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Optimisation of patient-reported outcome measurement for haematological cancer patients receiving novel immunotherapies: perspectives of multi-stakeholders

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Objectives: The primary objective of this project was to explore the challenges related to the implementation of patient-reported outcome measures (PROMs) in myeloma, lymphoma and leukaemia patients undergoing chimeric antigen receptor T-cell (CAR-T) and T Cell engager bispecific antibody (BsAbs) therapies. The secondary aims focused on identifying and promoting opportunities to optimise PROM use for improved alignment, consistency, and interpretability of PROM data related to these innovative treatments.

Methods: Data was collected through online focus groups and interviews with patients, carers, representatives of patient organisations from myeloma, lymphoma, leukaemia communities, researchers, industry, regulatory and payer representatives. The information was transcribed for qualitative thematic analysis, using a deductive–inductive mixed approach.

Results: A total of 38 individuals participated; 14 interviews were conducted with 16 participants and two focus groups were conducted with 15 and 19 participants in each. Challenges reported included the unique complexities within trials of CAR-T and BsAbs in haematologic cancers such as the logistical challenges in the early post-infusion period for CAR-T and the wide variety of different BsAbs side-effects for patients occurring over different time periods. Further difficulties included balancing stakeholders' expectations, and uncertainties about what to measure and when.

Conclusions: CAR-T and BsAbs therapies present distinct challenges for PROM to capture treatment-related side effects and burden accurately. Use of generic and disease-specific instruments risk missing key elements of patients' experiences and the use of *ad-hoc* strategies to complement these tools presents challenges for evidence synthesis. Clearer guidance, including early high-frequency assessments, systematic inclusion of patient-important domains currently

under-captured, continued PRO data collection beyond clinical progression and transparent and comprehensive reporting of PRO findings will lead to substantial improvements in understanding the impact of CAR-T and BsAbs treatments.

KEYWORDS

bispecific antibodies, chimeric antigen receptor T-cell therapy (CAR-T), clinical trials, haematological malignancies, patient-reported outcome measures (PROM), patient-reported outcomes (PRO)

Introduction

Newer immunotherapies, such as chimeric antigen receptor T-cell therapy (CAR-T) and T-cell engaging bispecific antibodies (BsAbs), offer innovative ways to treat haematological malignancies (i.e., myeloma, leukaemia, and lymphoma). In recent years, the EMA and FDA have approved multiple CAR-T therapies and BsAbs for haematological malignancies (1–4). While they offer promising survival results, they have potentially serious side effects that impact on patients' quality of life (QoL) (5, 6) and their cost-effectiveness for health systems is not yet clear (7).

CAR-T or BsAbs therapies may cause immune effector cell-associated neurotoxicity syndrome (ICANS) and cytokine release syndrome (CRS), which are considered as a non-somatic event triggered by the immune system. ICANS is a clinical, neuropsychiatric syndrome with symptoms ranging from mild tremor, confusion, headache, to severe complications such as haemorrhage, coma and death (8). CRS occurs where the immune system becomes overactive and may cause fever, nausea, headache, low blood pressure and, potentially, multi-organ failure and death (9). Estimates of how commonly patients experience CRS or ICANS vary depending on the type and stage of the cancer and specific treatment. CRS occurs in 87% of CAR-T patients, and in 67% receiving BsAbs (10) although with the improvement of preventive and supportive measures, incidence figures may be lower with time. Neurotoxicity is reported in 40-64% of CAR-T patients (28% of grade≥ three) (11) with 27% of patients requiring intensive care admission (12). BsAb-related neurotoxicity is less common (5-14.5%), varying by treatment and dosing schedule (13). Patients are most likely to experience acute toxicities within 1–4 weeks after treatment, with CRS and ICANS most likely to occur 1–2 weeks after treatment begins (8). However, the longer-term experiences are rarely assessed and reported (14). Patient experiences and perceptions of treatment toxicities have, to date, not been given sufficient attention with PROM use evident in only 27% of CAR-T trials (15).

Patients' experiences, values and preferences are a crucial part of the data that needs to be collected so that reimbursement decision-making is informed by what matters most to patients (16). Patient-reported outcome measures (PROMs) are a key method of capturing the nuances of patients' experiences, not necessarily captured by other clinical outcome measures. Current regulatory expectations emphasise the importance of patient-focused clinical outcome assessments including PROMs in clinical trial design and regulatory submissions. Recent FDA and EMA guidance encourage the inclusion of PRO endpoints in oncology trials with a clear rationale for instrument choice and relevance to patients' and regulatory decision-making (17–20). CAR-T and BsAbs are high-cost therapies with controversy about their potential cost-effectiveness (7) and PROMs have the potential to inform these evaluations by capturing the treatments' effects on patients' QoL. However, there are unique considerations for collecting patient experiences of CAR-T and BsAbs through PROMs. CAR-T therapy involves an extensive preparation period that is very different to other anti-cancer therapies and disease progression may occur during the manufacturing time. PROM capture in BsAbs haematologic oncology trials is also challenging due to the broad and heterogeneous side effect profiles. Toxicity rates vary markedly between agents and across studies (21) and the timing of onset is variable and not entirely predictable, often occurring early after dosing but sometimes later or independent of other toxicities (22).

Until recently, no PROMs were specifically developed for use among people with haematological cancers receiving CAR-T and BsAbs. In 2023, the MDASI-CAR (23) was validated as a measure to assess symptom burden and daily functioning after CAR-T treatment, however, currently this is only available in English. Measures such as EORTC QLQ-C30 (24) are widely relied upon, however this is designed as a generic instrument intended for wide applicability rather than therapy-specific sensitivity. The EORTC Quality of Life Group acknowledges that symptoms and concerns associated with novel treatments may fall outside the scope of the core and current module questionnaires bringing uncertainty about how well the nuances of patients' experiences of these novel therapies are currently being captured (25). A recent review of CAR-T trials reported 15 distinct PROMs used within just 16 studies highlighting heterogeneity in PROM use in this space (26).

There is a growing expectation from regulatory bodies for fit-for-purpose, robust evidence that reflects the aspects of health that matter most to patients (27, 28). Optimising PROMs is increasingly important as novel therapies present complex and evolving patient experiences. PROM optimisation includes ensuring the implementation of validated assessment tools that capture patient-prioritised concepts, at appropriate times to capture treatment-relevant change.

This research project aimed to understand the challenges around implementing PROMs and capturing patients' experiences whilst receiving CAR-T and BsAbs and contribute to optimisation of PROM in this space. We sought to identify ways to encourage alignment, consistency, interpretability and reporting of data collected using PROMs in CAR-T and BsAbs trials. We have applied a multi-stakeholder lens to include diverse perspectives from patient communities, regulators, payers/HTA bodies, the pharmaceutical

industry, academic researchers, clinicians, and trialists. Inclusion of multi-stakeholder perspectives is increasingly recognised as best practice for optimising PROMs. Within the complex haematologic treatment setting particularly, it helps to ensure that PROMs capture outcomes that are meaningful and relevant to those receiving treatments and informs feasibility, methodological rigor and interpretability in clinical trial and real-world practice contexts (18, 26, 29, 30).

Methods

Study participants were recruited through known contacts, patient organisations, direct outreach and snowball sampling to include; i) stakeholder groups (patients, informal/family carers, patient advocates, academic researchers, trialists, clinicians and representatives from the pharmaceutical industry, patient organisations, regulatory and HTA agencies), ii) myeloma, lymphoma and/or leukaemia expertise and iii) CAR-T and/or BsAbs expertise.

Eligibility criteria for each stakeholder group was as follows: i) patient stakeholders with direct experience of CAR-T and/or BsAbs, or patient advocates able to represent community-level experiences of these treatments, informal/family carers with direct experience of supporting someone with myeloma, lymphoma or leukaemia whilst receiving CAR-T or BsAbs; ii)academic researchers with expertise in PRO/QoL measurement within the three cancer types; clinicians and trialists with expertise treating and/or conducting trials within the three cancer types; iii) regulators and HTA stakeholders from European, US, and national-level organisations; iv) pharmaceutical industry representatives with PRO/QoL expertise from companies developing CAR-T and/or BsAbs for the three cancer types. Recruitment aimed to include participants representing all three cancer types and individuals with personal or professional experience of both treatment modalities.

Two focus groups were held in March 2024 with different groups of participants balanced by stakeholder groups and expertise, following the same topic guide and lasting approximately two hours each. Focus group topics (available as Supplementary File) were developed based on a review of the literature and to reflect the project aims. Focus groups discussions were conducted in English, audio and video recorded and the main themes and findings captured by a professional note-taker. Semi-structured interviews (available as Supplementary File) were conducted to explore focus group topics in depth as well as any wider/holistic issues faced by the haematology community when measuring QoL in CAR-T and BsAbs treatments. Upon participants' consent, the interviews were recorded verbatim then transcribed, validated for accuracy and anonymised. The transcripts were assigned ID codes: ACT academic researchers, clinicians, or trialists (with some participants holding multiple roles); PT patient participants; IN industry representatives; HT Health Technology Assessment body representatives or regulators; and CA informal/family carer participants.

Thematic analysis, following conventional content analysis was used (31). Data were organised, coded and analysed using ATLAS.ti, (version 25.01). We used a deductive-inductive approach drawing from the prior research phase to develop initial codes alongside key themes present in the data. Codes were organised into broader thematic clusters and coding was iterative and reflexive. Each transcript was double coded independently by a second researcher working with a flexible coding framework that was refined throughout analysis. Researchers met regularly throughout coding and discussed coding changes, resolved discrepancies, and ensured consistency across codes and code groups.

Results

A total of 38 individuals participated in the study. Fourteen interviews were conducted with 16 participants, and two focus groups involved 31 unique participants (15 in group one and 19 in group two, including three individuals who attended both focus groups). Of the total sample, seven participants took part only in interviews, 22 took part only in focus groups, and nine participated in both an interview and a focus group. Further participant characteristics are displayed in Table 1. From the patient stakeholder participants, five had direct experience of being in a trial and two had specialist knowledge of PRO/trials in their capacity as patient advocates. Three patient representatives had experience of both CAR-T and BsAb treatments and one patient advocate representative had no direct personal experience of either treatment. The regulatory and HTA stakeholders were from the FDA (n=1), EMA (n=1) and from a European national HTA body (n=2). The focus group facilitator directly encouraged responses from each stakeholder group for each topic where relevant.

The four key themes across focus groups and interviews are summarised below and included i) the distinctive challenges for PROM in BsAbs and CAR-T trials, ii) what to measure, iii) when to measure it and, iv) improvement opportunities for PROM in this space.

Distinctive challenges for PRO assessment in BsAbs and CAR-T trials

CAR-T treatment is provided within treatment centres that can provide specialised care coordination. This can mean that patients may need to travel long distances to treatment centres and undergo periods of hospitalisation. However, during follow-up, patients may be referred to their local provider. The involvement of multiple centres and geographical distance adds complexity to PROM data capture and patient management and can contribute to missing data.

"The majority of patients have to travel to come to the centre and … they usually are more than 100 km or so from the centre and they go to the local hospital for the primary care." (ACT093206 interview).

Participants acknowledged that while there is considerable evidence on CAR-T-related side effects, such as toxicity, much of this data is clinician-reported. There is still a lack of patient-centred data, particularly about long-term side effects, the duration of short-term toxicities, and the potential emergence of side effects at later stages, which may remain undocumented.

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TABLE 1 Participant characteristics table.

Characteristic	Total (n=38)	Patients (n=11)	Carers (n=3)	Academic researcher/ clinician/ trialist (n=10)	Pharma industry representative (n=10)	Regulatory/HTA representative (n=4)
Participation type						
Interviews only	7	0	2	3	1	1
Focus groups only	22	9	1	4	6	3
Both	9	2	0	3	3	1
Gender						
Female	19	6	3	5	5	0
Male	19	5	0	5	5	4
Country						
Belgium	1	0	0	1		
France	2	1	0	1		
Germany	3	0	1	0		
Israel	2	2	0	0		
Italy	2	0	0	2		
Netherlands	4	1	0	3		
Poland	1	0	1	0		
Portugal	2	2	0	0		
Spain	1	1	0	0		
Sweden	1	1	0	0		
Switzerland	1	1	0	0		
UK	4	1	1	2		
US	3	1	0	1		
Cancer type*						
Myeloma	17	5	3	5	4	
Leukaemia	6	4	0	1	1	
Lymphoma	6	2	0	1	3	
Expertise/Experience*						
Bispecific antibodies	11	4	0	4	3	
CAR-T	20	9	3	4	4	
Patient-reported outcomes/Quality of life	25	7	1	7	10	

* characteristics are not mutually exclusive, some participants had experience across multiple cancer and expertise areas. Country is not reported for pharmaceutical industry due to global remit of companies, nor for regulatory/HTA representatives who were from US, European-level and national-level organisations.
Cells shaded in grey indicate characteristics that do not apply.

Participants discussed the challenges of capturing the impact of adverse events such as ICANS, and CRS when patients may experience cognitive impairment and/or be too unwell to fill out questionnaires.

"I know from studies that we've conducted for CAR-T patients, there's a big dip from pre-lymphodepletion to week two …. That dip doesn't even capture the real sick ones. Just captures the sick ones who are fit enough to still fill out the questionnaires. Missingness of data is very important. Why data was missing. Were they too sick? Or some other reasons? Especially earlier on is very important." (ACT154902 interview).

Discussions stressed how the wide variety of different BsAbs side effects for patients, and the timing differences in these occurring and resolving, make selecting what and when to measure within the PROM strategy challenging.

"… certain bispecifics are very important that we need to capture on an ongoing manner. With talquetamab which is a GPRC5d bispecific, quality of life is very different. … GI side effects, skin toxicity, patients can't taste anything, their nails are falling off, they have a skin rash, their skin is itchy and the itchiness and everything gets better … over several months but the taste doesn't. The weight loss doesn't. Those are certain special domains that we

need to focus on with talquetamab and related bispecifics." (ACT154902 interview).

Participants also raised the context in which CAR-T agents are being trialled, with patients who have advanced cancer and who may not have many options left open to them. Concerns were expressed that this set of circumstances may mean that patients want to stay on treatments 'at any cost' and thereby minimise their reporting of the toxicity they experience and the impact of this.

"We are using those agents [cilta-cel and ide-cel], mostly, for patients that are very advanced, and the patients are knowing very well that their disease is progressing and probably this treatment will be the last one for them. What they want, in fact, is efficacy first and some of them may minimise the toxicity because they want to stay on treatment at any cost. Because they are understanding that they really need this therapy. I'm not sure that we are really capturing exactly what the patients are feeling, in fact or what can be the real toxicity of those agents, in fact." (ACT113102 interview).

A further unique aspect of CAR-T treatment is that it is fixed duration compared to other ongoing treatment options. Regulators and industry representatives discussed "treatment-free survival" as a novel concept for PROMs and an important facet to capture when assessing CAR-T treatment.

"[…] we need to quantify the patient's experience in a long-term way, assessing the disease related symptoms, but also … that patients would be enjoying a treatment-free survival. … it is a very novel concept, I think, in a clinical trial to measure the experience of someone who's not receiving a treatment. So hopefully in a CAR-T trial, patients would receive the CAR-T but then after that there's no maintenance therapy, which is very novel for myeloma, there's no ongoing combination therapy … how do we quantify the experience of a patient who is not receiving any maintenance therapy or combination therapy. And theoretically, hopefully, if the CAR-T is successful, is much better than the baseline that was assessed." (HT837637 interview).

BsAbs, in contrast, involve continuous treatment along with the potential for accumulation of time toxicity (i.e., the time patients spend managing treatment and its effects) and burden for patients. Participants noted that indefinite use of BsAbs may not be optimal and emphasised the need to better understand administration cycles and intervals as well as evaluate patients' recovery in terms of role and cognitive functioning.

Measurement challenges: what to measure and how

Participants from focus groups and interviews agreed there is an increased interest and need to understand the QoL impact of CAR-T and BsAbs, especially to aid regulatory decision-making. However, the lack of clear guidance on the choice of PROM was noted as producing variation and inconsistency in trials.

A further complication highlighted was the use of legacy PROMs, along with the perception that some regulators and payers prefer specific PROMs. This leads to older tools continuing to be used despite limitations.

"One of the fundamental problems that exists in measuring patient reported outcomes, is when we get comfortable and the regulators and the HTA agencies get comfortable with one particular measure, [it] gets embedded in people's mind, into the bureaucratic system of the regulatory agencies and HTA bodies, [the PROM] becomes the norm despite their huge limitations." (ACT02942 interview).

Current PROMs undervalue aspects of patients' experience

Participants, particularly patients, mentioned the limitations of existing PROMs to capture a true impact on QoL and experiences with CAR-T and BsAbs. "[skin and nail effects] has an impact on your quality of life for sure because some people cannot wear their shoes because it's just too painful … I couldn't open boxes when I was cooking for example. I always had to ask someone else just because your nails are so frail, that's very painful. In the report of the clinical trial, it suggested that it's manageable, that it's resolved or that it's manageable with going to the dermatologist but that doesn't really help, the dermatologist … cannot do a lot against it." (PT120454 interview).

Discussions highlighted further potentially important side effects that may not be currently captured in existing PROMs. For example, emerging concepts like time toxicity (i.e., time patients spend managing treatment and its effects) have been largely neglected to date.

PROMs were seen as inadequate in capturing the wider emotional and psychological impact of illness, side effects and treatment. Patients described the intense mental strain of waiting for CAR-T, including stress over meeting eligibility requirements. During the interval between apheresis and infusion, many feared their health would deteriorate rendering them ineligible. For those who had exhausted other therapies and viewed CAR-T as their last option, these uncertainties were particularly overwhelming. They noted that healthcare providers often overlooked their anxiety and emotional health, focusing mainly on managing the physical aspects of infusions with little consideration to psychological well-being. Patients expressed a need for better management of both the emotional and mental health impacts of novel immunotherapy treatments - both in the short and longer term.

"The doctors and nurses were more interested in the physical side effects more than my mental health. And I think all these measurements that they did, after they were just asking me about how my physical health worked, and if I can walk or run, if I can be around other people, and if I have the energy to do things, but never about the mental part about it, which was the most difficult part. And my doctor basically told me that we can help you with your body and your cancer, but the mental part you're gonna have to do by yourself." (PT735078 focus group).

Additionally, patients often travel or relocate to specialised centres for the treatment, which creates mental stress, financial strain, family disruptions, and logistical difficulties for patients and those close to them. There was widespread acknowledgement in the data that this burden on families is not captured or given enough emphasis.

The realities of managing an extremely high infection risk with these therapies, and living with an immunocompromised state,

include impacts on ability to work, social isolation, and QoL despite feeling physically well. Participants noted that the emotional and mental well-being impact is also not prioritised from a regulatory standpoint and consequently does not receive the same level of importance as physical measurements within clinical trials.

Measurement challenge: when to implement PROMs

Clinical trials time points (i.e. the specific instances when data is collected and analysed) are selected strategically to determine the onset and duration of treatment effects and to allow for trial monitoring and interim analyses. Participants raised the need to establish specific recommendations for timing for initial (baseline) and periodic PRO assessments within CAR-T and BsAbs trials.

Baseline assessments

Baseline measurement in clinical trials needs to be consistent to allow for an accurate reference point. Baseline should be collected to represent the patient's health and QoL state pre-treatment, before any potential therapeutic effects. This allows the best chance of the data reflecting the patients' full experience and response to treatment. However, discussions acknowledged that patients are not asymptomatic at baseline, they may be in significant pain from rapidly progressing disease or may have existing side effects from previous treatment, which can negatively bias scores. HTA representative interviewees expressed the opinion that "baseline should mean study baseline. It means treatment decision or randomisation and not at any later time point." (HT110231 interview).

Moving the baseline assessment to when patients are first offered treatment would likely provide a more accurate measurement of 'change from baseline' compared to the traditional assessment method at the time of treatment administration. Regulators highlighted the possibility of implementing multiple baseline assessments throughout the pre-treatment process, although they recognise the practical challenges of this.

There was general agreement that baseline assessments for CAR-T and BsAbs trials should occur earlier than those for older anticancer therapies. Yet, participants acknowledged uncertainty about the precise definition of the 'baseline' time point and called for further alignment. The CAR-T process spans several weeks and includes pre-treatment steps such as leukapheresis, bridging therapies and periods of hospitalisation. During this time the patient's disease status, emotional and physical well-being may change. Participants expressed support for multiple baseline assessments.

"I think this is an area that needs to be investigated. I don't think that we know the exact answer. …I really feel that all the analysis for the next couple of years should have two baselines. One that's right before lymphodepletion and one that's at the time of the CAR-T concept or apheresis." (ACT02902 interview).

Follow-up after treatment

Evaluating PROs over time is essential for understanding the full impact of treatments such as CAR-T and BsAbs. Participants suggested that assessments as early as one week after infusion could serve as a crucial "anchor" time point to capture the frequency, intensity, severity, and resolution of side effects. However, industry participants expressed concerns about the feasibility of this approach, noting that patients are often hospitalised and may face severe complications like CRS shortly after infusion. Many interviewees stressed that early time points, when side effects are most intense, are sometimes overlooked in clinical trials. One participant remarked, "Those first days can be dramatic" (ACT02108 interview) while another noted, "That's where [the early time points] a lot of the symptoms happen and so we need to capture at least weekly for the first four weeks." (ACT02902 interview). A similar concern was raised in relation to the risks of CRS with BsAbs and step-up dosing, where PROs should be collected after each dose to capture changes in QoL and toxicity.

"With bispecific antibodies, we have these step-up doses when the patients are receiving three doses during week one. Certainly, we should explore, after each dose to my opinion because there is a risk of cytokine release syndrome, … and that may occur immediately after the first dose. We should explore quality of life and toxicity after dose one, after dose two, after dose three and subsequently after each dose until the response." (ACT02102 interview).

There was broad agreement, that the timing of PROM administration should align with both patient experiences and treatment schedules. Many believe that the two months following infusion offer an ideal window to monitor side effects and other bothersome symptoms. As one regulatory representative explained:

"[We need] more frequent assessment during the first two months after the CAR-T is administered, and also during bridging therapy. So weekly assessment, because it is likely that patients are undergoing quite a bit of toxicity and tolerability issues. So, this means use of an Item Library to select really important symptoms. So, headache, fatigue, you know, all of the symptoms … And then also a very good assessment of overall side effects impact, which is an amalgamation or a combination of all of those symptoms … not just about specific narrow symptoms, but also in general how they're feeling in terms of the combination of all of those side effects. And then I think also physical functioning. So, it may not be a one specific symptom that's most bothersome, more impactful on patients. But it could be just a general feeling that results in limitations and ability to move around. So physical function is also extremely important to measure, again on a high frequency basis." (HT769934_focus group).

At the same time, industry representatives pointed out that while frequent assessments are critical for comprehensive data, they must be balanced against minimising patient burden and streamlining trials. This challenge is compounded by the diverse priorities of stakeholders. For example, while the FDA advocates for frequent data collection, Health Technology Assessment (HTA) bodies are more focused on long-term outcomes, including data collected post-disease progression.

"[…] There are so many stakeholders that we need to consider, and they don't all have the same focus points. […] the FDA has a lot of strong recommendations for more frequent capturing of PROs. Whereas the patient voices, we don't have, especially if you're in such a condition of cancer, it's hard to ask them to keep filling in

all these questions and […] we also have the HTA bodies who are requesting a long-term or post-disease progression as well so it's a lot for a company to really get everyone's alignment." (IN150427 interview).

Long-term time points

Participants suggested that long-term effects should be captured by administering PROMs every 6- or 12-months during follow-up, along with an annual evaluation of role, cognitive function and overall health impacts.

"Especially, in the long term, it might be important to assess more general aspects which refer to how the patient is returning, let's say to normal. So, for example, as [deidentified] was saying, as in role functioning, and cognitive functioning, so including some selection of this question into clinical consultation of this patient." (ACT32675 focus group).

When to stop

Interview discussions included consideration of how long PRO data capture should be continued. The HTA representative interviewees encouraged researchers to capture the entirety of the treatment regimen.

"In order to get a full picture of the mental health or emotional health or emotional burden that a treatment poses, you need to measure really from start to finish and with finish we mean end of study, not end of treatment, but end of study … as long as possible. In any case, beyond progression or end of treatment. In order to capture the entire treatment strategy or treatment path any patient would go through with all that that entails." (HT110231 interview).

Industry interviewees echoed the HTA perspective but acknowledged the difficulties.

"We try to collect PRO data until the end of study. That's kind of always our default. That's not what happens every time because sometimes that's seven, eight years and just operationally we lose those patients." (IN143734 interview).

Researchers, clinicians, trialists and patient interviewees shared the perspective that the optimum length of follow-up for CAR-T trials is currently unknown.

"I would say until we know more about CAR-T, until we have a bigger sample of CAR-T treated patients, clinical trial or commercial, whatever, we're going to have to follow up these patients for a long time." (PT080209 interview).

Patients expressed support for ongoing capture of PRO data particularly when this was aligned with regularly scheduled visits to their haematologist.

"It must have been a good six or seven months where I saw the haematologist regularly [after CAR-T], and then they spaced it out to two months, and now I see her every quarter … you could even carry on with the PRO every quarter for a follow up period of at least two years, and then in the third year you might space it out to every six months." (PT080209 interview).

Investing in long term assessment of PROs (i.e. impact and symptoms) beyond termination of treatment is the only way to find the optimum length of follow-up for CAR-T trials.

Improvement opportunities

Development of a new specific PROM for CAR-T and BsAbs treatment

There was support for the development of further specific PROMs for CAR-T and BsAbs to capture the specific nuances of patients' experiences.

"Anytime we have a new treatment like CAR-T, it is possible that you might come across different type of problems that these patients may experience including specific symptoms, so you really need a treatment specific measure." (ACT02711 interview).

However, doubts were also raised about the development of treatment specific tools for each treatment and the challenge this may present to making comparisons in the future. Participants discussed the potential for a modular approach, with an instrument that included a core module supplemented by customisable disease- or treatment-specific modules.

Facilitators for the uptake of new PROMs

Participants stressed the need for validation of any new tool to confirm psychometric properties and ensure robust measurement of physical and psychosocial functioning. The importance of patient involvement in tool development was emphasised as a critical driver in the choice of PROMs. Endorsement by relevant bodies, organisations and payers would assist the uptake of new PROMs.

Interim improvement opportunities

Whilst new tools are in development, such as one from the EORTC (32), there are improvement opportunities that could help make the most of the data being captured in the interim. Several opportunities for improvement emerged from the discussions. First, the use of mixed-methods approaches could strengthen the capture of patients' lived experiences especially in relation to emotional and psychological well-being. PROMs may struggle to fully reflect the depth of experiences associated with treatment. Incorporating targeted items or modules, alongside qualitative approaches such as interviews or free-text responses can provide richer, more nuanced insights. Second, combining tools may help to narrow persistent measurement gaps. Using multiple instruments or adding supplementary items to primary PROMS can provide an interim solution. For example, items from the PRO-CTCAE were viewed as valuable additions. Finally, enhancing patient education and involvement is essential. Patients generally support completing PROMs when they understand how their data will be used and feel confident it will not be wasted. Clearer communication about the purpose of PROM collection, how responses contribute to improving care and how findings will be shared may foster stronger and more sustained engagement.

Discussion

This multistakeholder pan-haematology project addressed the pressing need to optimise PROM use for CAR-T and BsAbs in

haematological malignancies. Table 2 shows patient-identified important domains for CAR-T and BsAb experiences alongside three commonly used PROMs in trials, the EORTC-QLQC30 (24), MDASI-CAR (23) and the PRO-CTCAE (33), and highlights where key gaps can be found. As shown in the table, although general distress is captured, important nuances are not. None of these tools capture the experience of waiting anxiety or anticipatory fear described by patients as occurring during CAR-T treatment. Also not captured is the burden of treatment including the logistical burden, time toxicity and burden on the patients' informal/family carer. Longer-term survivorship experiences are also absent from these existing tools.

Provisional strategies undertaken by the participants to attempt to comprehensively capture patients' experiences include combining multiple instruments and/or adding specific items to the primary tool to more comprehensively capture all relevant symptoms, side effects, and treatment outcomes. For example, PRO-CTCAE items were frequently proposed as a valuable supplement to other measures. Patient interviews are also used in combination with standard PROMs to provide opportunities for patients to discuss their experiences including the nuanced aspects that standardised instruments cannot capture. Including the opportunity for open-ended responses within PROMs is another opportunity to ensure comprehensive data capture. However, these strategies come with the need for extra resources to implement effectively.

The uptake of future new modules (e.g., EORTC Quality of Life CAR-T and BsAbs (32)), or existing but less established ones (e.g., MDASI-CAR) (23), also requires consideration. Since it would be extremely challenging to fulfil every stakeholders' priority, there should be efforts to establish a set of core measurement elements that respond to diverging stakeholder expectations whilst prioritising patient's needs, concerns and lived experiences. Professional organisations like the International Myeloma Working Group (IMWG) (34) and the European Haematology Association (35) play an influential role in shaping PROMs selection and implementation, and guide clinical and research practice. Consensus and guidance on what should be the core set of PRO domains and any additional CAR-T or BsAB modules or items from validated item libraries would be beneficial.

When setting PROM assessment schedules, it's crucial to account for the unique characteristics of CAR-T and BsAbs treatment protocols and how they differ from traditional anticancer therapy trials. The CAR-T treatment process spans several weeks during which the patients' disease status may change between the initial stages and the time of infusion. The waiting period required during manufacturing can affect patients' emotional well-being and quality of life and comes with the potential for risk of manufacturing issues and failure. Including at least two baseline assessments allows for the disease and QoL evolution to be monitored during this period, thereby allowing for more accurate interpretation of outcomes and more precise assessments of safety and QoL impact.

TABLE 2 Mapping patient-identified domains to commonly used PROMs domains.

Patient-identified domain	EORTC-QLQC30	MDASI-CAR	PRO-CTCAE
Emotional distress (fear, uncertainty, anxiety)	✓ Emotional functioning scale	✓ Distress general	✓ Anxiety, sadness
Waiting anxiety, anticipatory fear, uncertainty during prolonged hospitalisation	×	×	×
Taste changes/dysgeusia	×	×	✓ Problems with tasting
Appetite/weight changes	✓ Appetite loss item	✓ Appetite loss	✓ Appetite loss
Dermatologic toxicity – dry skin, rash, nail changes	×	×	✓ Rash, dry skin, nails
Cognitive changes/neurotoxicity (ICANS-related cognitive effects)	✓ Cognitive functioning scale	✓ Difficulty remembering, difficulty paying attention, difficulty speaking	✓ Concentration, memory
Physical functioning during recovery (post-inpatient fatigue)	✓ Physical functioning scale	✓ Fatigue	✓ Fatigue
Time toxicity (frequency of hospital visits, time in clinic, caregiver time burden)	×	×	×
Medication-/treatment-specific burden	×	×	×
Long-term survivorship concerns (immune reconstitution, infection worry, chronic cytopenias)	×	×	×
Financial toxicity	✓ Financial difficulties item	×	×
Logistical burden	×	×	×
Burden of treatment on patient's caregiver/family	×	×	×
Functional independence/return to normal life	✓ Role functioning scale	✓ Work, general activity, relationships, enjoyment of life	×
Treatment-free survival	×	×	×

Cells shaded in grey indicate characteristics that do not apply.

Insufficient attention has been paid to the experiences of patients undergoing CAR-T with the use of PROMs in CAR-T trials below the industry average (15) and important gaps highlighted in PROM evidence, namely within the first two weeks after CAR-T treatment and after the first year (14, 26). This study has provided insights into why this under-collection may occur, including highlighting the logistical challenges around patient hospitalisation and the difficulties experienced in obtaining PRO data from patients experiencing acute toxicities like ICANS and CRS. Alternative approaches including proxy reporting or nurse-assisted capture for patients in these circumstances are not without their own drawbacks, will not have the same level of insight as from patients themselves, and are not interchangeable (36). Moreover, proxy reporting is discouraged by the FDA and EMA (37).

The participants in our study were supportive of more frequent capture during the acute phase of early treatment to better understand patients' experiences of side effects including CRS and the impact this treatment phase has on QoL. As a minimum, for CAR-T PROM implementation there should be: 1) a pre-apheresis baseline, 2) a pre-lymphodepletion baseline, and 3) an early post-infusion anchor (e.g. day 7).

Longer-term follow-up was also stressed as important to better understand how patients fare in the years after receiving treatment. CAR-T is a high-intensity, short-duration intervention with the potential for initial short-term QoL reduction but long-term QoL gains. Furthermore, understanding the potential QoL benefits for any treatment-free intervals is an important focus for longer-term data capture after CAR-T. BsAbs, on the other hand, are long-term chronic therapies with the potential for ongoing cumulative burden requiring a data capture strategy to understand ongoing experiences and the burden of treatment and side-effects for patients over time and in the longer term. Neither of these treatments' QoL trajectories and longer-term patient survivorship experiences are likely to be captured sufficiently currently. Survivorship for haematological malignancies is substantially different to that for solid tumour cancers and has been historically overlooked (38, 39). Ongoing risks such as chronic immunosuppression, relapse and prolonged psychological and functional impacts makes surveillance for late effects and management of chronic symptoms fundamentally important. Long-term PROM collection is not only important for regulatory interest but also supports survivorship care optimisation through ongoing, consistent symptom monitoring and enhancing the early detection and action on issues.

More frequent, longer-term capture requires significant patient commitment, raising concerns about patient burden and missing data. Computerised adaptive testing (CAT) is one potential strategy that provides the opportunity to tailor PROM assessment more precisely to individuals. CAT iteratively selects only the most relevant and informative items for a participant, reducing the overall number of items a participant has to complete and thereby reducing participant burden whilst maintaining acceptable accuracy (40).

The patients in our study were willing to complete PROMs but expressed a need to clearly understand the purpose of data collection. Ensuring that trial staff receive proper training on how to convey this information effectively is essential (41). Communication should include feedback on how patients' PRO data is being used and ongoing study updates whenever feasible. The under-reporting of PRO data is not just a significant concern for the validity and generalisability of research findings and for health economic modelling, it is also an unethical (42) waste of patients' time and energy. Under-reporting PRO data diminishes the value of patients' participation and lived experiences. It implies that self-reported information is afforded less importance than clinician-reported or biomarker data, despite key dimensions central to living with cancer, such as fatigue, pain and emotional distress, being accessible only through self-report. Participants consent to PRO collection under the understanding that their contributions will meaningfully inform knowledge generation. When PROs are not analysed or reported, this implicit agreement between researcher and participant is broken. This is especially concerning because PRO completion can be burdensome and often takes place during periods of intense treatment or ill health. Making plain language summaries of trial findings, including clear and transparent reporting of PRO results, standard practice would honour patients' contributions and support patients, families, and clinicians to make more informed treatment decisions. informed decision making about treatments.

Strengths and limitations

As with much qualitative research, the participant sample was not intended to be statistically representative and there is the potential for self-selection bias among the participants who chose to take part. In addition, the focus group setting may have constrained some participants' willingness to express dissenting or sensitive views. This limitation was mitigated through the inclusion of one-to-one interviews, which provided a more private forum for participants to articulate their perspectives. The focus groups were not transcribed verbatim in their entirety due to resource constraints. Instead, they were condensed into key discussion points with supporting quotes by a professional note-taker. However, the use of both focus groups and interviews enabled triangulation of findings, supporting cross-validation of themes and the capture of both shared priorities and more nuanced individual experiences. All interviews were double-coded by two independent researchers, enhancing methodological rigor, minimising bias and strengthening the credibility of the analysis. A further key strength of the study lies in the breadth of stakeholders included, enabling the identification of concerns and priorities across multiple perspectives. This diversity enhances the relevance, credibility and potential actionability of the findings and resulting recommendations.

Conclusions

Current PROMs used in trials of CAR-T and BsAbs are failing to capture the nuances of patients' experiences of treatments and specific novel side effects. Alignment of PROMs, both in terms of what to measure and when is needed to enhance our understanding of patients' experiences. Clearer guidance from payers and regulators on instrument selection, assessment schedules and overall use/reporting would

be beneficial and would help to address the current gaps in the evidence on patients' experiences of these novel therapies. This study highlights the need for future guidance to incorporate: 1) a dual-baseline strategy appropriate for initial rapid clinical changes, particularly preceding CAR-T infusion; 2) mandated early high-frequency assessments to capture acute post-infusion or step-up dosing effects (i.e. weekly for the first four weeks), 3) systematic inclusion of patient-important domains currently under-captured, such as emotional well-being and time-toxicity; 4) continued PRO data collection beyond clinical progression; and 5) transparent and comprehensive reporting of PRO findings. Embedding these recommendations within formal guidance would substantially improve the quality and patient-centredness of PRO data in this rapidly evolving field.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The requirement of ethical approval was waived by National Health Service Health Research Authority for the studies involving humans because the study was conducted in accordance with the local legislation and institutional requirements. Ethical approval was not required because the study does not involve a clinical trial, medical device, sensitive or identifiable patient data, NHS or social care service users, human tissue or DNA, adults lacking capacity, offenders or any other health- or social-care-related activities that fall within the remit of formal research ethics review. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board also waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Verbal informed consent was obtained due to virtual nature of interviews and focus groups.

Author contributions

ED: Conceptualization, Funding acquisition, Investigation, Writing – review & editing, Writing – original draft, Validation, Methodology, Project administration, Formal analysis, Supervision. JS: Formal analysis, Writing – original draft, Project administration, Validation, Writing – review & editing, Data curation. CK: Methodology, Writing – review & editing, Supervision, Writing – original draft, Conceptualization. SN: Project administration, Writing – original draft, Writing – review & editing, Supervision. SO: Writing – review & editing, Methodology, Conceptualization, Supervision, Writing – original draft. SS: Writing – original draft, Writing – review & editing. KM: Supervision, Writing – original draft, Conceptualization, Resources, Funding acquisition, Writing – review & editing. KJ: Writing – original draft, Writing – review & editing, Resources, Conceptualization, Funding acquisition, Supervision.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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