels following therapy.

All four studies assessed cognitive function, largely using different measures, which makes direct comparisons somewhat difficult. However, significant improvements were observed in attention and information processing speeds in all four studies and memory scores improved in three studies (no significant change found by Robbins et al. 2021) (Zant et al., 2022, Robbins et al., 2021, Zilberman-Itskovich et al., 2022, Bhaiyat et al., 2022). Pain scores were measured in two studies (Zant et al., 2022 and Zilberman-Itskovich et al. 2022) and improvement in joint and muscle pain and a reduction in pain interference, were respectively reported.

Consequently, while there is a small, emerging evidence base, research to date, suggests that HBOT may help to alleviate some of the main long COVID symptoms, in the short term at least. However, research in this area remains limited, particularly in relation to participants' experiences of HBOT service provision and the potential impact of therapy on participants' symptoms and/or activities of daily living, during and following completion of HBOT.

Study design

Aims

The aims of this small scale, collaborative pilot study were to:

- Explore participants' experiences of HBOT service provision in a community setting
- Assess potential changes in chronic fatigue, quality of life and shortness of breath during and, following completion of HBOT
- Explore potential recommendations for future service and/or research development.

Research approach

To address the study aims, this longitudinal, pilot study was undertaken using a mixed methods approach, which incorporated several, related work packages, which are outlined below.

The Stakeholder Advisory Group

At the start of the study, a small stakeholder advisory group (SAG) was developed, which consisted of two key stakeholders from the Long COVID Wales Facebook group, both of whom had experienced long COVID for around 18 months and had recently completed HBOT (privately) with an MS charity in South-West England. They met with the project Chief Investigator (CI) (PG) three times during the study. Key information from the meetings were then discussed further with the wider research team.

The SAG offered expert advice on the study design, HBOT intervention development, approach to recruitment and sampling, participant facing documentation and the approach to data collection.

Recruitment and sample

Prospective participants were purposively recruited into the study, , via the long COVID Wales Facebook group and Gravells Pharmacy Facebook group, using an agreed inclusion/exclusion criteria. The inclusion/exclusion criteria were developed following a review of the literature and are were based on existing HBOT industry guidelines and informed by criteria further refined by Robbins et al (2021). These criteria are designed to ensure that prospective participants have confirmed symptomology associated with long COVID and also meet the requirements for the safe provision of HBOT in a community setting. The exclusion criteria were largely based on existing conditions that may preclude HBOT, for example, due to changes in pressure and/or oxygen levels.

Inclusion criteria:

- 18 years of age or older

- Previous confirmed COVID 19 infection (e.g. positive lateral flow test and/or PCR test) and/or:
- Suffering with long COVID (enduring, common long COVID symptoms for at least 12 weeks post-acute infection; based on self-report)
- Able to provide informed consent.

Exclusion criteria:

- History of traumatic brain injury (or other non-COVID brain pathology)
- Active malignancy (e.g. cancers)
- Excessive substance misuse at baseline (e.g. excessive alcohol use)
- Unstable non-COVID related physical disorders or major cognitive deficits
- Recent previous use of HBOT (for any reason)
- Chest pathology incompatible with high oxygen/pressures (e.g. COPD),
- Epilepsy, ear or sinus pathology incompatible to pressure changes and/or claustrophobia.

Prospective participants initially contacted the CI by email if they were interested in knowing more, without obligation, about the study. The project research assistants (RA's) then arranged a telephone call with prospective participants to discuss the study in more detail, answer any questions that they had and establish potential eligibility to participate. Prospective participants then had at least 24 hours to decide if they wanted to take part in the study. Those wishing to take participate, completed an informed consent form with the project CI and they were then referred to Gravells Pharmacy for HBOT consideration.

Given the nature of the study, it was anticipated that the maximum number of participants that could be recruited into the study was 10. Participant details are provided in the results section.

Work package 1

HBOT was provided, gratis, to eligible, consenting participants by trained personnel from from Gravells pharmacy, Llanelli, using a single person HBO chamber, which was acquired via the Accelerate programme. The HBO chamber was hosted in partnership, in a private treatment room at Parc Y Scarlets, Llanelli.

Once participants had been referred to Gravells, an additional therapy eligibility check was undertaken by them. HBOT was then discussed in more detail and any additional queries were addressed. Participants who met the inclusion criteria then consented (using an additional consent to therapy form) to therapy with Gravells, prior to undertaking HBOT.

All HBOT was provided via a Henshaw Sport Recline XL (https://www.henshawsport.co.uk/recline-xl-chamber/) single person chamber, which

provides HBO at 1.4 atmosphere absolute (ATA). High concentration oxygen (approx. 100%) was administered at pressure, in the chamber via a standard, tight fighting oxygen facemask. Oxygen was provided via an inbuilt air compressor.

The aim was to provide to provide all eligible, consenting participants with approximately 15-20 HBOT sessions over a consecutive four week period (up to a maximum of 5 sessions per week, with a minimum consecutive two day break in therapy). However, due to staff sickness, participant daily living challenges (e.g. exacerbation of symptoms) and the timeframes of the study, it was not possible to achieve this regimen with some participants. Consequently, there are variations in the number (and duration) of sessions of each participant and the results of the study therefore have to be considered with this in mind.

The participants received between 7-20 sessions (median 17.5), typically over a 4 week period. Participant demographic data are provided in the results section.

Work package 2

To evaluate key, perceived short term changes in health and wellbeing associated with HBOT, data were collected via email or telephone, according to personal preference, from participants at baseline (pre-treatment) and at 1, 2, 3 and 4 weeks during treatment and 4 week post HBOT.

Due to the anticipated challenges associated with participants' ongoing chronic fatigue, the research team were cognisant to ensure that data collection was not unduly burdensome for them. Consequently, the following short, validated questionnaires were used at all stages of data collection; The Chandler fatigue scale (CHF) (scored 0 to 33, high scoring indicating greater fatigue), Dyspnea-12 (D-12) scale (range 0-36, high scores indicating worse dyspnoea) EQ-5D-5L Index, (0 represents worst health and 1 best health) and Visual Analogue Scale (VAS) 0-100 high scores indicating better health) (Quality of life scale) (see appendix 1). All participants also completed a bespoke, baseline socio-demographic form, collecting data on age, gender, BMI, long COVID symptoms, ethnicity, marital status, and date of COVID infection (see appendix 2).

As this is a pilot study, data were analysed using descriptive statistics and managed using SPSS 27. Continuous data were checked for normality and, as skewed, were described as median [interquartile range (IQR)] as well as ordinal data. Categorical data was described as frequencies. Longitudinal analysis included participants who had fully completed questionnaire data at the 4 time points. The 4-week post HBOT data will be analysed on completion of data collection.

Work package 3

Two online focus groups were conducted with all willing participants shortly after completion of HBOT, to explore their experiences of service provision, perceived benefits/disadvantages of therapy and recommendations for future service provision and related research. The focus groups were conducted via zoom, audio-recorded and transcribed verbatim afterwards.

The focus group was led by the project CI (PG) and facilitated by the study co-applicant (NG) and project RAs, using an interview schedule, which was developed following a review of the literature (see appendix 3). Three participants attended the first focus group and two attended the second. Three participants were unable to attend either.

All focus groups were managed in a considered manner and informed by 'Chatham house rules', which were outlined to all participants at the start of the discussion. Each focus group lasted approximately 90 minutes. Focus group data were analysed thematically, using Braun and Clarke's (2013) six stage process.

An online, unstructured interview was also conducted with pharmacy director at Gravells pharmacy, around one month after completion of HBOT. The interviewed explored their experience of HBOT service provision and identified potential opportunities for further development of HBOT and the pharmacist's role in a community setting. The discussion was conducted via MS Teams and lasted approximately 20 minutes. The interview was audio-recorded, transcribed verbatim (using teams auto-transcribe) and analysed thematically, using Braun and Clarke's (2013) six stage process.

Ethics and governance

School of Healthcare Science (Cardiff University) Research Ethics Committee (REC) approved the study in September 2022 (see Appendix 4). Participation in all phases of the study was voluntary. All prospective participants were provided with a participant information sheet about the study (see Appendix 5) at the expression of interest phase.

Participants contacted one of the project RAs to discuss the study in more detail and were then given at least 24 hours to decide whether they wanted to participate. Participants were assured of anonymity and confidentiality and advised that they could withdraw from the study at any time, without prejudice. Informed consent, via email, was obtained from all eligible, willing participants by the project CI (PG).

To ensure anonymity and confidentiality, all participant names were replaced by a code, known only to the project team. All data were stored securely, in accordance with REC and GDPR (2018) requirements and will be destroyed 5 years after submission of the final report and/or any related publications.

Results

Work package 1

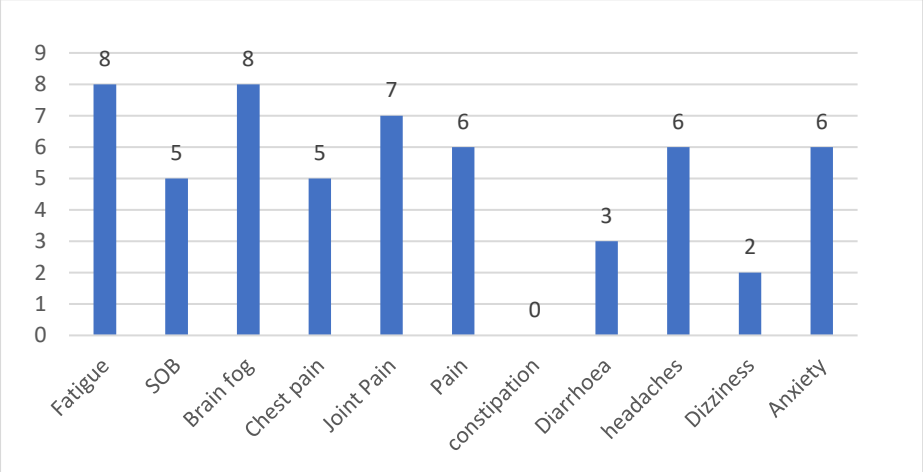
10 participants with long COVID were recruited into the study at baseline, however 2 participants, withdrew from the study (reason for withdrawal; claustrophobia n=1, travel difficulties n=1) prior to commencing treatment. Therefore, the analysis included eight participants.

Demographic data

Of the 10 participants recruited, 8 (7 females) completed 4 weeks of therapy. Date of reported infection ranged from March 2020 to November 2021. Ages ranges from 26-35 (n=2), 36-45 (n=3), 46-55 (n=2) and 56-65 years (n=1), BMI categories were BMI 25-29.9Kg/m^2 (n=4), 30-39. 9Kg/m^2 (n=3) (1 missing data).

The most frequently reported symptom at baseline was fatigue and brain fog, followed by joint pain (n=7), pain, headache and anxiety (n=6), chest pain (n=5, diarrhoea and dizziness. In addition, 2 people reported depression and 2 people reported altered sense of smell (Figure 2).

Figure 1. Frequency of long COVID symptoms reported by participants



Baseline data

At baseline, median [interquartile range] data was: fatigue (CHF) 30.5 [29.3-32], Dyspnoea-12 was 17 [3-22], EQ-5D-5L index was 0.29 [0.08-0.41] and VAS 39 [23.25-47.5].

Table 2. Baseline Fatigue, Dyspnoea, EQ-5D-5L index and VAS score n=8

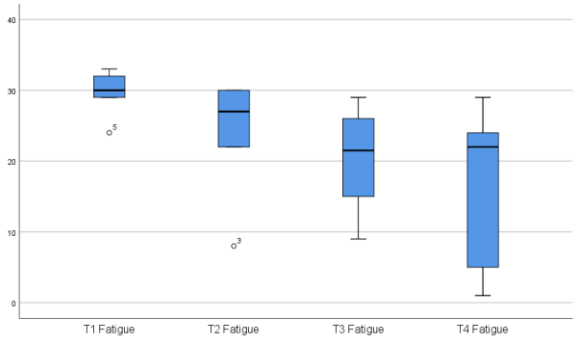
	Baseline data Median [IQR]	Post 4 week HBOT
Fatigue	30.50 [29.25- 32.00]	22.00 [4.0-25.25]
Dyspnoea 12 total	17.00 [3.00-22.00]	4.00 [0.00-11.25]
EQ-5D-5L Index	0.29 [0.09-0.41]	0.61 [0.21-0.80]
EQ-5D-5L VAS	39.00 [23.25-47.50]	55.00 [48.75-72.50]

Longitudinal data

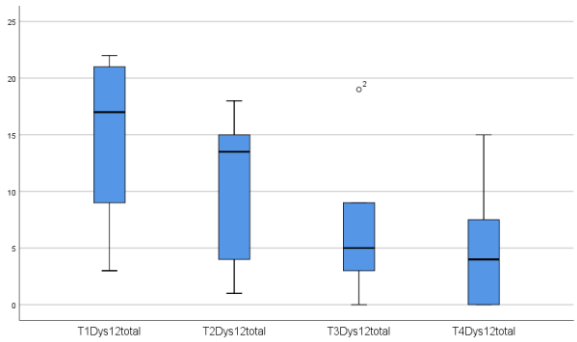
Of the 8 participants who completed 4 weeks of HBOT, 6 participants had fully completed questionnaire data. The data showed a decline in CHF (fatigue) and D-12 (dyspnoea) with an increase in EQ-5D-5L and VAS score (Quality of Life/Health) (Figure 2).

Figure 2. Boxplots showing change Fatigue, Dyspnoea, EQ-5D-5L index and VAS score with HBOT over 4 weeks

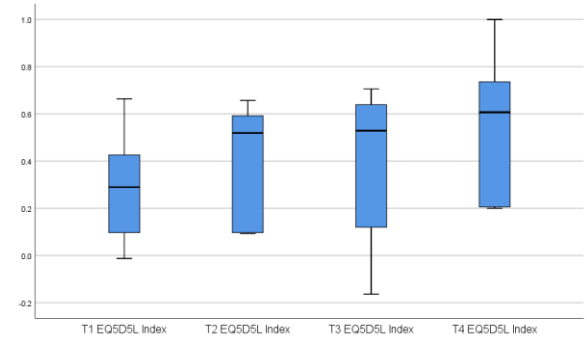
a) Fatigue



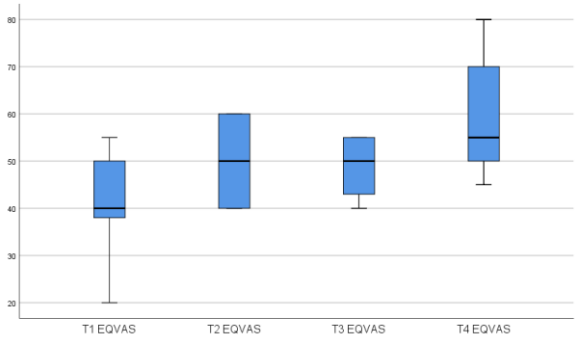
b) Dyspnoea



c) EQ-5D-5L index



d) EQ-5D-5L VAS



Discussion

Work Package 2

At baseline, the most common symptoms reported by participants align with previous work in 201 people with post COVID syndrome, where the most frequently reported symptoms were fatigue (98%) and shortness of breath (88%) (Dennis et al. 2021).

Fatigue baseline scores were almost maximal (33) indicating high fatigue levels. This is notably higher than community dwelling individuals mean age 34 ± 7.6 years who scored 3.27 ± 3.21 on CHF. Previous studies of fatigue in long COVID demonstrated lower mean CHF of 15.8 ± 5.9 (Townsend et al. 2020).

Dyspnoea was higher (17) than previously reported in patients (mean age 42 years) within 40 days of COVID infection (D-12 12.26 ± 5.9) prior to a rehabilitation intervention (Gonzalez-Gerez et al. 2021). A number of other studies have reported increased breathlessness using the MRC scale (1-5) (Sigfrid et al. 2021).

Quality of life at baseline (EQ-5D-5L index 0.29 and VAS 39) appeared to be considerably lower than published population norms. Data from Wales for the EQ-5D-5L index are over 0.8 and mean VAS scores above 85 for age ranges 25-64 years (Kind et al. 1999). A previous study in COVID reported a mean EQ5D-3L index score was 0.57 ± 0.23 and EQ-5D-5L VAS mean score was 56.6 ± 18.2 (Moens et al. 2022) but it is unclear if this sample included those who recovered and those with long COVID symptoms, which may explain why the results are higher than our study at baseline, in people with established long COVID.

Although the present study was not powered to look for statistical differences, there appeared to be a trend of improvements in fatigue, dyspnoea and quality of life with HBOT. A previous study showed similar improvements in CHF, global cognition, executive, function, attention, information processing, verbal function, neurocognitive score and executive function (all < p=0.05), with 10 HBOT sessions over 10days at 2.4 ATA ($p<0.05$) (Robbins et al. 2021). The RCT by Zilbermans-Itskovish et al also showed improvements in Quality of life (SF36: energy, PSGI global symptoms, BSI global and somatization, BPI: pain interference (all $p < 0.05$) with 40 daily sessions of HBOT 2ATA five sessions per week provided over a two-month period. Increased perfusion of the brain was seen after HBOT and it has been suggested that HBOT can induce neuroplasticity, modulate the immune system, promote angiogenesis, restore mitochondrial function, which may contribute to the changes seen (Zilberman-Itskovich et al. 2022). Zant et al. (2022) also demonstrated improvement in mean dyspnoea using the modified Borg scale ($p<0.05$).

There is some evidence of the efficacy of HBOT to improve symptoms and quality of life in chronic fatigue syndrome (Akarsu et al. 2013).

Work package 3 findings

Three main themes were generated from the collective analysis of both focus groups:

- Participants' experiences of HBOT service provision
- The impact of therapy
- Recommendations for practice and further research

Participants' experiences of HBOT service provision
Participants' experiences of HBOT service provision were broadly positive. All reported that the pharmacy staff were friendly, supportive and informative. Most participants lived a relatively short distance away from the chamber location, which made attending sessions, by car, fairly easy. However, as the chamber was located in a first floor, private treatment room, several participants often found it difficult to navigate the stairs, due to their long COVID symptoms, notably fatigue, muscle aches and joint pain.

Most reported initially feeling anxious about therapy, particularly in relation to what to expect from HBOT. However, discussions with pharmacy staff largely helped to allay such concerns, prior to starting therapy. Some participants initially found the chamber quite daunting, due to its relatively small size and the need to be 'zipped in for therapy' [in order to achieve 1.4 ATA] but all quickly got used to it and most found it comfortable and sufficiently spacious inside. The main challenge, however, was fitting in regular therapy sessions, alongside family life and/or work (where appropriate), whilst also negotiating the ongoing challenges associated with long COVID:

> *The availability of the appointments made it difficult with my work schedule… I had certain things in work I couldn't get out of and then school runs… it took over my life when we did it. I was glad of it, but to find the extra two hours in the day was really difficult for me because I already haven't got enough hours in the day, despite having long Covid, with my job and family life and the fact I've got this chronic fatigue and everything else. It was quite time-consuming, but I was very grateful to be able to do it* **(P2; FG1).**

The unpredictable nature of the condition, also sometimes made regular attendance for HBOT problematic and some participants had to cancel some scheduled sessions, as they did not feel well enough to attend.

The impact of therapy
What was notable in both focus groups was the diverse range, fluctuating nature and impact of long COVID symptoms on all participants. The 'most significant' symptoms varied

amongst participants but commonly included 'breathing problems' (e.g. shortness of breath), 'brain fog', fatigue and/or pain (typically joint type pain).

Many discussed feeling exhausted most of the time and were subsequently unable to do many of the 'simple things in life' that they used to enjoy, such as exercising or walking the dog. Some were no longer able to work, due to ongoing chronic fatigue and/or brain fog. Several felt that they had 'lost something of themselves' and many wondered if life would 'ever be the same again'. All discussed having to pace themselves just to get through a typical day. Consequently, the wider effects of long COVID on family life was also considerable. The emotional impact of the condition was also profound and several participants reported being depressed, for which they were receiving medical and/or supportive therapy. Many also reported ongoing frustration with the NHS:

> *I don't go to the GP anymore because they don't know what to say to me, and I haven't got time to go to the GP either! I'm still waiting for a long Covid appointment assessment even though it's been about nine months since I was referred.* **P2, FG1.**

While some participants found that some of their key long COVID symptoms (e.g. fatigue and brain fog) had not improved as much as they had hoped following HBOT, all reported a noticeable improvement in their most bothersome symptoms; for example breathing (n=3), fatigue (n=4), brain fog (n=4) and pain (n=2):

> *It's definitely made a positive impact on my long Covid… I find my breathing has massively improved, my shortness of breath has almost gone away. My energy levels, as well, have improved. It's intermittent… but on the whole, I'm able to do a lot more now. I wasn't even able to walk my dog before, so now I can. I have costochondritis, as a side effect of my long Covid, which is inflammation of the intercostal muscles and the bones… and that was causing significant pain when I was walking. I don't really have that anymore, it's very minimal, so that's another improvement I've noticed.* **P3, FG1.**

All reported being able to do more, without feeling so exhausted, and some reported improvements in their sleep patterns since completing HBOT. Whilst no one felt that they were yet 'back to normal', many felt that HBOT had offered them some hope that there was now, perhaps, some 'light at the end of tunnel'. While many reported a steady, ongoing improvement in symptoms since completing HBOT, one participant (P2) reported an exacerbation of long COVID symptoms, following her recent ~~covid~~ COVID booster vaccine, which was hugely frustrating.

All participants a gradual improvement in symptoms during therapy and, for most, this typically occurred in the second or third week of HBOT:

> *I think I was further along because I remember thinking, Oh, I'm not seeing much change here and then it started, I felt like my fatigue levels were lifting a bit*. **P4, FG1.**

> *When I first started the hyperbaric therapy, it made me feel really fatigued and I was falling asleep, then I'd go home and I was exhausted and I would just sleep, so I was a bit concerned if that was normal, so I did do research on it and that is normal. So it took a little while, the first week I didn't notice any kind of improvement… then the second week is when I started noticing I perked up quite a lot, after about twenty minutes I'd have a big rush of energy, so I'd be able to go out and I'd walk the dog… which I haven't been able to do for months…. On the whole, I noticed week two, week three that I was getting improvement then.* **P3, FG1.**

What was also noticeable in both focus groups was how incredibly grateful all participants were to take part in the study. Many talked about the study being the first meaningful, potentially therapeutic option offered to them for their condition and several emphasised that they felt they had been properly 'listened to', which they found very helpful.

Recommendations for practice and further research

Participants had several recommendations for HBOT service provision in a community setting and/or further related research. Several discussed the importance of a mobile therapy chamber (like the one used in this study, which could therefore be easily set up and moved, where appropriate) that was accessible (e.g. free parking and ground floor access), affordable and 'closer to home'.

Several participants believed that a flexible, online therapy booking system would have been helpful and many emphasised the importance of offering HBOT sessions, where possible, in the evenings and on weekends, particularly for those who were working and/or had families.

Many participants also discussed how helpful peer support could have been during the study. For example, via WhatsApp or a dedicated, closed Facebook group:

> *It would have been nice to know how other people were finding it because I remember at the start thinking, 'I'm not seeing any differences'…, so perhaps it would have been nice to have a little group, and if anyone wanted to say… or some side effects, I think it would have been a good idea.* **P4, FG1.**

However, participants were keen to emphasise that such discussions needed to be safe, secure and, where appropriate, properly moderated.

The questionnaires used in the study were found to be appropriate, although some found that the dyspnoea questionnaire sometimes did not quite fit with the fluctuating nature of their condition. All were also keen to highlight the importance of using accessible, online surveys in any future research, as it was felt that they would be more user friendly for those with long COVID. Participants also emphasised the importance of regular, considered survey reminders, as they often forgot to complete questionnaires due to their condition.

A narrative summary of the unstructured interview

An unstructured interview with the pharmacy director of the industrial partner was conducted several weeks after completion of all HBOT. Data were analysed thematically but for the purpose of this report, key findings are reported in a concise narrative summary format.

He had enjoyed working in partnership with the research and funding team on the project and found the study incredibly rewarding. Subjective feedback from participants during the study was incredibly positive and gratifying. He and the team had developed new, transferrable skills, as a result of the project. There was also a real sense that the study had had a positive impact on participants and could also help to inform future, related work. The size and [external] location of the chamber, however, were deemed to be problematic in the longer term for a small, independent pharmacy:

> *You could only put one person in at a time. That was the big sticking problem… I've seen it online now, they've got like mini tents and you can have… five people at the time in there…. So if you had something like that, you could treat four or five people at the time and then… you could improve services much more….*
>
> *It would be difficult to carry on using it and taking people over there. It would take one of my staff out because we did struggle in the pharmacy because we were one down. So that was a real problem. So doing that in the future would be very, very difficult.*

He did, however, see significant commercial potential and future advanced pharmacy role development associated with HBOT. Besides long COVID, it was felt that HBOT could potentially be used to manage a range of other conditions, including wound healing, sports injuries, neurological conditions (e.g. Parkinson's disease and multiple sclerosis) and possibly as a supportive therapy for those with certain cancers. The other collaborative partner, who kindly agreed to host the chamber [because of its size] in one of their treatment rooms are

apparently already using HBOT to help manage sports injuries in some of their elite rugby players.

While he felt that HBOT offered significant potential, he concluded by emphasising the commercial and empirical importance of a larger chamber, in a larger, accessible location:

> *Within a Community Pharmacy is a bit harder and you might only get one machine where you can only treat one person at a time. The problem with it is, it does take a long time and you've got to sit in there for an hour and a half… But if you have a massive treatment room and whether you have a string of single units or the whole room where 3-4 people could sit in there… you could treat 3-4 people at the time, open seven days a week… I think that would be fantastic….You're in a proper unit where you can treat lots of people. I think it should be looked at because a community pharmacy, as I said, you can only have one Chamber in there and it's the time. It's one and a half hour treatment per person minimum... So having a bigger room where you can treat more people… that's where I would see it in the future.*

Discussion
Work package 3

While there is a small but emerging evidence base in this area, to the best of our knowledge, this is the first study to explore the impact of HBOT on long COVID symptoms, which has also included a qualitative component. Findings therefore further inform the quantitative data from this and other related research and offers additional insight into participants' experiences, which can help to develop future practice and research developments.

Findings demonstrate the profound physical and psychosocial impact of long COVID on participants in this study. While a diverse range of fluctuating symptoms, of varying severity, were reported, the most common, bothersome problems were fatigue, breathlessness, brain fog and pain, which adversely affect most aspects of personal, professional and family life. The inability to work as normal (for short or extended periods), drive or participate in 'normal' daily living activities appears to be common in those most affected by long COVID (Robbins et al., 2021) and can have a significant and far-reaching impact.

However, as results from work package 2 demonstrate, a dedicated HBOT regimen appears to help improve many, but not all, of the most significant long COVID symptoms, including fatigue, brain fog, dyspnoea and joint pain. Similar findings have been reported elsewhere (Zant et al., 2022, Robbins et al., 2021, Zilberman-Itskovich et al., 2022, Bhaiyat et al., 2022), which suggests that HBOT may, where appropriate, offer potential treatment options for suitable patients with long COVID (Bhaiyat et al., 2022). However, as the aetiology of long

COVID remains unclear, further research is needed to better understand the underlying causes of long COVID and the positive responses reported in relation to HBOT (Marshall 2021).

Longitudinal data, particularly in relation to the impact of HBOT on symptoms after therapy has ended, is somewhat limited. However, findings from work package 2 and 3 suggest that most participants experienced a gradual improvement in symptoms during HBOT and in the first month after therapy had ended. Nonetheless, this is also an area in need of further research (Robbins et al., 2021).

It is, however, notable that participants in this study were incredibly grateful for the opportunity to take part in the research and many reported how appreciative they were to have felt 'listened to'. It is therefore possible that participation in the study alone, may have had a quasi-therapeutic and/or possibly, even, a placebo effect on participants. Consequently, there is now a need for larger scale clinical trials, to evaluate the potential impact of HBOT in the context of long COVID (Robbins et al., 2021).

Qualitative findings also demonstrate the importance of incorporating meaningful co-design into future research. This study highlights that future HBOT clinical trials need to be flexible, accessible and accommodating, where possible, and should also include methods of data collection that are straightforward and not unduly onerous on participants with long COVID.

Limitations

Due to the size and nature of the sample, findings should not be assumed to be representative of the wider long COVID population. The uncontrolled nature of the study also limits any causal conclusions and the subjectivity of the outcome measures means that the changes observed may be due to several factors including participant bias, placebo effect and/or overall recovery. The focus groups illuminated the significant gratitude of participants, which highlighted the limited evidence in this area and the availability of effective interventions and this may have also influenced results.

Conclusion

Participants in this study experienced a variety of profound, fluctuating long COVID symptoms, including chronic fatigue, brain fog, joint pain and shortness of breath, which adversely affected personal, professional and family life. Consequently, the physical and psychosocial impact of the condition was considerable.

HBOT provision was generally found to be positive, although regular therapy sessions and data collection requirements were often difficult for most participants, due to the ongoing challenges associated with long COVID. Future related research should therefore be designed with these challenges in mind.

However, HBOT appears to help improve fatigue, dyspnoea and quality of life in those with long COVID and similar findings have also been reported in other studies (e.g. Zant et al., 2022, Robbins et al., 2021, Zilberman-Itskovich et al., 2022, Bhaiyat et al., 2022). While HBOT therefore appears to offer a therapeutic potential in long COVID, further controlled clinical trials are now urgently needed.

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Appendix

Appendix 1; Questionnaires (see supplementary file)

Appendix 2; Socio-demographic form

Accelerate project; participant socio-demographic form

Approximately when did you test positive for COVID?

Age Range, in years (please X)

18-25	
26-35	
36-45	
46-55	
56-65	
65+	

Gender

Female	
Male	
Non-binary	
Prefer not to say	
Other (please state):	

Martial status

Married	
Divorced	
Co-habiting	
Single	
Widowed	
Prefer not to say	

long COVID symptoms experienced

Chronic fatigue	

Shortness of breath	
Brain fog	
Chest pain	
Joint pain	
Pain	
Constipation	
Diarrhoea	
Headaches	
Dizziness	
Anxiety	
Others (please list):	

Ethnicity

Bangladeshi	
Black African	
Black Caribbean	
Chinese	
Indian	
Middle Eastern	
Mixed	
Pakistani	
White	
Other (please state)	

BMI

Below 18.5	
18.5-24.9	
25-29.9	
30-39.9	
40+	

Appendix 3; Focus Group topic guide

Main questions	Additional questions
How did you find the provision of HBOT delivered by Gravells Pharmacy	Clarify why you liked/disliked? Strengths/challenges of service provision
What impact, if any, did the HBOT have on your long COVID symptoms?	Clarify any changes (positive or negative) in health and wellbeing during or following HBOT Any particularly positive/challenging changes and, if so, roughly when did they occur?
Having completed HBOT, what would you have liked to have known more about, before you started therapy?	Clarify what these factors are If you were chatting to someone considering undertaking HBOT for long COVID, what would be your key tips?
On reflection, what would be your key recommendations for: • Future HBOT service provision for Gravells Pharmacy? • Recommendations for future research in this area?	Clarify key points
Is there anything else you'd like to discuss in relation to the project that we've not yet explored?	

Appendix 4; Research Ethics Committee approval letter (see supplementary file)

Appendix 5; Participant Information Leaflet

Study title

Development of a Hyperbaric Oxygen Therapy service to treat people with long COVID in a community pharmacy setting

Invitation and brief summary

I would like to invite you to take part in a study that would help us to better understand the potential impact of Hyperbaric Oxygen Therapy (HBOT) on some of the key symptoms (e.g. chronic fatigue, 'brain fog' and breathlessness) associated with long COVID. Joining the study is completely voluntary and before you decide if you would like to take part, it is important that you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish.

Thank you for reading this.

1. What is the purpose of this research

Very little is known about the cause(s) of long COVID and, as yet, there are no effective treatment options. However, some emerging, small scale research indicates that, in the short-term, HBOT may help to improve some common symptoms (e.g. chronic tiredness) associated with the condition. Researchers at the School of Healthcare Sciences, Cardiff University are collaborating with Gravells Pharmacy, Llanelli on this project. Trained personnel at the pharmacy will provide HBOT to a small number of people (around 10) affected by long COVID and the research team will then explore potential changes in symptoms such as chronic fatigue, quality of life and shortness of breath during and following completion of HBOT and explore potential recommendations for future service development and research. The results of the study will help to inform the development of HBOT service provision in a community setting and may also help to guide treatment options and future larger scale research for those affected by long COVID.

2. Why have I been invited to take part?

You have been invited to take part in the project, as you are suffering from long COVID (e.g. symptoms lasting for at least 12 weeks) and may, therefore, be eligible to take part in this study. As this is a small, short-term project, we are only aiming to recruit around 10 people into the study. Unfortunately, it is therefore possible that not everyone who volunteers to take part will be able to participate. Gravells Pharmacy will be responsible for HBOT provision and, if you are eligible to take part in the project, they will further discuss the appropriateness of HBOT with you prior to any therapy. However, to ensure that you have confirmed symptoms associated with long COVID and also meet the requirements for the safe provision of HBOT in a community setting, the following inclusion/exclusion criteria have been developed:

- Inclusion criteria: 18 years of age or older; Previous confirmed COVID 19 infection (e.g. positive lateral flow test and/or PCR test); Suffering with long COVID (common long COVID symptoms lasting for at least 12 weeks post-acute infection; based on self-report); Able to provide informed consent.

- Exclusion criteria: History of traumatic brain injury (or other non-COVID brain pathology); Active malignancy (e.g. cancers); Unstable non-COVID related physical disorders or major cognitive deficits; Recent previous use of HBOT (for any reason); Chest pathology incompatible

with high oxygen/pressures (e.g. COPD); Epilepsy, ear or sinus pathology incompatible to pressure changes and/or claustrophobia; Pregnant.

3. Do I have to take part?

No, your participation in this project is entirely voluntary and it is up to you to decide whether or not to take part. If you decide to take part, we will discuss the research with you and ask you to sign a consent form. If you decide not to take part, you do not have to explain your reasons and it will not affect your legal rights. You are also free to withdraw your consent to participate in the research at any time, without giving a reason, even after signing the consent form.

4. What would taking part involve?

Taking part in the study will involve receiving HBOT in a single person hyperbaric oxygen chamber. HBOT will be provided by Gravells Pharmacy, Llanelli. A trained operator from the pharmacy will meet with you and establish HBOT eligibility and, subject to your consent, a therapy regime will be discussed and arranged with you. However, it is anticipated that most participants would require around fifteen, one hour HBOT sessions (3-5 sessions per week) over a period of 3-4 weeks. HBOT will be provided free of charge in Llanelli, by trained personnel at Gravells Pharmacy. **Researchers at Cardiff University will not be involved in this process.**

Participation will also involve completing three short questionnaires at the following time points; before commencement of HBOT, once weekly during HBOT and four weeks after completing HBOT. Questionnaires will be administered via email, phone or freepost, whichever you prefer and you can complete these in your own time. You are free to omit answers if you prefer. You will also be invited to take part in an online focus group after HBOT has ended to explore your experiences of service provision, perceived benefits/disadvantages of therapy, potential changes in long covid symptomology and recommendations for future service provision and research. The focus group will be conducted via zoom and audio-recorded and this will then be written up word-for-word, your anonymity will be maintained. **Only the evaluation of the service and potential impact of HBOT on your symptoms will be managed by researchers at Cardiff University.**

5. Will I be paid for taking part?

No, but if you are eligible to take part, we will provide your with a £10 gift voucher on completion of the study, as a gesture of goodwill. However, you should understand that any data you give will be as a gift and you will not benefit financially in the future should this research lead to the development of a new treatment/method/test/assessment.

6. What are the possible benefits of taking part?

It is possible that HBOT provided by Gravells Pharmacy may help to alleviate some of your key long COVID symptoms, but this is not guaranteed. However, it is anticipated that this project will generate information to better understand the short-term impact of HBOT on some of the key long COVID symptoms and also help to identify future related service provision and larger scale research priorities, which may help others, in the future, affected by long COVID.

7. What are the possible risks of taking part?

HBOT will be provided by trained operators from Gravells Pharmacy and they will provide you with a separate information leaflet about the possible advantages and disadvantages associated with

HBOT. However, HBOT can be provided safely, in a range of community settings. They will also seek your written informed consent for HBOT prior to the first therapy session. **Cardiff University staff will not be involved in this process.**

There are no known risks attached to the evaluative component of this study, for which we are conducting. However, it is possible that due to the nature of the project you may find it tiring to complete questionnaires. We therefore advise you to complete these as and when you feel able to do so and, if you need any assistance, please ask. If there are any questions you feel uncomfortable answering, you are free to omit them. It is also possible that you may find the focus group upsetting. Should you feel anxious or upset, the group discussion will be paused or stopped and you will be offered emotional support and signposted to relevant professional support. The group discussion will reconvene if and when you feel you are able to and you are also free to leave the discussion if you would prefer.

8. Will my taking part in this project be kept confidential?

All information collected from (or about) you during the project will be kept confidential and any personal information you provide will be managed in accordance with data protection legislation. Please see 'What will happen to my Personal Data?' (below) for further information.

9. What will happen to my Personal Data?

Personal data, according to the General Data Protection Regulation (GDPR) means any information relating to an identifiable living person who can be directly or indirectly identified in particular by reference to an identifier. This may include information such as an individual's name, address, email address or date of birth.

Cardiff University is the Data Controller and is committed to respecting and protecting your personal data in accordance with your expectations and Data Protection legislation. Further information about Data Protection, including:

- your rights
- the legal basis under which Cardiff University processes your personal data for research
- Cardiff University's Data Protection Policy
- how to contact the Cardiff University Data Protection Officer
- how to contact the Information Commissioner's Office

may be found at https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection. Printed copies of the above-mentioned documentation and privacy notices will be available on request.

We will need to collect some demographic information from you (e.g. age range and symptom details) but we will not reveal your name or contact details to anyone beyond the research team. Your research data will have a unique code number instead, known only to the researchers. All information about you will be kept safe and secure on a University networked drive and password-protected.

Completed questionnaires and focus group data will be kept securely on a University networked drive and password-protected. All research data will be kept for five years, following University policy, and will then be permanently deleted. Any personal information will be stored separately from any other data we collect as part of the study on a University password-protected networked drive. It will be permanently deleted within two months of completing the study. Your consent form will be stored for five years in line with Cardiff University data retention schedules.

You are free to withdraw from the study at any time without giving reason. If you withdraw from the study information you have provided up to the point that you withdraw will still be used.

10. What happens to the data at the end of the project?

All data will be stored securely on Cardiff University servers for five years. Data collected will be used in the write up of final report for the funders of the project (Accelerate) and published in an academic journal.

11. What will happen to the results of this study?

The findings of the study will be published as a final report to the funders and in relevant journals and presented at conferences. You can request a copy of the findings if you so wish. You will not be identifiable in any reports, publications or presentations. Where appropriate, we will use verbatim quotes from participants, however these will be anonymised.

12. What if there is a problem?

HBOT will be provided by trained operators from Gravells Pharmacy and if you have any concerns about therapy, you are encouraged to discuss this with them. However, if you have a concern about any aspect of the evaluative component of study, please contact me on the email address or phone number below and I will do my best to answer your questions. If you remain unhappy and wish to complain formally about the evaluative component of the study, you can do this by contacting the director of research governance (Dr Kate Button) at the School of Healthcare Sciences, Cardiff University (ButtonK@cardiff.ac.uk).

13. Who is organising and funding this study?

The study is funded by Accelerate https://www.cardiff.ac.uk/medicine/research/clinical-innovation/accelerate and the Sponsor of the evaluative component of the study is Cardiff University. Gravells Pharmacy, Llanelli will provide HBOT. Indemnity insurance for the evaluative component of the project will be provided by Cardiff University insurers (a copy of the insurance policy can be provided on request). Gravells Pharmacy are solely responsible for the provision of HBOT and have the requisite indemnity insurance for this activity. If you wish to know more, you are advised to discuss separately with them.

14. Who has reviewed this study?

The study has been reviewed and given a favourable opinion by the Research Ethics Committee in the School of Healthcare Sciences, Cardiff University.

15. Further information and contact details

if you have any questions relating to this project, you may contact me during normal working hours:

Dr Paul Gill
Senior Lecturer (Adult Nursing)
School of Healthcare Science
Cardiff University
gillp3@cardiff.ac.uk
029 206 88605 (voicemail)

Thank you for considering to take part in this project. If you decide to participate, you will be given a copy of the Participant Information Sheet to keep for your records.