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Original Article

A patient and public involvement (PPI) review exploring patient reported outcome measures in adult CAR T-cell therapy patients

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SUMMARY

Background & Aims: Chimeric Antigen Receptor (CAR) T-cell therapy is a novel anti-cancer treatment option for patients with refractory or relapsed haematological malignancies. Preliminary research shows a significant proportion of patients receiving CAR T-cell therapy develop malnutrition and cachexia during treatment, with these nutritional issues associated with adverse patient outcomes. There is a lack of literature and no specific validated measures on patient experience and burden of symptoms for CAR T-cell therapy patients as well as the importance of clinical outcomes for these patients. Patient and public involvement (PPI) is a fundamental feature of proper research execution as it informs issues in the research that are most important in patients. The aim of this review was to identify priority patient-reported outcome measures in CAR T-cell therapy patients using PPI, in addition to exploring patient experiences, burden of symptoms, priorities, and knowledge of nutritional priorities in cancer. The PPI outcomes will also aid to inform the design and development of a future novel cohort study.

Methods: Using participatory research (PPI), six adults aged 26–70 years who have received CAR T-cell therapy in the past two years, participated in one-to-one interviews. The interview questions were focused on the aims of identifying patient recommendations regarding clinical outcome measures of interest, their relevance to patient's experience of CAR T-cell therapy, and optimal design of the future cohort research protocol.

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Results: Eight main themes were identified through the interviews: unfamiliarity of terms malnutrition and cachexia; weight loss during treatment not considered a main concern; exercise deemed a main priority in all participants; fatigue as the main side effect; importance of survival, psychosocial concerns; nutritional supplementation issues and dissatisfaction in hospital food.
Conclusions: The responses have revealed that the themes of exercise, fatigue, intensity of side effects and survival were deemed as highly important in all participants. In addition, consideration should be placed on the psychosocial concerns of participants in the future cohort study regarding assessments that may have higher patient burden, such as indirect calorimetry and body composition assessments. Moreover, reports regarding nutritional supplementation along with hospital meals provided during treatment, have shown that they are not fulfilling the participants' satisfaction and priorities. Future research undertaken in the novel area of CAR T-cell therapy should take measures to focus on these outcomes of importance to participants, to minimise burden and provide adequate support.

Introduction

CAR T-cell therapy has emerged as a novel anti-cancer treatment for patients with B-cell haematological malignancies [1]. Conventional chemotherapy and stem cell transplantation are often used in the treatment of haematological malignancies, however, there is a vast population of patients who fail to respond to second-line chemotherapy, or who relapse within one-year post-treatment [2]. Long-term remission has been reported in less than 20% of participants with diffuse large B-cell lymphoma (DLBCL) following chemotherapy [3]. The development of CAR T-cell therapy has emerged as a potential treatment option for these patients with relapsed or refractory B-cell haematological malignancies [4]. Absolute remission has been reported in approximately 40% of participants following CAR T-cell therapy, although adverse side effects including cytokine-release syndrome (CRS), neurotoxicity and psychosocial concerns are major considerations experienced by patients [5,6]. Cancer cachexia (CC) wasting has been shown to develop in 60–80% of haematological cancer patients and can have acute and chronic consequences on quality of life and physical function [7,8]. CC has long been under-recognised as a significant syndrome and misinterpreted in its universal definition, despite its high prevalence in haematological malignancies [9]. Numerous mechanisms have been associated with the progression of CC including anorexia, inflammation with the increased production of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumour necrosis factor-alpha (TNF-α), reductions in physical activity levels with subsequent loss of lean muscle mass and function, altered production of anabolic hormones such as reduced androgens, and growth hormone–insulin-like growth factor (GH-IGF) activity, and alterations in nutrient metabolism [10,11]. These nutritional and metabolic alterations can arise from both the cancer itself and various anti-cancer therapies, thereby making cancer cachexia highly prevalent in cancer patients [12,13]. Nevertheless, its mechanisms, diagnostic criteria, and prospective treatment options still remain a challenge for healthcare professionals [14,15]. CC commonly develops in high-grade lymphomas such as B-cell Non-Hodgkin Lymphoma, where patients have been observed to have body weight reductions of 31% [7]. Additionally, the significance of attenuating disease-related malnutrition in standard anti-cancer therapies such as chemotherapy has been well documented, with malnutrition being a known predictor of multiple adverse participant outcomes such as response to cancer treatment and prognosis [11].

However, in CAR T-cell therapy, there is currently minimal research available regarding the significance of these nutritional issues [16,17]. From the limited research currently available in CAR T-cell therapy, high prevalence of malnutrition and cachexia have been identified ranging from 34% to 61.4% [13,18,19]. These malnutrition rates exceed those seen in any other form of standard anti-cancer therapy in haematology patients; although, as stated, only pilot data has been explored so far [20,21]. Furthermore, these deteriorated nutritional status syndromes presenting in CAR T-cell therapy are significantly associated with adverse participant outcomes, such as increased treatment toxicities and overall survival [17].

NIHR guidelines, and the increased use of PPI in research internationally corroborates that patient involvement is essential, identifying issues in research that are most important to them and improve research relevance [22]. However, minimal research, and a dearth validated measures are currently available on CAR T-cell therapy patient experience or burden of symptoms, as well as the importance of clinical outcomes [3]. It is essential to involve the patients who have undergone the treatment process in any research design, as they provide specialist insight into the experience, side effects, and quality of life impact, as well as aid in identifying the patients' highest priority concerns and considerations during CAR T-cell therapy. PPI is an important underutilised resource which is regarded for potentially enhancing the quality of research [23]. Furthermore, methods and approaches for PPI include a variety of different formats, including qualitative and quantitative research methods (e.g., interviews, focus groups and surveys), which can be used separately or in combination [24]. Therefore, the aim of this review was to identify patient-reported outcome measure of importance, patient experience, burden of symptoms, priorities, and understanding of nutrition concerns in CAR T-cell therapy patients through PPI activities, in order to undertake future effective and efficient nutrition-related research in this population.

Materials and methods

Patients who had previously received CAR T-cell therapy in the past two years at University College London Hospitals (UCLH) were approached to be involved in these PPI activities. Activities were undertaken as part of the PIs UCL MSc dissertation; members of the research team involved in the screening or contact of potential participants, were permanently employed at UCLH or obtained honorary contracts. To ensure appropriate methodology, consenting and reporting, NIHR-endorsed PPI training was undertaken by the research team, in addition to regularly communications with experienced PPI researchers and the PPIE Leads at the NIHR Applied Research Collaboration (ARC) North Thames. Ethical approval was not required to undertake this evaluation given the nature of PPI, as confirmed with the NIHR UCLH Biomedical Research Council (BRC) and Research Ethics Officer at UCL. Random allocation of participants ($n = 6$) who have previously received CAR T-cell therapy were identified for recruitment from the UCLH electronic health records. The only participants that were excluded from initial contact were those who were unable to understand/consent to the PPI activity (cognitive disorders) or, were deceased. Recruitment of participants from diverse ethnic minority groups was ensured to account for potential differing treatment experiences and improve generalisability of results [25]. One-to-one interviews - completed by telephone or virtually due to participants' locality - were conducted, restricted to maximum one hour and were digitally recorded (range, 20–30 minutes). Following the obtainment of verbal consent at the beginning, these interviews were recorded, transcribed verbatim, subsequently deleted, and analysed using thematic analysis. Confidentiality was assured to the participants, with removal of all identifying information and participants informed that these interviews were solely intended as PPI. Initial potential participant identification, contact (by telephone) and verbal consenting was conducted by a member of the research team permanently employed at UCLH. The agreeing participants were contacted again by telephone to arrange the formal interview time. The INVOLVE budgeting tool funded by the National Institute for Health Research (NIHR) was used to inform participant rewards for participation in the interviews [26]. Vouchers worth £25 were provided via email or by post to each participant per interview as a compensation for participation, which is commensurate with the nature and demands of the PPI activity [27]. Any identifiable participant data was stored on secure UCLH servers. The interview questions ($n = 15$) were formulated in advance in collaboration with the Principal Investigator for the future

cohort study and were focused on this study's aims, including identification of patient-reported priority clinical outcome measures, and participants' experience of CAR T-cell therapy. This included what 'research impact' meant to the participants, as well as the acceptability of future research protocols including the feasibility of performing regular objective and subjective assessments during treatment. Further, understanding the participants' knowledge of nutritional consideration in haematological cancers/treatments was sort. The questions contained within the interview can be found in Table 1, including open, closed, and scaled questions. Additionally, we sort to establish a patient advisory panel (PAP) for consenting participants, for ongoing involvement with elements of co-production for the future study. This PAP would enable ongoing involvement, feedback, and provision of study updates.

Table 1
Questions contained in the interview focused on the aims of the PPI activity.

Interview questions (n = 15)
Question
1. Were you made aware of the terms cachexia or malnutrition either during CAR T-cell therapy or any of your previous cancer treatments?
2. Did your doctor or healthcare professional (physiotherapist, dietitian, oncology doctor/nurse etc.) ever explain to you what cachexia is when you were going through treatment?
3. Were you experiencing weight loss due to cancer or during CAR T-cell therapy or any other treatment? If yes, what were your thoughts about your weight loss? How did it make you feel? Did it affect the way you viewed yourself?
4. Were you referred to a dietitian to manage your weight loss?
5. Did you feel that your weight loss affected your quality of life?
6. Did you feel that your weight loss was acknowledged/supported by healthcare professionals, and did they try to combat this issue?
7. Did you do any exercise in hospital, either because you felt up to it or because a healthcare professional (e.g., physiotherapist) recommended it? If so, did you do the exercises (why/why not), and did they talk to you about why it is important to do exercises?
8. Were you aware when you went through CAR T-cell therapy, or any of your previous cancer treatments that keeping your weight the same, could improve your response to the treatment and make you feel better?
9. What side effects that came from the treatment affected your life the most?
10. We want to understand what side effects or things that happened during your treatment or even after were the most important to you for us to consider/try to help with through research: If I list a few options, can you tell me how important they were to you (0 = not important at all, 5 = somewhat important, 10 = extremely important):
a. Changes to your energy levels and fatigue
b. How long you stayed in hospital
c. Losing weight (specifically losing your muscles)
d. How intense the side effects from your treatment felt?
e. Changes to your physical function, relating to not feeling up to doing your normal daily activities (e.g., cooking, showering)
f. 'Quality of life'
g. Surviving your cancer and the cancer treatment
11. Would you be happy for a dietitian to use two simple devices to monitor you nutritionally every 4–7 days per week whilst you're at hospital? 1. Indirect calorimetry - tells us how much nutrition you need each day to keep well and keep your weight and strength the same. The way it works is it measures how much you breathe in and out therefore, you will have an oxygen mask that will go over your nose and mouth and then you sit there, and you breathe in and out for 5–10 min. 2. Bioelectrical Impedance Analysis (BIA). There are 2 types of BIA: the first one has a normal scales where you stand on and you hold a light piece of metal with your arms in front of you extended and you hold it for 20 seconds. The other way that a BIA device works – they will put a clip on both your arms and legs whilst you're lying down, and it sends a message up and down your body and it tells us how much muscle and how much fat is on your body. Duration is around 1–5 minutes.
12. Would you feel at ease/more comfortable doing exercise at the hospital or at home? Reflecting on how you felt when you were going through CAR T-cell therapy, do you think you would have felt up to doing small amounts of exercise every day or so?
13. Would you feel more comfortable doing exercise with a qualified trainer or by yourself?
14. If you weren't eating as well as you normally do, or if a dietitian recommended it, would you be happy to take a 'nutritional supplement' – you may have seen these before or taken them before, they are a high protein milkshake that provide all the nutrition of a main meal. For example, 'Ensure supplement' – would you be okay to take this regularly at the hospital?
15. Would you feel comfortable to be contacted again by a dietitian to be a part of an advisory panel? (Additional information explained to participants regarding advisory panel):
o It will be similar to this interview, and will take place every 6–8 months

(*continued on next page*)

Table 1 (*continued*)

Interview questions (n = 15)
o It will help continue to shape the research we are doing. We will be discussing what we have done so far with our research, what you think of this and what you recommend we could do differently. It will also ask your advice regarding how to write things (including participant information sheets (PIS), which is the handout given to the participants who agree to be a part of the research during treatment).
o It will likely be maximum 20 minutes
o You will again receive a 25-pound voucher each time you are contacted.
o There is no pressure to join the advisory panel, and you can change your mind (and leave the advisory panel) if you want to in the future.

Results

The characteristics of the six (median age 52 [25–70] years, 50% female, 50% male) participants who have previously received CAR T-cell therapy participating in the PPI can be seen in Table 2. The answers to the closed interview questions can be found in Table 3.

Table 2
Characteristics of PPI participants.

Participant characteristics	
	Total (n = 6)
Gender	
Male	3 (50%)
Female	3 (50%)
Median age (years) and range at approval for treatment	
Age at approval for treatment (years)	52 [26–70]
Ethnicity	
Mixed white and black Caribbean	1
'Other ethnic group'	1
Irish	1
Unknown	2
White British	1
Year received treatment	
2020	2
2021	4

Categorical variables are expressed as frequency (n,%); non-parametric continuous variables are shown as median and range.

Table 3
Answers to the closed interview questions–(Q1-11).

Interview questions	Interview answers	
	Yes; n (%)	No; n (%)
1. Were you made aware of the terms cachexia or malnutrition either during CAR T-cell therapy or any of your previous cancer treatments?	2 (33.3)	4 (66.7)
2. Did your doctor or healthcare professional (physiotherapist, dietitian, oncology doctor/nurse etc.) ever explain to you what cachexia is when you were going through treatment?	2 (33.3)	4 (66.7)
3. Were you experiencing weight loss due to cancer or during CAR T-cell therapy or any other treatment?	2 (33.3)	4 (66.7)
4. Were you referred to a dietitian to manage your weight loss?	4 (66.7)	2 (33.3)
5. Did you feel that your weight loss affected your quality of life?	1 (16.7)	5 (83.3)
6. Did you feel that your weight loss was acknowledged/supported by healthcare professionals, and did they try to combat this issue?	4 (66.7)	2 (33.3)

Table 3 (*continued*)

Interview questions	Interview answers	
	Yes; n (%)	No; n (%)
7. Did you do any exercise in hospital, either because you felt up to it or because a healthcare professional (e.g., physiotherapist) recommended it? 7a. and did they talk to you about why it is important to do exercises?	6 (100) 5 (83.3)	0 (0) 1 (16.7)
8. Were you aware when you went through CAR T-cell therapy, or any of your previous cancer treatments that keeping your weight the same, could improve your response to the treatment and make you feel better?	1 (16.7)	5 (83.3)
9. Would you be happy for a dietitian to use two simple devices to monitor you nutritionally every 4–7 days per week whilst you're at hospital? Thinking back for when you were in hospital, would you be able to do it? If you decided one day that you didn't want to do it, you could always change your mind.	5 (83.3)	1 (16.7)
10. If you weren't eating as well as you normally do, or if a dietitian recommended it, would you be happy to take a 'nutritional supplement' – you may have seen these before or taken them before, they are a high protein milkshake that provide all the nutrition of a main meal. For example, 'Ensure supplement' – would you be okay to take this regularly at the hospital?	4 (66.7)	2 (33.3)
11. Would you feel comfortable to be contacted again by a dietitian to be a part of an advisory panel?	5 (83.3)	1 (16.7)

Understanding the terms 'cachexia' and 'malnutrition'

66.7% (n=4) of participants were not made aware of the terms, or the potential risk of development of cachexia or malnutrition during CAR T-cell therapy, or any of their previous cancer treatments. Reports of dissatisfaction for not being made aware of the terms were also made prevalent.

> "*No one ever explained to me what those terms meant, and I did not receive much help in the nutritional area at all, which would be very helpful to know*".

Weight loss

Only 33.3% (n=2) of participants reported experiencing weight loss, either during CAR T-cell therapy treatment or any previous treatments received.

These participants both described their thoughts about their weight loss as not concerning or alarming, as they reported they felt 'overweight' at the start of the treatment. In addition, this weight loss did not negatively affect the way they viewed themselves, but rather, they reported preferring it, given historical societal perceptions of weight loss being beneficial.

Furthermore, two of the participants who did not experience weight loss, expressed feelings of encouragement from family members to maintain their weight which was deemed as highly important for the participant to maintain this goal.

> "*When I was having the treatment, I was crying because I didn't want to eat anymore but my family told me to eat one more spoonful for them, so I don't lose weight which was very helpful*".

However, five out of six participants, agreed that they were not made aware that keeping their weight the same during CAR T-cell therapy or previous cancer treatments could improve their clinical outcomes.

Dietetic input for weight loss management

50% of the participants (n=3) reported that they were referred to a dietitian to manage their oral intake/weight loss. One participant described that the dietitian explained how to prepare and choose

appropriate dietary options higher in calories and protein recommended during oncology/haematology treatments, such as smoothies. Another participant described their experience with the dietitian including reports of what was deemed to be the role of the dietitian: *"to generally prescribe a diet to help you lose weight, but the dietitian provided information of the importance of eating during CAR T-cell therapy"*.

The same participant reported that *"The dietitian did not expect me to lose weight and did not care about what kind of food I ate but rather that I needed to eat so I keep my weight up. I remember at one point I had ordered McDonalds"*.

83.3% (n=5) of participants were not aware of the evidenced-based dietetic recommendations of maintaining weight/muscle mass to improve outcomes during any previous treatment, or CAR T-cell therapy. One respondent expressed understanding of the importance of maintaining oral intake, despite not receiving any previous dietetic input. This participant reported receiving this dietary advice from a registered nurse.

Weight loss effects on quality of life

Only one participant reported that their weight loss affected their quality of life.

The remaining 83.3% (n=5) reported that their quality of life was not affected by any weight change. This included those who did not lose weight because they preferred the weight loss they experienced as they perceived themselves as overweight prior to starting the treatment.

> "*I thought it was great. I was 19 stone when I began CAR T-cell therapy and dropped to about 16 stone in weight when I left the hospital*".

66.7% of participants (n=4) felt that their weight loss was acknowledged by healthcare professionals. This included the participants who perceived their weight loss as preferential.

Physical activity/exercise

All six participants performed exercise in the hospital either of their own accord, or because a healthcare professional recommended it.

83.3% (n=5) of participants performed exercises prescribed by a physiotherapist and were explained the importance of staying active to prevent muscle mass loss.

> "*I tried doing some exercises because I was made aware of the risks of inactivity*".

In addition, exercise was positively emphasised by one participant in relation to its beneficial effects on mental health during treatment.

One participant did not receive recommendations for physical activity from any healthcare professional, or why it is considered important. They expressed that healthcare professionals were more concerned about the weight loss in general, with advice focused on increasing oral intake. Although, this participant reported taking it upon themselves to keep active.

Of interest, 100% of participants, including those that received physical activity recommendations from healthcare professionals and those who did not, all reported walking daily in their hospital room, with the goal of staying mobile and improving strength.

> "*I felt happier after exercising because it helped me get stronger*".

However, one participant who underwent CAR T-cell therapy during the COVID-19 pandemic, expressed feelings of frustration as they were restricted to their hospital room due to infection risks, limiting their ability to perform physical activity in a larger environment.

> "*I had to walk up and down my hospital room*".

Side effects experienced and its impact on quality of life

50% (n=3) of participants reported extreme fatigue as the side effect from treatment that most greatly affected their quality of life (Figure 1).

Fever was identified as the second most common side effect, reported by 33.3% of participants (n=2). The other patient-reported important side effects, including feelings of being mentally and physically drained, reduced levels of white blood cells (WBCs)/neutropenia, nausea, chronic diarrhoea, skin rashes, and changes in emotional state and sleep pattern were reported by singular participants only.

Those who reported the extreme fatigue stated this continued to persist post CAR T-cell therapy admission, remaining below their baseline for approximately two years. One participant reported that they felt that this was due to low levels of WBCs.

> "*I experienced drops in my WBCs which kept going down for almost two years. It took me two years to get back to normal from having fatigue and until my WBCs return to normal levels which took some time as well*".

However, one participant reported that the benefits of CAR T-cell therapy treating her malignancy far outweighed the ongoing burden of side effects such as fatigue.

> "*Obviously, CAR T-cell therapy was a life-saver for me. It saved my life*".

Outcomes of CAR T-cell therapy

Using scaled questions, all six participants reported 'how intense their side effects from treatment felt' and 'surviving cancer and the cancer treatment' as the most important clinical outcomes during or after CAR T-cell therapy (Figure 2).

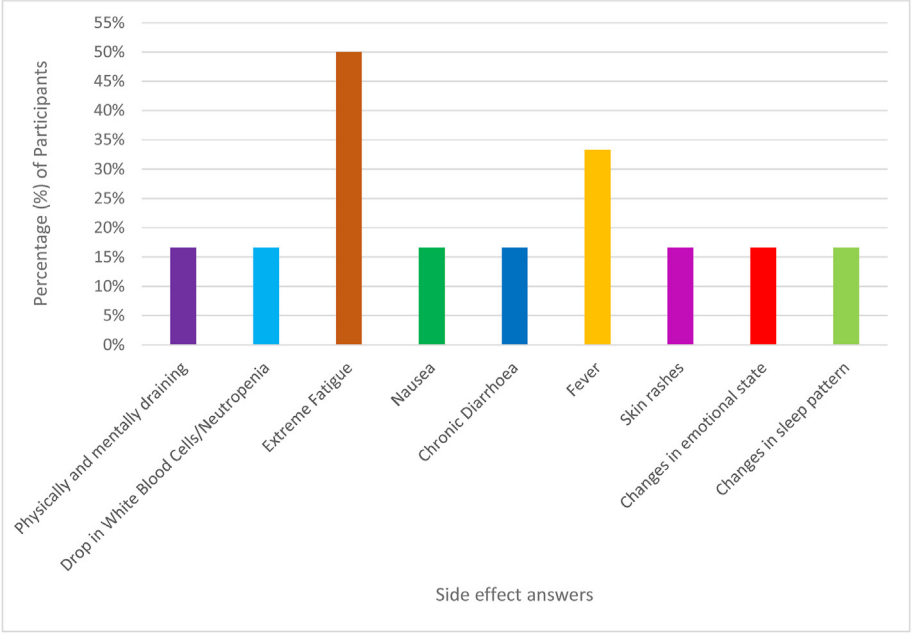

Figure 1. Side effects from CAR T-cell therapy that affected the life of participants the most.

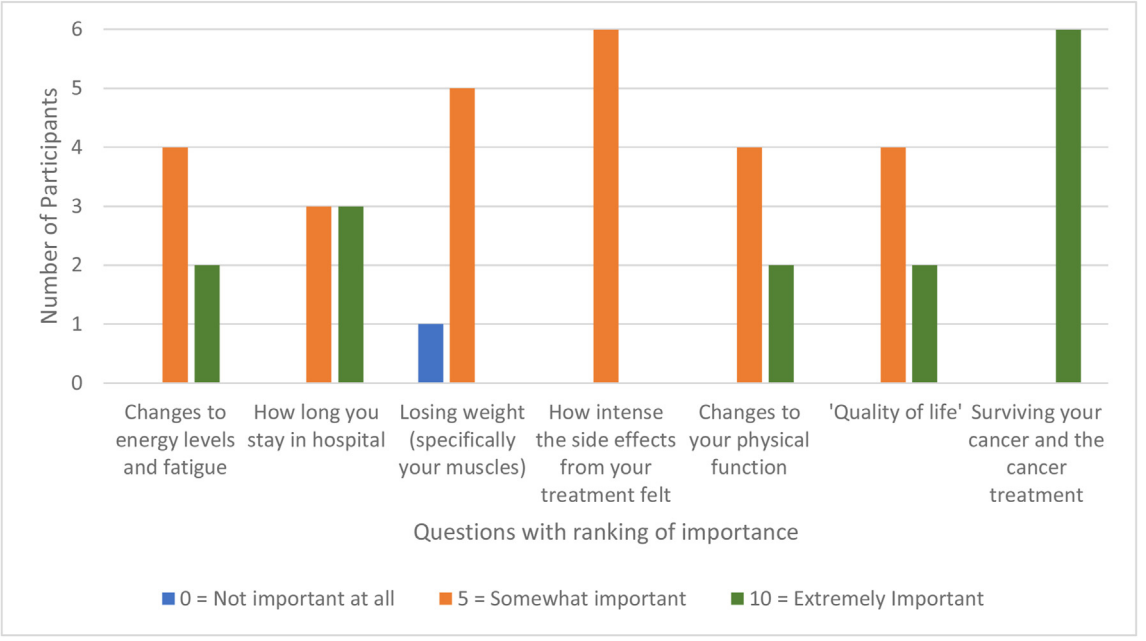

Figure 2. Side effects/other factors during or after CAR T-cell therapy that were ranked as the most important for participants.

83.3% of participants (n=5) ranked 'losing weight' as somewhat important, whilst one participant reported it as not important at all. 50% (n=3) of participants ranked changes to energy levels and fatigue, changes to physical function and quality of life as somewhat important. The remaining 50% of participants deemed this outcome as extremely important and described them as a priority. 50% of participants expressed 'how long they stay in hospital' as somewhat important, with the remaining stating this as extremely important. Another participant described the intensity of treatment side effects as being an important consideration, as they experienced some degree of neurotoxicity, a common side effect of CAR T-cell therapy, which affected their memory.

> "*They would come in everyday and ask me 'where are you?' 'which hospital are you in?'. It wasn't too bad but at the time I was surprised. I would get it right 99% of the time but still sometimes I wouldn't get it right. It had some effect on me*".

Feasibility of proposed assessments in future research protocol

Regarding informing the design and feasibility of the future nutritional status research protocol, the proposed methodology and detailed descriptions of proposed assessments were provided to the participants for their feedback. Four participants reported no concerns with the prospect of undertaking regular nutritional assessments in this study, including indirect calorimetry and Bioelectrical Impedance Analysis (BIA) assessments. Two out of these four participants were familiar with the processes involved with BIA and indirect calorimetry assessments. However, the remaining two participants reported considerations should be made for these assessments to take place when treatment side effects were subsiding; this relates to assistance they predicted they may require in standing for different assessments.

One participant reported mixed feelings regarding the assessments stressing the same considerations as above regarding the burden of side effects whilst undertaking assessments.

Regarding the feasibility of undertaking indirect calorimetry assessments and the different methods available (Hans Rudolph Mask or canopy), this same participant also reported preference for using the canopy, as opposed to the standard face mask.

> "*During the days I was having high fever, it would be tough [to undergo assessments] because I had a lot of different drugs pumped into me, I was woken up a lot, I was too hot or too cold, my face started to swell up at any point. Having more [assessments] during those days, would be too much*".

Four participants reported nil concerns or preference for the different indirect calorimetry assessment methods, however one participant did not agree with either method proposed, as they reported feelings of claustrophobia and feelings of exhaustion.

> "*It would be a problem for me [to undertaken indirect calorimetry]. I could struggle putting the mask on or lying down. It would feel claustrophobic. It would be tiring*".

All six participants stating walking as their preferred method of exercise, with 50% (n=3) reporting being more comfortable performing exercise at home rather than in hospital. As stated above, one of these three participants expressed concerns regarding the hospital room being too restrictive to perform this preferred exercise, requiring them to walk repetitively around their room. The burden of side effects such as fevers were reported as additional limiting factors for participants to undertake this recommended exercise, due to associated light-headedness.

> "*I had to get a scan and they needed to wheel me up [due to light-headedness]. There's a period where you should rest and there's a right time to walk. Even when I left the hospital I was still walking slow*".

Two participants preferred performing exercise at the hospital rather than at home. One of the two participants also expressed the same concept as other participants, in regards to the hospital room being too restrictive to walk in. One participant expressed no preference to exercising at the

hospital or at home. 83.3% of participants (n=5) reported feeling more comfortable doing exercise with a qualified trainer than by themselves. One participant reported they were pleased to receive ongoing support post-discharge, including weekly virtual sessions with a physiotherapist/occupational therapist.

> "*I felt much more confident having my trainer and ensuring the right level of stretches/exercises for me*".

Only one participant reported a preference for performing exercises by themselves.

'Oral nutritional supplementation'

Five participants described that they would be happy to commence oral nutritional supplements if they were experiencing reduced oral intake. However, four out of these five participants had previous experience with receiving prescriptions for oral nutritional supplements during treatment, where a main theme was identified. Reports of the supplements being "too artificial tasting" were made, as well as being too little to support the satiation for participants who identified themselves as larger-bodied.

> "*They're very small cups, tiny cups. A bigger guy like me would need something more substantial to keep me full*".

One participant reported declining these recommended 'oral nutritional supplement', as again reported familiarity with the supplement and associated negative feelings due their "foul in taste".

Hospital food

All participants raised concerns regarding the hospital food provided during treatment. Reports included the food being unappetising, limited choices and regular unavailability of meals.

> "*I looked forward to looking through the menu and searching for what I wanted to eat. But, they didn't have everything on the menu. So, when I ordered something, they didn't have it, so they would bring me something else. That was very frustrating*".

> "*The way the food was cooked was very unappetising. I didn't eat much due to that. I thought it would be better with all the care we had but the food was awful*".

The one participant with reported poor appetite during treatment described eating in the hospital as "very challenging". The combinations of poor appetite with limited hospital food choices were reported as the main barriers for this participant attempting to maintain their weight during CAR T-cell therapy. This participant reported family members would purchase external food from fast-food chains near the hospital for them as an alternative.

> "*We had no appetite, so having that poor food choice [in hospital] made us unable to eat. I had soup most of the time. My husband was bringing me Itsu. I felt that the hospital didn't meet the requirements*".

Psychosocial concerns

Another important consideration raised by one participant included discussions regarding body dysmorphia, cancer, and CAR T-cell therapy. The participant expressed experiencing body dysmorphia issues and an 'obsession' with dieting before their initial haematological malignancy diagnosis. Despite

receiving psychological input and reporting improvements in her body dysmorphia, the participant reported they were concerned they may receive negative comments from healthcare professionals during the CAR T-cell treatment regarding her increased body weight. However, they reported receiving support from their health care professionals.

> "*I thought I would be told that I was overweight, but no one said anything. They were pleased that I was eating well. It was something that I didn't have to feel the pressure of listening to anymore. It was the only time I had known medical professionals to be pleased with my increasing weight*".

Patient advisory panel for the future study

Regarding ongoing PPI through a PAP for the future study, only one participant declined. This was due to feeling extreme emotional pressure and psychological concerns related to their previous long haematological treatment history. This participant reported distress at the use of the word 'cancer' in conversation, and indicated this should be considered with future participant interactions.

At the end of the interview, the participants were given the opportunity for an open dialogue, to provide additional comments or feedback regarding their general experience. This included 83.3% of the participants reporting no appetite loss following CAR T-cell therapy.

Discussion

The aims of this study were to identify priority patient-reported outcome measures in CAR T-cell therapy patients using PPI, in addition to exploring participant experiences, burden of symptoms, priorities, and knowledge of nutritional priorities in cancer. The information obtained through this PPI would also aid to inform the design and development of a future nutrition-focused cohort study in this population. Eight main themes have emerged through the participant interviews.

Understanding the terms 'cachexia' and 'malnutrition'

Most participants reported dissatisfaction for not receiving education on the concepts, or importance of the term's 'cachexia' or 'malnutrition' by their doctor or healthcare professionals during CAR T-cell therapy or any other cancer treatment. A recent study has identified that 74% of CAR T-cell therapy patients would like more information about their treatment or the expected side effects of their treatment [28]. This is in line with former studies which have identified a trend with healthcare professionals lacking efficient communication with patients and their family members regarding malnutrition, cachexia, and their potential negative effect on patient outcomes [29,30]. The role of educating participants and families on the risks and consequences of malnutrition and cachexia in oncology and haematology should be considered as a high priority for healthcare professionals, given the abundance of research identifying the impact these deteriorated nutrition status syndromes. This need has been emphasised by the Clinical Framework for Quality Care in Cancer Cachexia [31]. However, to support the increased education of malnutrition and cachexia in CAR T-cell therapy, ongoing research is required to continue establishing the evidence base in this field. Nevertheless, there are still gaps in the literature regarding the knowledge of nurses on cachexia in cancer participants [32]. Our findings demonstrate that there are gaps in the patient-healthcare professional dynamic that need to be addressed, and the need for ongoing research in this field to assist with implementing and funding this change.

Weight loss

Weight loss is commonly reported as a significant side effect from CAR T-cell therapy, and a key diagnosing symptom of cachexia and malnutrition [33]. However, only two out of six participants interviewed reported weight loss, which was considered preferential by the participants due to their

self-reported higher Body Mass Index (BMI), prior to commencing treatment. The participants' perception regarding weight loss, and self-reported limited knowledge of nutrition during cancer treatment indicates a need for further dietetic resources. This would enable increased dietetic screening, interventions, improved patient knowledge and empowerment to implement strategies to maintain weight and muscle mass to patients with haematological malignancies, and empowerment to implement strategies to maintain weight and muscle mass.

Insufficient nutritional intake is significantly associated with decreased survival and poor clinical outcomes in oncology and haematology [34]. Studies have revealed that approximately 40–60% of participants with a haematological malignancy, have a BMI of $\geq$25 kg/m^2 [35]. Thus, the identification of muscle loss in participants with increased adiposity (sarcopenic obesity) can be more difficult to observe and assess [35]. This raises concerns as sarcopenic obesity is highly prevalent in many haematology and oncology patients, where weight loss may not be identified due to excess adiposity. This sarcopenic obesity has been associated with reduced quality of life, response to treatment, reduced survival [36]. In addition, poorer clinical outcomes have been reported during chemotherapy in participants with a higher percentage body fat [37]. This highlights the need for sensitive body composition assessments (e.g., dual energy X-ray absorptiometry [DEXA], BIA), both in research and clinical practice, to accurately identify muscle wastage in all patients.

Physical activity/exercise

All participants performed exercise in the hospital, specifically walking, which was found to be a main priority for all participants. This further highlights the importance of allied health input (including physiotherapy and occupational therapy in CAR T-cell therapy, to promote physical activity in order to minimise muscle wastage, frailty, and cachexia progression. Our findings showed that five out of six participants were prescribed exercises by a healthcare professional and were educated on the importance of remaining active to prevent muscle loss and mitigate the risks of inactivity. Furthermore, as the majority of participants reported feeling more comfortable performing exercises with a qualified healthcare professional, ensure adequate funding for allied health in this setting hence personal training or group exercise sessions might be a better option than home-based exercises performed by themselves. This is considered particularly important as maintaining physical activity throughout CAR T-cell treatment has been shown to decrease the burden of side effects and toxicities, decrease hospital length of stay and improve patient-reported outcomes [38].

Fatigue is a key symptom

Studies have shown two primary symptoms experienced by CAR T-cell therapy patients include fatigue and decreased appetite: precisely 360 days post-treatment [39]. With one participant reporting persisting fatigue for approximately two years post-treatment, this finding is consistent with a one-year follow-up study in CAR T-cell therapy patients where fatigue was observed to persist in 33.33% of participants [40]. Fatigue has been shown to be one of the main symptom impacting oncology and haematology patients' activities of daily living such as walking, enjoyment of everyday life and employment status [41]. The decreased physical function of these patients due to fatigue and its associated symptoms have also been consistently associated with a reduced quality of life [41]. Furthermore, fatigue is a key diagnostic criterion and characteristic of frailty; this clinical syndrome is shown to be heavily prevalent in oncology and haematology patients and can impact on clinical outcomes. Therefore, long-term follow-up of CAR T-cell therapy patients by doctors and allied health is important to monitor and manage side effects, such as fatigue, which impact quality of life [42].

Survival

Unsurprisingly, despite the burden of symptoms experienced by the CAR T-cell therapy participants during treatment, survival was deemed as the most important clinical outcome. This has also been

demonstrated by Schofield *et al.* where CAR T-cell therapy patients reported accepting the side effects and toxicity risks associated with treatment in exchange for the chance of remission and survival [43].

Psychosocial concerns

In addition, outside the scope of this review, different psychosocial concerns were voiced. This includes body image concerns and reported distress with specific medical terminology (e.g. “cancer”) given the participant's prolonged medical and treatment history. Adequate provision of psychological support should be considered for CAR T-cell therapy patients, both in research and clinical practice.

Oral ‘nutritional supplementation’

Oral nutritional supplementation is an important and regularly utilised dietetic intervention in oncology and haematology, assisting patients to meet their protein and energy requirements to prevent and or reduce the risk of deteriorated nutritional status syndromes such as malnutrition and cachexia [44]. Participants that had previously trialled oral nutritional supplements reported dislike in the taste, or concerns of it being insufficient to satisfy their satiety. Consideration needs to be placed on the feelings and preferences of these participants as this may lead to poor compliance. However, studies have shown that haematology and oncology patients experience an array of side effects during various treatments which can impact nutritional intake [45], resulting in changes to eating behaviours and weight loss, impacting patient outcomes including response to treatment, quality of life and survival [46].

Hospital food

All participants reported dissatisfaction with the hospital meals provided during treatment, and subsequent concerns for their inability to maintain their body weight. Despite participants not reporting appetite loss as a major side effect, meals on the menu were either out of stock or unappetising to consume. As a result, most participants or their families opted for fast-food options to satisfy their appetite and maintain their nutritional intake. However, this may not be an option for all participants due to potential financial constraints and should be considered in strategies to improve the nutritional status of patients receiving CAR T-cell therapy.

Limitations

This review has several limitations such as the small sample of participants recruited, potentially not capturing the experiences, side-effects, and priorities of the wider CAR T-cell therapy patient population. This includes the adequate representation of patients who have experienced malnutrition and cachexia, as their perspectives may differ from those who have not faced these nutritional challenges. Furthermore, participants were recruited over a two-year period following CAR T-cell therapy, therefore all participants had achieved a response to which aided in survival. Hence, it is acknowledged that these experiences may differ from participants where CAR T-cell therapy did not achieve a prolonged response. This omission may have resulted in missing participants' valuable perspectives and insights into their experiences, emotional wellbeing and identifying mechanisms to support such participants. Additionally, our review did not investigate patients' viewpoints on initiating alternative feeding approaches (e.g., enteral or parenteral nutrition) when clinically indicated. A recent service evaluation found 17.5% of patients undergoing CAR T-cell therapy required enteral and parenteral nutrition [47]. Understanding patients' perspectives regarding the need for these approaches, potential obstacles, and effective implementation strategies could enhance their utility in clinical settings.

Benefits

This review involved participants of variable ages, genders, and ethnicities. This assisted with ensuring the experiences, perspectives, and concerns voiced were covered from a broad range of participants; this is important in PPIs as their input assists with developing future patient-oriented research and subsequent clinical care decisions.

Conclusion

Many key themes have been identified through the PPI activities such as fatigue being the most common and major side effect from CAR T-cell therapy, alongside a lack of participant education on the definition and impact of malnutrition and cachexia. This is further evidenced by participant reports of weight loss not being regarded as a main concern for participants. Reports regarding nutritional supplementation and hospital meals provided during treatment, have shown that they are not fulfilling the participants' satisfaction and priorities, which may further limit the success of dietetic interventions for maintaining nutritional status during treatment. Increasing research and subsequently resources available for multidisciplinary services in CAR T-cell therapy to provide interventions focused on maintaining nutritional status, muscle mass and psychological support should be considered for the future.

The data collected from the PPI and subsequent PAP activities will provide essential information to aid in the development of future nutrition-focused cohort studies in this population, including prioritising patient-reported clinical outcome measures, strategies to minimise participant burden, with patient co-production elements.

Statement of authorship

Adrian Slee, Brittany Cucchiaro and Nikoletta Mama conceptualised the research idea. Nikoletta Mama completed participant interviews and wrote the initial draft manuscript. All authors contributed to the final development of the paper.

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Conflict of interest

There are no conflicts of interest to disclose.

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Appendices

‘Instructions to Authors’ by Clinical Nutrition ESPEN:

SUBMISSION TEMPLATES

Template: Full Length Article submission

SUMMARY				
Submission Files	**Manuscript elements (mandatory order)**	**NEW**	**REVISION**	**Remark**
Cover Letter		optional	optional	
Response to reviewers			required	
Manuscript		required	required	format: double-spaced
	Title Page	required	required	
	Abstract	required	required	Structure: Background&Aims - Methods - Results - Conclusion
	Key Words	required	required	Max 6
	Abbreviations	optional	optional	
	Introduction	required	required	1.5 page
	Material & Methods	required	required	
	Results	required	required	
	Discussion	required	required	Add titles to paragraphs, max 4 pages, 1200 words
	Conclusion	required	required	
	Acknowledgement	optional	optional	
	Funding statement	required	required	
	Conflict of Interest	required	required	
	Author Contribution	required	required	
	References	required	required	
	Figure legends	optional	optional	mandatory when Figures are submitted
	Imbedded figures and Tables	optional	optional	For peer review only
Figure		optional	optional	
Table		optional	optional	

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