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# The myeloma patient perspective on the use of patient-reported outcomes (PROs) in CAR-T clinical trials

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EDITION

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# INDEX

1. ABOUT MYELOMA PATIENTS EUROPE (MPE).....	4
2. ACKNOWLEDGEMENTS .....	4
3. INTRODUCTION.....	4
4. LITERATURE REVIEW .....	6
5. PATIENT DISCUSSION GROUPS .....	7
5. CONCLUSION AND RECOMMENDATIONS.....	19
6. REFERENCES .....	21



## ABOUT MYELOMA PATIENTS EUROPE

Myeloma Patients Europe (MPE) is an umbrella organisation representing 49 myeloma (also known as multiple myeloma) and AL amyloidosis patient groups and associations from across Europe and further afield. Our mission is to provide education, information and support to members, and to advocate at European, national and local levels for the best possible research and equal access to the best possible treatment and care. Together, we support thousands of myeloma and AL amyloidosis patients, as well as their caregivers, every day.

This research is part of the CARAMBA project, which is researching an **innovative immunotherapy for the treatment of myeloma, known as Chimeric Antigen Receptor T-cell therapy (CAR-T)**. Through strategic collaboration with a wide range of stakeholders, including MPE, this European consortium, funded by the European Union's Horizon 2020 research and innovation programme, aims to ensure the streamlined transition of CAR-T from the laboratory through to myeloma patients in the clinic.

## ACKNOWLEDGEMENTS

MPE would like to extend a special thank you to the patients who participated in this study; we are grateful for your time and generosity in sharing your experiences and insights. We thank our members for sharing this project with their patient community, all those who helped us with patient recruitment, and our staff and member organisations for facilitating the focus group discussions required for this research.

The CARAMBA project (*SLAMF7-CAR T-cells prepared by Sleeping Beauty gene-transfer for immunotherapy of multiple myeloma – a rare hematologic disease*) has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 754658.

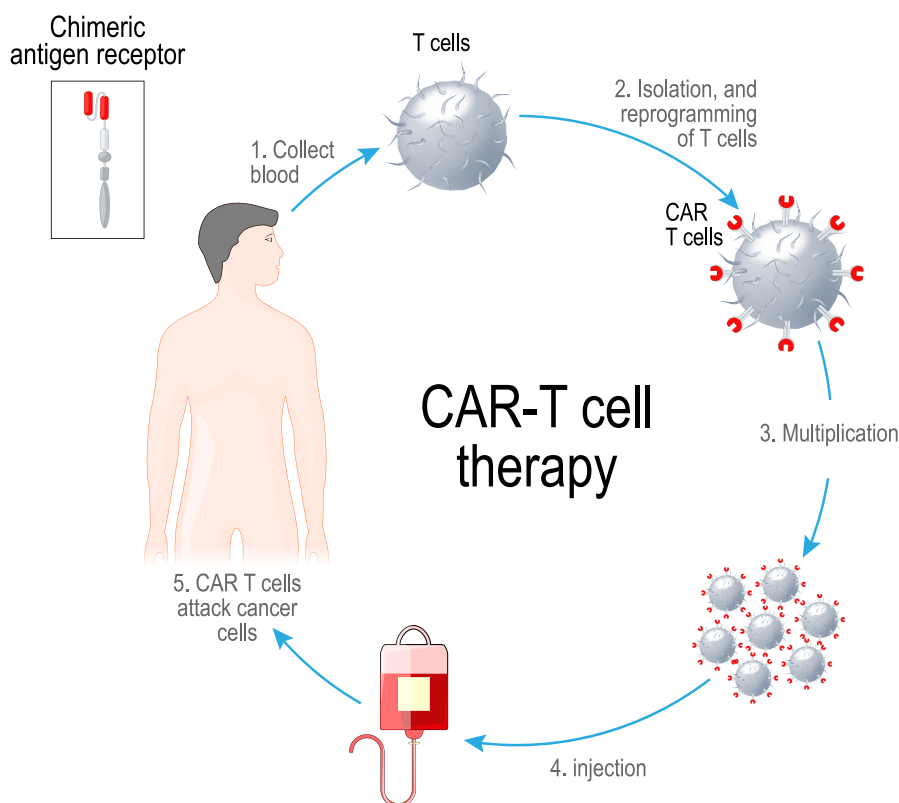
## INTRODUCTION

Although considered a rare disease, myeloma is the second most common form of blood cancer, with 50,918 people diagnosed in Europe in 2020. It is characterised by malignant proliferation of plasma cells (cells ordinarily responsible for antibody production in the bone marrow) resulting in the production of abnormal paraproteins. This disease is more common in men than women and the average age at diagnosis is 70. It is a relapsing and remitting condition. Patients undergo treatment can result in improvements in their disease, known as periods of remission, but will eventually experience a subsequent relapse requiring continuous treatment. Remission and relapse will continue over several years until the disease eventually becomes refractory or no longer responds to the standard of care options.

The treatment landscape for myeloma has evolved substantially, and life expectancy has continued to increase with 54% of patients surviving 5 years or more. As a cure is still not available, myeloma patients usually spend the rest of their lives on and off treatment, resulting in considerable effects on their quality of life. The worsening impact on a patient's quality of life often stems from repeated treatment exposure, worsening disease symptoms and the normal aging process. As novel therapies emerge, there is a need to capture the effects of these treatments on quality of life in a clinical trial setting to better aid the patient decision and regulatory processes.

The development of promising novel therapies has shown to be effective, yet these are not without their toxicities. For example, Chimeric Antigen Receptor T-Cell Therapy, or CAR T-cell therapy, is a type of

immunotherapy that harnesses the immune system by genetically programming a patient's T-cells, a type of immune cell, to find and destroy malignant myeloma cells. First, a patient undergoes leukapheresis, where T-cells are separated from the patient's blood before they undergo treatment with high dose chemotherapy. Then, CAR T-cells are genetically programmed and expanded in centralised manufacturing centres, at times taking up to six weeks for processing and then reinfusion.



**Figure: CAR T-cell therapy, from T-cell collection to CAR T-cell infusion. For further information on CAR T-cell therapy, see our [CAR-T treatment educational resources](#).**

Recent clinical studies showed very good response rates to CAR T-cell therapy among relapse refractory myeloma patients. On the other hand, CAR-T is associated with cytokine release syndrome (CRS) and neurotoxicity, side effects not often seen in the current standard of care treatments for this disease. CRS is a systemic inflammatory condition that appears as a flu-like illness and includes symptoms such as fever, fatigue, nausea, headache, shortness of breath, increased heart rate and - in severe cases - seizures or death. Neurotoxicity, also known as immune effector cell-associated neurotoxicity syndrome (ICANS), may appear as confusion, lethargy, headache, agitation and - in rare but severe cases - seizures or death. For further information on CAR-T-associated side effects, see our [CAR T-cell therapy side effects Q&A](#).

As a result, treatment with CAR T-cells is complex, with the risk of life-threatening side effects. The administration process of CAR-T is complicated and requires patients to remain in tertiary care centres with access to intensive care units, various specialists and monitoring for about two weeks or longer. Given the toxic side effects and novel methods of administration, there is a need for data collection that highlights the impact on myeloma patients and caregivers during CAR-T treatment.

This research addresses the measurement of quality of life and health-related quality of life data using patient-reported outcome (PRO) questionnaires. A patient-reported outcome is any health outcome (or



report on the health status of a patient) that comes directly from the patient without being interpreted by someone else such as a clinician, a nurse or any other health care professional. PROs are important to understand whether health care plans make a difference to a patient's health status and quality of life.

PRO questionnaires are typically used in clinical trials. Data can be collected via paper (questionnaires filled out by hand) or electronically (referred to as electronic patient-reported outcomes or ePROs) through an electronic device such as a smartphone or a tablet. Patients can use devices given to them by health care professionals or install an app on their own device. Questionnaires can feature one to over 30 questions related to various topics, like mobility, self-care, activities, pain, anxiety, overall health or specific treatment side effects. PRO questionnaires can be general, disease-specific (e.g., tailored to myeloma symptoms and associated treatment side effects), or symptom-specific. While many of these questionnaires are validated, there are no standardised methods or requirements for incorporating this data collection in clinical trial design – particularly in CAR-T clinical trials. There are also no CAR-T-specific PRO collection tools that are validated. As CAR-T is associated with novel side effects (CRS and neurotoxicity) not found in the current standard of care treatments, there is a need to have validated tools and adequately capture patients' quality of life.

This research evaluated the patients' perspective on commonly used PRO collection tools and their effectiveness in capturing the patients' quality of life, including CRS and neurotoxicity, in and outside of CAR-T clinical trials.

### Methods

MPE chose to gather insights on the use of PRO collection tools and CAR T-cell therapy through patient discussion groups.

## LITERATURE REVIEW

The first phase of the project was a targeted literature review conducted by MPE research staff in 2021 to review clinical trial protocols and learn about the use and integration of PROs in CAR-T clinical trials in myeloma. We observed a lack of use of PRO tools in myeloma CAR-T clinical trials: only 10.5% (11/105) of myeloma CAR-T clinical trials were found to use patient-reported outcomes as a secondary endpoint. This lack of use of PROs as a secondary endpoint was particularly important in industry-sponsored clinical trials. The gap in the use of PROs in myeloma CAR-T clinical trials is concerning, especially in the setting of toxic and novel side effects



that are likely to have a significant impact on quality of life. There is no standardised use of PROs in clinical trials and not much understanding of how PROs capture the quality of life impact when patients receive CAR-T treatment. Therefore, there is a need to understand the patient experience in clinical trials to aid in patient and regulatory decisions, and to guide future clinical trial design. MPE then defined the PRO tools to be reviewed by patients in the study. Questionnaires were chosen according to their use in Europe and various lengths and themes.

## PATIENT DISCUSSION GROUPS

Four virtual discussion groups were organised with a total of 10 myeloma patients from across Europe who had previous experience with CAR-T and who were recruited via MPE's network and other patient organisations. One patient was accompanied by their carer.

Characteristic	Patients (n=10)
<b>Gender</b>	
Male	6
Female	4
<b>Age</b>	
41-60	9
71-80	1
<b>Country</b>	
Israel	2
France	3
The Netherlands	1
Belgium	1
Spain	3
<b>Time with myeloma</b>	
<3 years	1
4-6 years	4
8-10 years	1
10-13 years	4
<b>BCMA CAR-T treatment</b>	
CAR-T clinical trial in the EU	7
Commercial CAR-T in the EU	1
Other setting	2
<b>Time after CAR-T</b>	
1-6 months	4
18-30 months	6



Characteristic	Patients (n= 10)
<b>Disease status</b>	
Remission	9
Unknown	1
<b>Distance to CAR-T treatment center</b>	
<15km	5
30-60km	1
300-500km	3
>10,000km	1

Table 1: Participant information.

The discussions were held virtually between January 2022 and February 2023, and were video recorded, transcribed and analysed to identify themes and quotes. The discussion guide can be found the [appendix](#). Patients' perspectives on the use of PROs in myeloma CAR-T clinical trials are presented in this report.

### PRO questionnaire completion time

Patients were asked to complete three validated PRO questionnaire tools (EQ-5D-5L, Hospital Anxiety and Depression Scale (HADS) score and EORTC-QLQ-MY20) and record the time for completion.

- **EQ-5D-5L** consists of two pages: one with questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression (5 dimensions, or 5D), with five levels (5L) from no problems to extreme problems; and one with a vertical visual analogue scale (a line with anchor statements at the top and bottom), recording the patient's self-rated health from 'The best health you can imagine' to 'The worst health you can imagine'.
- **Hospital Anxiety and Depression Scale (HADS)** is a one-page, self-report rating scale of 14 statements with four levels from 0-3, designed to measure anxiety and depression.
- **EORTC-QLQ-MY20** is a two-page questionnaire specifically designed for myeloma patients. It includes 20 myeloma-specific questions on disease symptoms, side effects of treatment, future perspective and body image, with levels from "Not at all" to "Very much".

Many participants were already familiar with the chosen PRO questionnaires. It takes patients significantly less time to fill in these questionnaires when they are used to it, compared to the first time they see them.



*"I know these questions by heart because I get the same questionnaires every time I go to the hospital."*

MYELOMA PATIENT

In general, they thought the surveys were quick to complete.





*"In fact, it is always the same questions. And, in my case, it is on a tablet, so it is quickly done."*

MYELOMA PATIENT

Questionnaire	Average completion time (minutes)
EQ-5D-5L	5.65 (min = 1, max = 20)
HADS*	7.75 (min = 2, max = 30)
EORTC-QLQ-MY20	6.15 (min = 2, max = 10)
<b>Total:</b>	<b>19.5 (min = 5, max = 55)</b>

\*HADS: Hospital Anxiety and Depression Scale

Table 2: Average completion time per PRO questionnaire and in total (n= 10 patients).

## Relevance and structure of the PRO questionnaires

### Relevance

Overall, patients felt that the questionnaires were relevant, comprehensive and captured their CAR-T experience.



*"(the questionnaires) look pretty much comprehensive."*

*"These questions are relevant, but it is difficult to remember everything."*

*"I think the questions were good and very encompassing."*

MYELOMA PATIENTS

However, the general feeling was that the questionnaires did not include enough questions. They thought more questions should be asked before, during and after treatment because CAR-T is so unique and, according to the participants, not like autologous stem cell transplantation (which eligible patients undergo as a first line of treatment and also involves long hospital stay).



*"There are more questions to be asked before treatment, during the treatment and after treatment because it's a unique treatment."*

MYELOMA PATIENT

Participants mostly agreed that the PRO questionnaires were easy to complete, understandable and, importantly, covered things from a patient quality of life perspective. Questions were similar to questionnaires they were used to filling in. However, questions were mostly orientated towards specific

functions rather than symptoms, myeloma complications or side effects that one might experience during or following CAR-T. One patient suggested linking the answers given to the functional questions in PRO questionnaires to specific symptoms, complications or side effects they might experience (e.g., patients are at increased risk to develop infections).



*"I had a lot of infections after the CAR T-cell procedure. It affected me in different ways. And I think it would help to link some of my answers to the questionnaire to why I might have that."*

MYELOMA PATIENT

## Structure

Patients raised that they were not entirely satisfied with the questionnaires' format, in particular, the low number or limited type of answers they were able to provide (e.g., simple responses). One patient also suggested the option to say "I don't know" or "this does not apply to me" when answering the questions.



*"I would put more options not just three answers that are like "Are you OK? Are you bad or are you regular"? I would always give four or five options."*

*"Avoid odd numbers (of possible answers) to avoid the answers to stay in the middle."*

MYELOMA PATIENTS

"Redundance" was raised by a number of patients referring to the presence of questions that might not have applied to them or questions that seemingly repeated themselves.



*"I understand that sometimes the same question is asked in a different way, and it could be that they're just checking to see if you're consistent in your response. So, the redundancy doesn't bother me."*

*"I find them complimentary. I mean, some redundancy but, you know, I hadn't seen the anxiety and depression scale before that."*

MYELOMA PATIENTS

One patient pointed out that, in general, PRO questionnaires need to be more relevant and take into account answers to previous questions.



*"There is one that I fill in at the hospital, asking if I'm able to take long walks and then the next question is, "are you able to take short walks?" Well, if you're able to take long walks, I think probably also (short walks)."*

MYELOMA PATIENT

Several patients said they would rather write their answers down or talk to someone who would ask them questions about their issues and feelings. For example, one patient said they prefer talking to someone, e.g., a psychologist, instead of ticking boxes on a questionnaire. They had experienced this after their first stem cell transplant and found it more valuable, and said that the presented lists of questions are limiting.



*"Many times, our situation is not reflected, because perhaps instead of choosing an option, we should develop an answer"*

MYELOMA PATIENT

### Call for change

Participants were asked about what might be lacking in these PRO questionnaires (in relation to CAR-T) or not addressed, and what they would change. They reported the following main topics: isolation, boredom, energy levels, types of pain, mental and emotional wellbeing, unexplained changes, sexual function, ability to plan for the future and side effects, including infections, CRS, neurological symptoms, concentration, memory and sleep issues and loss of reflexes.

**Isolation** is something that significantly impaired patients' quality of life, however, it was not measured in the questionnaires. These questionnaires did not capture their feelings of isolation and how they evolved over time after CAR-T. Although several of them experienced additional isolation and hygiene rules due to the COVID-19 pandemic, most outlined that COVID-19 was not the only cause of isolation.



*"For me, the most significant quality of life problem was isolation (...), not being able to see the amount of people we saw before and do the things that we used to do even when I was sick was the most significant thing that affected our life during this period."*

*"COVID or not, people who have had CAR-T and/or are immunosuppressed to a degree that we are all, they will be isolated to some degree even after COVID is gone."*

*"Chronic diseases come with a lot of loneliness and sad moments."*

MYELOMA PATIENTS

### Side effects

Patients wished that the questionnaires better captured the side effects they experienced (or still experience) as a result of CAR-T.



*"I find that side effects are not captured enough. I kept a diary during my CAR-T treatment and identified 22 different side effects at different grades, including some that were debilitating. I think that in these questionnaires, there should be room to talk about side effects during the treatment."*

MYELOMA PATIENT

In particular, the following side effects were cited by the participants:

- **Infections**, for which they sometimes hospitalised and/or which led and/or were the cause of great weakness.
- **CRS**, there were concerns about the physical and emotional impact and consequences on patients' lives that were not addressed.



*"There are some things that nobody who has not had CAR-T will know about. For example, something very specific for CAR-T: cytokine storms."*

*"If somebody is pessimistic, then it gives you a pessimistic view on what CRS is. And if somebody is optimistic, it gives an optimistic view. There's no data or ways to ask people. It could be helpful maybe to enter some questions or ask some questions about how you felt, how you felt about having the CRS."*

MYELOMA PATIENTS

- **Neurological symptoms:** Patients expressed that they were very scared about these side effects, but they were not provided with much information. They outlined that while a lot is now known about CRS management and patients feel this is handled well by the clinical team, there is more uncertainty about neurological symptoms.



*"You might want to add something about your fear of neurological symptoms. Did the fears materialize?"*

*"There's some kind of fear and apprehension that something might go wrong neurologically, which is for me the worst thing that can happen, to lose my mind to a certain degree. That should be better reflected in one of your questionnaires. On what you expect, what you were told. Regarding your expectations, what really happened in the end, etc.?"*

MYELOMA PATIENTS

Patients felt that the questions asked at the hospital after the infusion to detect neurological issues (outside of PRO assessments) were well designed for this purpose but not to assess their impact on quality of life, especially in the long term.



*"I was told to count backward from 100 to 0, 10 by 10, to say who the president is, what day it was etc. But this was not talking about quality of life, this was just to see if I had neurological symptoms or not."*

MYELOMA PATIENT

Some patients also reported having **immediate memory** issues. As part of the clinical management of CAR-T, patients were asked to repeat sentences from one day to another to check their memory. However, these memory aspects were not reflected in the PRO questionnaires.



*"I dare not talk about it but at the moment I forget a lot of things."*

MYELOMA PATIENT

Patients also reported **sleep** issues, loss of **reflexes** and **confusion**.



*"I remember moments of great confusion, immediately after CAR-T infusion. It is a well-known, studied and followed-up phenomenon and there are medicines to treat it. I know people can also develop parkinsonism. And this can appear several months after. So, it really depends on when the questionnaire is given. And one should not only identify neurotoxicity as a whole, but all side effects."*

MYELOMA PATIENT

Many patients reported **concentration** issues that they think are not addressed in the PRO questionnaires. They think these can have multiple causes such as stress, anxiety, or body weakness.



*"I've been a reader all my life. I've read a lot of books. I like to read, it's one of my biggest hobbies. And, you know, after the CAR-T, I couldn't read; during the CAR-T, I couldn't read. Only now I can concentrate enough to read a book."*

*"Your body has to rest. Your mind has to rest. You're less focused. You care less about things. You just want to get better. (...) Your priorities change."*

MYELOMA PATIENTS

## Energy

Several patients mentioned that their energy had been low for some time and that this was not captured by the questionnaires. However, this had a big impact on what they could or could not do.



*"My energy level is not so high. I would say that every day I have very little battery, that's dangerous for me (...). If I go too much in the red, then I need two, three days to be back on a good level and feel good. (...) I must select what I do and what I don't."*

MYELOMA PATIENT

## Pain

Patients reported that the pain-related questions were not specific enough, especially the types of pain and their origin(s) (e.g., from neuropathy).



*"I would really like to change some questions, especially the pain ones, in particular the bone pain ones."*

*"About pain, what kind of pain are we talking about? Bone pain, stomach aches, headaches? When I had my myeloma problems, I had bone pain, it was extremely painful, I often had broken ribs. It was a very difficult time. I think when they write these questions they think about that kind of pain, not about other kinds of pain, whatever their origin is."*

*"(Neuropathy) is bothering and some patients are debilitated by these (...). Sometimes to the point of not being able to walk. I fell several times playing tennis after totally losing the feeling in my leg."*

MYELOMA PATIENTS

It was also suggested that questions are only useful if the pain can be associated with the treatment and/or the disease, and dissociated from other activities (e.g., sport). The question on whether pain increases with activity or not should indicate if, in "normal time" outside of treatment and disease, this pain would not be there.

## Sexual function

Some patients reported that the questionnaires are lacking questions on sexual function.



*“One very basic question is how (CAR-T) can impact sexual function and your physical relationships.”*

MYELOMA PATIENT

## Unexplained changes

One patient reported having seen no information on the potential of developing dietary issues following CAR-T. Better ways to assess unexplained life changes should be explored in order to detect them, and determine their nature and impact on quality of life.



*“I don’t know if this is related to CAR-T, but since I’ve had CAR-T, I’ve developed a very severe lactose intolerance.”*

MYELOMA PATIENT

## Mental state

- Emotional wellbeing

Patients found that questions focused a lot on physical functions, but less so on mental wellbeing. Patients also reported that the medical team, and by extension the trial sponsors, are only interested in the physical dimension of their health, but not in their emotional wellbeing. However, their emotional wellbeing and their mood have an impact on their physical status and vice versa.



*“The psychological issue is talked about very little, and it is important because the physical and psychological wellbeing go together. I know it’s not something pharma usually asks but I think (...) it’s important to ask us.”*

*“When we are physically better this makes the mood much better. When we are worse, well, your mood is not the best. Everything is seen in grey tones.”*

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- Boredom

Boredom at the hospital, especially for those who feel great rapidly, but are not allowed to be discharged, should be measured, and better taken care of. Patients also reported that they would like to see questions around their ability to pursue hobbies and physical activities in the short and long term, after they leave the hospital.



*“I found myself during this time very, very bored, too, because there’s nothing I can do. I don’t want to watch television. I don’t want to read books. I don’t want to see people. I don’t want to talk to people.”*

*“I threatened to tie my bedsheets together and rappel out the window. I was getting so tired of being in the hospital.”*

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- Fear of death

Some patients do not fear death, but this does not mean they don't think about it. Some questions to explore this could be "Can you make projects?", "Do you think positively about the future?" and "Can you schedule things in the future?" Answers indicated that is important for patients to have hope.



*"About (EORTC-QLQ-) MY20, at the end the question is "Have you been worried about dying?" but should really be "Do you think about death?"*

MYELOMA PATIENT

Frequently answering questions about being worried about death did not generate particular anxiety among the participants, but patients who had experienced difficult things in their life, such as war, discrimination, oppression and dictatorship, or exodus, reported that it helped them put other things like their myeloma and treatment into perspective.

### Timing of PRO assessments

Participants were asked about when and how often they think patients should be questioned on their quality of life during CAR-T and why. Patients said that it is important to compare quality of life before and after treatment, though some did not know how often these quality of life questions should be asked and some said that the first week is crucial.



*"You should compare the quality before the treatment and after the treatment."  
"During the height of the treatment, the most difficult time is the first week."*

MYELOMA PATIENTS

Some patients had no days when they were physically unable to answer the questionnaires. But one patient reported not remembering the first days after the infusion because they were very confused. Therefore, collecting data at this point could be difficult for some patients.

Most patients thought that, in the long term, it should be every 1-3 months and that it depends on how the person feels. When patients feel good, they do not think it is necessary to fill PRO questionnaires every month.



*"Every month is probably (appropriate) after you're through the process and back to pretty much normal life after you have healed and your body is recovered. (Then) I think every month is probably more than is necessary. I would say quarterly would probably be fine, maybe even depending on the patient twice a year."*

MYELOMA PATIENT



Patients shared how often they would fill PRO questionnaires during their CAR-T treatment. They had different experiences, but in general they filled them regularly at the beginning and after a while this became spaced out. Most thought the schedule was appropriate.



*“At first, I think they gave me surveys every month. Now it is more spaced out. The last time was four months ago, which was when I reached two years post-infusion.”*

*“I filled them only at the beginning.”*

*“I had three questionnaires to fill, monthly or bimonthly, with a tablet.”*

*“I was asked things 15 mins after CAR-T infusion, then half an hour, four hours, three days, six days, three weeks.”*

*“In the hospital, I think I was doing them daily and I think that was probably appropriate, so they could monitor how I was.”*

MYELOMA PATIENTS

Patients reported having issues remembering what they had experienced the week before, or even earlier, when filling in the questionnaires. Some would prefer reporting things whenever they occurred, through an app, for example. This would also prevent them from having to answer the same questions that they didn't feel were relevant after a certain point. Some patients did not see the point of answering questions about the past weeks or months, especially if they were feeling well.



*“When you're back home, not at the hospital anymore, many times I have thought I should write down things or say things (...). I have a job so very often I forget things. And when I fill the questionnaire about the past week, it's not the past week anymore and I just think that the past week was fine.”*

*“I would be fond of an app or something where one can react live, e.g. When I have back pain, when I have bone pain. Because in fact we don't necessarily remember. And I go every month. But soon I will go every three month and I would surely have forgotten what happened in between.”*

*“I have the feeling that I always say the same things, always give the same answers, and it is not in the moment, so I don't see the point and it is rare when I have something to say.”*

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The research also found that attention should be given to when the questionnaires are given during the day. The mood of the day can also have an impact on how patients fill in the questionnaires.



*“Sometimes the person would come with questions. It was in the middle of COVID and at dinner or lunch time. The one with the questionnaire would need to disinfect the pen, because everything needed to be disinfected and people had to wear a mask. And at the same time I wanted to eat. And the questions were there. So yes, maybe shift the questions half an hour later.”*

*“I think your emotional level also matters, how you're feeling when you take the survey.”*

MYELOMA PATIENTS

Patients did not, however, think it was burdensome to fill in the questionnaires, since they'd go to the hospital for other examinations anyway. It is naturally easier for patients who live close to the hospital. Some patients would be interested in filling in PRO questionnaires at home but also appreciate the feeling

of being followed up at the hospital regularly. However, if they had to go to the hospital just for the PRO questionnaires, they would unanimously rather do it at home.



*"It's just the matter of going into the hospital, completing the questionnaire, sitting, talking for 20 minutes with the research nurse etc."*

MYELOMA PATIENT

### Personal experiences with PROs

Many participants were used to the presented questionnaires, except for the HADS one, which patients were less familiar with. Some particularly appreciated the EQ-5D-5L questionnaire because of the possibilities of responses (five options) to each question and because of the health scale.

Importantly, patients thought it was important to gather quality of life data because they wanted to have feedback on the therapy and understand its impact on patients. It was outlined that this was particularly relevant for small countries where other patients who have experience with CAR-T might be hard to find. However, one patient did not feel that access to PRO data and PRO data collection was so important in this regard. This was because the doctor would choose the treatment for them anyway, so quality of life would not have an impact on their treatment choice.



*"I think it's very important because we're a relatively small country, and before, there were very few patients who had CAR-T, but I found one who already had it and my questions to this person revolved around what the quality of life was during and after the CAR-T."*

MYELOMA PATIENT

Aside from PRO data, discussing quality of life with another patient was very important for treatment decision-making for one patient. The other sources of information were publications. Information from patients and publications can be reassuring as they give insights on how one's lifestyle will be impacted. Patient participants agreed that they wanted to know this kind of information before undergoing the treatment and they would have liked to have known more about how the CAR-T procedure worked.

All participants who were enrolled in an EU registered clinical trial had filled PRO questionnaires during their CAR-T treatment and some were still filling them at the time of the discussion. The three patients who received their CAR-T treatment in other settings did not fill PRO questionnaires, although some were asked how they felt in a less formal way.



*"I was asked questions when the nurses would come in and the doctors would come in, they would ask me how I felt, but nothing in a research setting."*

*"No one asked me questions on my quality of life, on what I was experiencing. But I am not interested in survival, I am interested in life, therefore quality of life."*

MYELOMA PATIENTS

Some patients felt neglected by the medical team, although others, sometimes from the same country, had a different opinion.



*"I don't think here (...), the doctors or anyone else ask you about your life, how you feel. It's not relevant for them. They don't have time for it. (...) I don't know if they don't care but they have no time for this because they have many patients and there are not enough doctors or nurses."*

MYELOMA CARER

Most patients were used to completing these questionnaires at the clinic. One patient was not completely fluent in the questionnaire's language, but could ask the nurse for some help when needed.

For those who filled in PRO questionnaires as part of the clinical trial they were enrolled in, the questionnaires and/or the questions were quite similar or identical to the ones presented during this study. Most had around three different questionnaires to fill in regularly. Additional questions were asked during the hospitalisation time to detect neurological symptoms (e.g., telling their region of residence or what day it was, or counting backwards, or doing some calculation), but nothing about how they felt being at the hospital.

*"I also had a questionnaire about everything related to neurotoxicity. To know if I remembered what day it was. Then I had to do calculations. And this every 48h, the same questions for three weeks, and then I think during the first months of follow-up."*

*"There was a question about how I feel at the moment, how I felt the week before."*

MYELOMA PATIENTS

Some patients had so many tests that they did not remember filling in the questionnaires before CAR-T. Some filled them in on paper and some on a tablet, and there were different collection methods found in the same country. All were completed at the hospital.





## CONCLUSION AND RECOMMENDATIONS

We have held discussions with 10 myeloma patients from five different countries in the geographical area of MPE operations and who have shared their perspectives on three different PRO collection tools commonly used in CAR-T clinical trials: EQ-5D-5L, Hospital Anxiety and Depression Scale (HADS) and EORTC-QLQ-MY20. We qualitatively analysed whether these tools were appropriate and how we could improve them to capture the experiences of patients undergoing CAR-T treatment, a novel therapy for which administration and side effects differ greatly from existing myeloma treatments. Besides the limited number of participants, one limitation of our study is that none of the patients we spoke to had relapsed after CAR-T, even those who had received the treatment several years before. We found that people who are feeling well are more willing to share their experience, more available and physically able to do it. This is a potential bias to the results presented here. Another limitation is that we did not review all the PRO questionnaires that have been used in CAR-T clinical trials. Likewise, they are often given in combination with others (e.g., EORTC QLQ-C30). Therefore, this does not provide a comprehensive reflection of all quality of life assessments in CAR-T clinical trials, but rather an overview of what is important for patients and what improvements should be explored.

Our results show that participants need around 20 minutes to fill in the three questionnaires. This time is not burdensome for them if patients are already attending the hospital for other examinations. However, before considering additional questionnaires leading to additional time, trial designers should first evaluate the potential burden it would be for patients. PRO questionnaires are overall relevant and comprehensive but could be improved in terms of the topics and structure. They are more orientated towards functions than symptoms or side effects and there is not enough connection between the two. Relevance could be improved by linking the questions to side effects and real-life issues. Questions related to topics specific to CAR-T are missing and should be addressed or improved such as the following:

- Isolation
- Specific side effects such as infections, CRS and neurological symptoms, including ICANS, immediate memory, insomnia, loss of reflexes, confusion and concentration issues
- Energy and feelings of weakness
- Types and origins of pain
- Sexual function
- Unexplained life changes
- Mental state, including emotional wellbeing, boredom and ability to plan for the future

These findings could be validated by other CAR-T patients.

In terms of structure, patients were not entirely satisfied with the questionnaires' format. In particular, the low number or limited type of answers to each question they were able to provide, or the redundancy of the questions within or between questionnaires. Additionally, a way could be explored to make the questionnaire consider answers to previous questions. The format or method of delivery of the



questionnaires should be discussed as some patients reported they would rather speak to someone about how they feel, or write a more developed answer. In terms of materials, we recommend keeping both paper and tablet options so patients can choose, and providing good technical support with the tablet, as these often fail.

The timing of PRO assessment was generally considered good by patients who experienced it, while enrolled in a CAR-T clinical trial. It is important for them to compare quality of life before, during and after the treatment. The first week is particularly important to monitor how they feel, but this is potentially difficult given the side effects. Furthermore, especially when patients feel well, they prefer having the questionnaires spaced out - once a month at the beginning then once every three months. However, several patients reported having trouble remembering things from previous weeks or months and some would prefer a better means to report things in a more reactive way. It is important to capture issues when they occur, so these are not missed. This, too, would help patients avoid answering the same questions when no change has been seen for a while. More attention should also be given to when the questionnaires are given to patients at the hospital, as meals and other distractions, or even their mood, can impact their ability to answer questions. Patients who were not enrolled in an EU registered clinical trial were almost never asked about their quality of life, although they would have liked access to that kind of information in order to make their own decision to choose to have the CAR-T treatment or not. Many participants expressed the need to hear other patients' stories and experiences, or simply to be able to find and meet these patients.

With the advancement of novel immunotherapies, parallel advances must be made in PRO tools and patient experience data collection. Therefore, we recommend the following actions:

1. Improve current PRO tools to better capture CAR-T experience or create a specific one, in collaboration with the patient community
2. Enquire about quality of life even outside of clinical trials
3. Share the results obtained with PRO collection tools:
  - Publish PRO results in scientific papers
  - Include PRO results in lay summaries of clinical trial results
4. Communicate to patients about quality of life results and why PRO measurement is important

Ultimately, these results should be used to improve shared decision making around treatment and novel therapies.

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