



## Supporting People Treated with Immune Checkpoint Inhibitors: A Qualitative Study Exploring Oncology Healthcare Professionals' Experiences

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### ARTICLE INFO

#### Key Words:

Immunotherapy  
Immune checkpoint inhibitors  
Qualitative research  
Cancer  
Health care professionals' experiences

### ABSTRACT

**Objectives:** Immune checkpoint inhibitors have recently developed successfully in treatment for several advanced cancers, including advanced renal cancer, where options have previously been limited. However, while some are able to tolerate these treatments, others may experience unpredictable and sometimes severe immune-related adverse events. Oncology health care professionals have vital roles in optimizing safety and supporting positive outcomes for people receiving these treatments. This study aimed to better understand these professionals' experiences of supporting people receiving immune checkpoint inhibitors.

**Methods:** A qualitative exploratory methodology was adopted using semi-structured interviews with 18 purposively sampled senior oncology health professionals, including 12 nurses, who had experience caring for people being treated with checkpoint inhibitors. Data were collected between June and September 2020, transcribed verbatim, and analyzed using reflexive thematic analysis.

**Results:** The analysis identified three main themes: First, participants were positive about the potential benefits that checkpoint inhibitors afforded patients, balanced against challenges associated with ambiguities of the treatments and potential impact on existing workloads. Secondly, participants identified the importance of proactive patient monitoring for early detection and reporting of adverse events. Participants highlighted potential challenges if these events went undetected, particularly in the context of the expectation for patient recognition and prompt reporting. Finally, participants identified the need for continual enhancement of health professionals' knowledge and understanding of immunotherapy, supported by the prioritizing of formal immunotherapy education.

**Conclusions:** Whilst immune checkpoint inhibitors offer the possibility for improved disease outcomes, this is balanced against uncertainties regarding potentially unpredictable, often complex, adverse treatment events. This study shows that nurses have vital roles in supporting people receiving these treatments.

**Implications for Nursing Practice:** Effective care and treatment management for people receiving checkpoint inhibitors require nurses' support through their expert knowledge of immunotherapy and their skills for appropriate coordination and organization of cross-boundary care.

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### Introduction

Globally, more than 434,000 people are diagnosed with renal cancer (RC) annually.<sup>1</sup> Renal cell cancer (RCC) is the most common form of RC,<sup>2</sup> and many people have advanced or metastatic disease at

diagnosis.<sup>3,4</sup> Until recently, the first-line treatment for advanced RCC was targeted therapy with single-agent vascular endothelial growth factor receptor inhibitors, such as the tyrosine kinase inhibitors (TKIs) sunitinib and pazopanib. However, phase 3 clinical trials assessing first-line immune checkpoint inhibitor (ICI) therapy-based combinations have demonstrated efficacy and significant overall survival benefits for people with advanced and metastatic RCC.<sup>5,6</sup> Current and emergent advanced RCC treatment combinations include dual ICIs, such as nivolumab and ipilimumab, and ICIs combined with TKIs, such as lenvatinib and pembrolizumab as first-line treatments.<sup>6</sup>

Note: This work was conducted at Cardiff University, School of Healthcare Sciences.

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<https://doi.org/10.1016/j.soncn.2024.151745>

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## Layperson Summary

### What we investigated and why

Immune checkpoint inhibitors are a newer treatment for cancer. They work by helping the body's immune system recognize and attack cancer cells. Some patients can cope well with these treatments. Others might have erratic and sometimes serious side effects caused by the treatment. Because of this, it is important that health care workers such as nurses support patients and ensure the safe use of these treatments. This study wanted to learn more about the experiences of health care professionals who help patients with these treatments.

### How we did our research

We spoke with health professionals who care for patients using immune checkpoint inhibitors, including nurses. We recorded these conversations and then carefully analyzed them to find common themes.

### What we have found

The health care professionals we spoke with were hopeful about the benefits of immune checkpoint inhibitors for patients but also recognized there were challenges such as uncertainty about the effects of the treatments and extra strain on their workload. They thought it was very important to monitor patients closely to catch and treat side effects early and warned about the dangers if side effects go unnoticed. They also said it was important to educate health care workers about these treatments to help improve their knowledge.

### What it means

Immune checkpoint inhibitors can improve cancer treatment, but there are risks of serious side effects. This study highlights the important role of nurses and other health care professionals in supporting patients during these treatments.

ensure timely diagnosis of actual and potential irAEs, oncology health care professionals have fundamental roles in optimizing patients' safety and positive clinical outcomes. Yet, very little is known about oncology health care professionals' experiences of supporting these patients. This knowledge is important and needed to improve understanding, inform the development of strategies and models of ICI care, identify knowledge gaps and health care professionals' immunotherapy education needs, and ultimately enhance patients' health and clinical outcomes. We report oncology health care professionals' experiences of supporting people affected by cancer and treated with ICIs. The data were generated as part of a larger qualitative investigation of patients' and health care professionals' experiences of ICIs in the context of advanced cancer.<sup>35</sup> While the focus of the research was on experiences with ICIs, and reflecting participants' usage, the terms "immune checkpoint inhibitor" and "immunotherapy" are used interchangeably.

### Aim

We sought to better understand oncology health care professionals' experiences of supporting people receiving immune checkpoint inhibitors.

### Methods

#### Design

A qualitative exploratory approach underpinned by constructivism was adopted to provide a rich and more nuanced understanding of oncology health care professionals' experiences with ICIs for people with advanced cancers. The Standards for Reporting Qualitative Research Studies (SRQR) reporting guidelines were used to report this study<sup>36</sup> (see [supplementary information 1](#)). Further detail of the research methods used can be found in the a priori published protocol.<sup>35</sup>

#### Ethical Considerations

The project was reviewed by the West Midlands and Black Country Research Ethics Committee in October 2019 and received a favorable opinion (REC ref: 19/WM/0299). An amendment for telephone and secure video-conferencing software interviewing in light of the COVID-19 pandemic and physical distancing requirements was approved in June 2020. All participants provided written informed consent.

#### Sample

Using a combination of purposive and snowball sampling, and owing to COVID-19 restrictions, oncology nurses, physicians, and pharmacists across England and Wales with direct experience of caring for and supporting people receiving cancer immunotherapy were invited to participate in this study via targeted social media platforms and the UK Oncology Nursing Society bulletins. We sought to include clinical nurse specialists (CNSs), advanced nurse practitioners (ANPs), consultant nurses working in oncology, oncologists, specialist oncology pharmacists, and primary care practitioners. Health care professionals outside oncology centers were also considered important as patients often present to primary, unscheduled, and emergency care services for toxicity management and late-onset irAEs, including those arising after treatment completion.

#### Data Collection

With written informed consent, semistructured interviews were conducted by SJ and SA between June and October 2020. Due to the COVID-19 physical distancing requirements, one-on-one interviews were conducted by telephone or secure online video-conferencing as

ICIs constitute one of the most successful developments in immunotherapy treatments for some cancers.<sup>7</sup> Satisfactory progression-free and long-term survival outcomes<sup>8-10</sup> mean that ICIs are transforming the standard of care for advanced cancers, including ARC, where treatment options have hitherto been limited.<sup>9,11-15</sup> Access to some ICIs in a range of advanced cancers is improving,<sup>16,17</sup> and use in adjuvant settings is increasing.<sup>18,19</sup> Over time, more people affected by cancer, including ARC, will receive these treatments, either alone or in combination.<sup>20</sup>

Many people maintain a level of normalcy in their everyday lives during and beyond ICI treatments.<sup>21</sup> Yet while some people may tolerate these novel treatments, immune-related adverse events (irAEs), including, for example, autoimmune and inflammatory-related endocrine, musculoskeletal, joint, skin, breathing, and bowel-related problems,<sup>22-26</sup> are not uncommon. irAEs can vary according to ICI regimen, cancer type, and treatment duration and even develop post-treatment completion.<sup>22,24,27</sup> They can be unpredictable and severe<sup>28,29</sup> and substantially affect people's health, well-being, and quality of life.<sup>30-32</sup> Furthermore, as combined treatments become more prevalent, emergent irAEs will present new challenges for health care professionals.<sup>33,34</sup> irAEs can be reversible with early recognition, prompt assessment, and appropriate intervention. Yet without these actions, relatively minor irAEs might escalate rapidly to serious, potentially life-threatening events necessitating treatment interruption or even cessation.

irAE management is quite different from other systemic anticancer treatments (SACT). Through proactive, supportive interventions that enable early recognition, legitimate prompt reporting, and

**Table 1**  
Characteristics of Participants

Participant	Profession	Role	Workplace	Agenda for Change Grading
P11	Medicine	Consultant	Oncology centre	N/A
P12	Nursing	Site-specific clinical nurse specialist	Oncology centre	7
P13	Nursing	Acute oncology clinical nurse specialist	General hospital	7
P14	Nursing	Acute oncology clinical nurse specialist	General hospital	7
P15	Nursing	Immunotherapy clinical nurse specialist	General hospital	7
P16	Medicine	Oncologist	Oncology centre	N/A
P17	Nursing	Oncology advanced nurse practitioner	General hospital	8b
P18	Nursing	Acute oncology clinical nurse specialist	General hospital	7
P19	Medicine	Oncologist	Oncology centre	N/A
P10	Nursing	Site-specific clinical nurse specialist	General hospital	7
P111	Pharmacy	Oncology pharmacist	General hospital	
P112	Nursing	Site-specific clinical nurse specialist	General hospital	8a
P113	Pharmacy	Oncology pharmacist	General hospital	8b
P114	Nursing	Site-specific clinical nurse specialist	Oncology centre	8a
P115	Nursing	Acute oncology clinical nurse specialist	General hospital	7
P116	Nursing	Immunotherapy clinical nurse specialist	General hospital	7
P117	Nursing	Oncology advanced nurse practitioner	Cancer centre	7
P118	Pharmacy	Oncology pharmacist	General hospital	8b

per individual preference. The interviews were guided by a piloted interview schedule derived from the literature and professional knowledge and scrutinized by the project team's patient and public involvement members (see [supplementary information 2](#)). Interviews were recorded, ranged from 39 minutes to 1 hour 22 minutes in length, and were professionally transcribed. No participants withdrew from the study.

#### Data Analysis

Foreshadowed by the study's research question and aim, inductive, reflexive thematic analysis<sup>37</sup> took place alongside data collection. Two researchers (SJ and SA) independently coded the transcripts using NVIVO. Initial codes and relationships between these codes were agreed upon and assembled into provisional themes. A third researcher (TW) met regularly with the researchers online to discuss coding and ensure that the coding process and provisional themes reflected and accurately captured participants' meanings in both individual data and the data set as a whole, while also addressing the research question and aim.

This study's trustworthiness is enhanced through techniques to achieve credibility, confirmability, transferability, and dependability. Meticulous interview transcription and checks and rigorous data analysis involving three researchers contributed to credibility and confirmability. Detailed descriptions of participants' experiences aided transferability. Dependability was established through the audit trail of methodological decisions.<sup>38</sup> Reflexive thematic analysis accepts the researcher's influence on the research. For this study, 1 researcher (SJ) carried out recruitment, 2 researchers (SJ, SA) collected data and three (SJ, SA, TW) engaged in data analysis. One participant was known professionally to 1 interviewer. In terms of positionality and its impact, all researchers were White academicians: 2 women and 1 man. All had PhDs and were experienced qualitative researchers with academic backgrounds in nursing and social sciences. Two researchers were registered nurses with clinical backgrounds in oncology and specialist palliative care and supported self-management. While this could provide insights into the phenomena under investigation, it could also influence the interpretation of data. To mitigate this, the research team had weekly online meetings during data analysis to discuss the raw data and coding and review, refine, and define themes. Themes were also presented to and discussed in online meetings with the study's project advisory group, members of which had personal experiences of ICI treatment for advanced cancer, either as a patient or oncology and primary care health care professional.

#### Results

Eighteen senior NHS oncology health care professionals employed in cancer services within acute hospitals and cancer centers in Wales and England participated, as detailed in [Table 1](#). All participants were accustomed to supporting people with cancer being treated with ICIs and articulated rich accounts of their experiences.

The analysis identified three predominant themes: "We're in new territory," acknowledging benefits and recognizing challenges; "Toxicities can occur at any time point," doing immune-related adverse event management; and "It is all about education," prioritizing immunotherapy education enhancement.

#### "We're in New Territory": Acknowledging Benefits and Recognizing Challenges

The expanding use of ICIs outside of clinical trials in different cancers, including ARC and some adjuvant settings as the standard of care was welcomed. ICIs were frequently described as "exciting," "amazing" treatments. They were portrayed as having "changed the landscape" of cancer treatments and enabled movement into "new territory."

In the wake of the shattering impact of being diagnosed with advanced cancer, ICIs symbolized and engendered hope and cautious optimism. Positive regard was inextricably connected with promising results observed for many people with certain cancers that historically were hard to treat and for which the prognosis was poor.

*The great thing is that you do see patients who previously would really not have responded to traditional chemotherapies doing really, really well on the immunotherapy. (P114, acute oncology CNS)*

*I see patients doing well. I see patients three years on after brain mets who still have no disease who are well and that's inspiring. (P12, site specific CNS)*

In addition to improved survivorship outcomes, some participants articulated that people with advanced cancer, including ARC, and treated with ICIs retained a sense of normality and lived their lives for longer with a degree of quality.

*I find quite a few renal cancers as well, they tend to do quite well as well, just carrying on as they would do usually. (P13, acute oncology CNS)*

These perceptions were mainly connected with the observation that treatment frequency notwithstanding, as ICIs were administered

in a short time, people could integrate treatments into their everyday lives. Participants' accounts indicated that treatment effects were less visible to others. Furthermore, ICIs were often considered to be better tolerated than traditional SACT, with milder and fewer adverse effects.

*Patients have often had chemotherapy and radiotherapy previously or palliative treatment previously and have actually really struggled and have had a lot of side-effects and actually when people have the immunotherapy, they can actually tolerate it really well and for really long periods of time and you do see some really lovely outcomes of patients doing really well. (PI5, immunotherapy CNS)*

*On the whole, it [ICIs] is kind of well tolerated and does seem to have less side effects than kind of chemo and things. (PI6 oncologist)*

However, in the accounts of experience, challenges at several levels were evident. At an organizational level, concerns were raised about current and future demands expanding use of ICIs placed on service capacity, the oncology, and wider, nonspecialist oncology health care workforce and workloads.

*They're coming to hospital a lot more, hospital visits, scans and things like that. It's a big impact on our hospital teams because clinics have got an awful lot busier (...). And that's been a huge challenge because the workforce hasn't really changed. (PI1, oncologist)*

*Lung cancer patients seem to be having more and more immunotherapies, and I think there are a couple of new ones out as well, there are going to be more and more. Well, more and more of us are going to be diagnosed with a cancer, aren't we, sadly. I'm assuming that's going to have a knock-on effect for all types of treatment. So, yes. The workload for immunotherapy is only going to get bigger. (PI4, acute oncology CNS)*

At an individual level, concern about the ambiguity surrounding ICI treatment effects threaded through participants' accounts. In their everyday practice, many participants articulated that they were constantly navigating uncharted territory along a continuum of treatment uncertainties. Comparisons were frequently drawn to the differences with the known, predictable, and understood adverse effects associated with traditional SACT, notably chemotherapy. Ambiguity was manifest in terms of the impact of ICIs on the disease trajectory and the enduring possibility of IRAEs. Particular attention was drawn to the diverse range, unpredictability, and temporal pattern of IRAEs.

*You don't know what's going to happen when and where and what it's going to be. I think that's the difference between chemotherapy and immunotherapy, is it's much less predictable and it can affect absolutely any bit of your body. (PI5, immunotherapy CNS)*

*The uncertainty with immunotherapy is the fact that the toxicities can occur at any time point, so even when they've finished it, I think for up to 18 months, they're still said to be at risk of getting toxicities. (PI6, oncologist)*

Furthermore, as therapeutic indications for ICIs in different cancers changed and more people were consequently treated with ICIs, some participants encountered new IRAEs.

*New side-effects are coming to the fore because there's more patients are being treated we're understanding more and more the variety of things that you can see. I mean there's things I've seen this year in terms of side-effects that I haven't seen before. (PI1, oncologist)*

*It's changing all the time and new toxicities picked up, like the neurotoxicities, we've certainly had a few recent... within the last year. (PI8 acute oncology, CNS)*

Establishing whether a symptom was related to treatment or something else, for example, a preexisting co-morbidity or autoimmune condition, was reported to be particularly difficult. Furthermore, several participants highlighted how ICIs combined with other treatment modalities, for example, chemotherapy and, in ARC, TKIs, introduced additional layers of complexity and challenge, especially during telephone triage assessments

*[a patient] I saw come into the emergency department with really bad diarrhea, she was in a clinical trial whereby she was getting immunotherapy and a tyrosine kinase inhibitor. Now, TKIs can cause diarrhea, immunotherapy can cause diarrhea, and I'm, "Well, what the hell do I do here?" (PI7, ANP)*

*When you're triaging a patient, especially over the phone, it's trying to ascertain whether the side-effect is related to their chemotherapy or their immunotherapy, and the management of that side-effect could be quite different for the two things. (PI15, acute oncology CNS)*

Participants understood some IRAEs to be serious, life-changing, and potentially life-threatening. Accordingly, to protect patient safety and enhance patients' health and clinical outcomes and experiences and ensure appropriate IRAE management, the importance of proactive, timely reporting and identification of symptoms was recognized and understood. Yet the ability of many health care professionals, particularly those who were less experienced or not oncology specialists working in emergency, unscheduled, and primary care, to recognize IRAEs was a cause for concern.

*There's still a lot of uncertainty among lots of my colleagues about how to identify the toxicities. (PI9, oncologist)*

*A lot of primary care pharmacists, for example, in the community... chemists, they don't know what immunotherapy is really. They wouldn't be aware that if somebody came in asking for a couple of boxes of Loperamide on immunotherapy, or the dangers of colitis etcetera. (PI13, oncology pharmacist)*

#### "Toxicities Can Occur at Any Time Point": Doing Immune-Related Adverse Event Management

Ensuring safe and effective patient care through regular proactive monitoring for early detection, rapid reporting, and appropriate management of potentially serious IRAEs was at the core of ICI toxicity management during treatment and beyond. An established, fundamental component was scheduled, and mostly nurse-led assessments before each treatment cycle to ensure fitness for treatment. Nonetheless, across multiple accounts, the risk of delayed patient reporting of symptoms indicative of IRAEs between routine pretreatment monitoring and the potential for serious complications and even treatment cessation was recognized and understood.

In an effort to mitigate this risk, patients were actively encouraged to assume responsibility by proactively engaging in self-management behaviors, notably self-monitoring and early reporting of adverse symptoms experienced to their local cancer telephone triage helpline.

*Our patients are given a separate immunotherapy or checkpoint inhibitor treatment diary, [...]. So, that will include the triage tool, so that they can rate for themselves their symptoms and to identify obviously green, amber or red. And, at what point they should access help and advice, but normally what we say to them is, 'anything that's different from normal, just pick up the phone.' (PI10, Site Specific CNS)*

Prompt reporting of symptoms experienced to appropriate professionals was perceived to be contingent on patients' full

engagement with self-management of ICI treatment effects and the health care system across the treatment journey and beyond, and patients' interpretation of risk.

*There might be an odd one or two that aren't quite as good at reporting, or appreciating the severity of side effects.* (PI12, site-specific CNS)

*What you find in reality is that Mr Jones, Mrs Evans, might pop into a local chemist, 'oh I've got'... you know, 'I've got the runs'. 'I'll just get some Loperamide', and 'if it gets worse I'll phone up but otherwise I'll just manage it myself' [...]. We tell them who to ring, when to ring, and why to ring. But ultimately there's always a few that will think 'oh, I can self-medicate. I can sort it out myself'.* (PI13, oncology pharmacist)

A common thread across participants' accounts was patients' reluctance to report symptoms in an optimal, timely manner or even at all. Invariably this was perceived to be due to a range of interrelated reasons attributed to patients' health beliefs. These included perceptions that symptoms were minor or were not harmful or related to the ICIs, not wanting to bother health care professionals who they perceived to be busy, and fearing that treatment would be paused or discontinued.

*Patients don't always phone us as soon as they should. Well, you'd have two different aspects. One is the patient who doesn't want to phone, doesn't want to bother you. And no matter how many times you tell them that it's a 24 hour helpline and they can phone every day of the week, they tend to save up their problems over a weekend and phone first thing on the Monday really unwell, when they should have phoned us 48 hours earlier. So sometimes there is that perception that the service is busy and that they don't want to bother us or that the symptoms seem vague and minor.* (PI14, acute oncology, CNS)

*Patients are quite afraid that if they report a toxicity that the treatment is going to be stopped. I have come across a few patients where perhaps they are more unwell than they let on and they're struggling quite a bit with treatment, so they don't want to communicate that to us.* (PI11, oncology pharmacist)

However, it was recognized that inappropriate self-management, delayed and inadequate reporting of problems constituted a threat to patient safety and health outcomes. This was connected to the heightened risk of serious IRAEs, hospitalization, treatment cessation, and even new chronicity, richly exemplified in the following data extract.

*They'd been to the opticians off of their own bat because their vision had become more blurry, and the optician hadn't necessarily... just given them a prescription for some new glasses, hadn't really gone into any more depth, but I don't really know how much more an optician would, to be honest anyway. But when he was triaged on the helpline [...] he reported that he had an increase in thirst, an increased urine output, especially overnight and with the blurred vision. And then my colleague got him admitted for a review and his blood sugars were above 40 when he came in, and he was nearly in a diabetic ketoacidosis [...] And he was then diagnosed with a type 1 diabetes, so he then completed his treatment, his disease is in response [sic]. So he is no longer needing treatment, but he now had a type 1 diabetes.* (PI15, acute oncology, CNS)

Furthermore, delayed reporting and thus timely, multiprofessional management of serious IRAEs could, in some instances, result in death.

*We can get a toxicity in any organ or system of the body(...). They become really unwell and they could die from these side-effects if*

*they're not managed appropriately.* (PI12, site specific CNS. Emphasis original)

Participants described how people with serious IRAEs were often admitted to acute general hospitals via emergency departments. In these acute settings IRAE management cut across acute and general oncology, specialist services, and related interprofessional boundaries. This generated a very real possibility for fragmented care. To mitigate this, the timely and knowledgeable contribution to IRAE management of acute oncology nurses was important and substantial. Their role entailed gathering and synthesizing relevant patient information: checking medical records, listening to and comprehending patients' stories, conducting meticulous acute oncology nursing assessments, identifying patterns in the patient data generated, and making and documenting decisions about appropriate courses of action. Some participants indicated that their assessment and decision-making were guided by the United Kingdom Oncology Nursing Society acute oncology guidelines.

*I literally pick up the immunotherapy guideline document, which is 25 pages long, and go and... regardless of what the doctors have done, I actually go and see this patient, sit down (...) and go through all the signs and symptoms with them. There are some physical ones which you obviously ask the patients about. There are some that are purely based on blood. So I would go and do all of that with them.* (PI4, acute oncology, CNS)

*We've got quite clear clinical guidelines, so we work within those.* (PI17, acute oncology ANP)

Within the acute hospital, safe and effective care was contingent on timely, effective communication with the right professionals with the requisite knowledge. This required careful alignment and coordination of work within and across interprofessional specialty boundaries and even organizational interfaces.

*Liaising with the doctors that are looking after them on the ward, on what our take on why they've come in is and how we feel that, if they need to do anything in the management more than they're doing. And then linking back into their oncologist with the... oncologists don't cover the acute setting, so our role is doing that assessment on the oncologist's behalf.* (PI8, acute oncology CNS)

To accomplish interprofessional, cross-boundary working with noncancer specialists and thereby ensure the best possible patient support, nurses embraced responsibility for proactively developing relationships with multidisciplinary teams outside of oncology. Strategies for relationship building included raising the profile of ICIs, increasing visibility, and reaching out.

*They've [Immunotherapy CNSs] done a lot of work contacting the other [non-cancer] specialties to create links and get a greater understanding of how immunotherapy can have adverse effects on a different body of systems and what help we need from them. And it's been a very much of, "We need your help. Can you help us?"* (PI15, acute oncology CNS)

Nevertheless, relationship building in itself could be challenging work. Furthermore, when faced with a person experiencing a serious IRAE, timely access to appropriate medical specialists with the right knowledge could be problematic.

*Barriers I've experienced: if a patient develops a toxicity, is getting access to the specialist to manage that. So, if it's a thyroid or hormone problem, is getting access to an endocrinologist that has an interest in the management of immune-related toxicity. The same for gastro, if they get colitis, it's about accessing colonoscopy in a timely matter [...] They're all so busy with their*

general medical work, to then take on a specialist interest in oncology-related toxicities, it's quite challenging for them, I expect. (PI6, oncologist)

#### 'It Is All About Education': Prioritizing Immunotherapy Education Enhancement

To enhance the delivery of safe and effective care, patients' health outcomes, and experiences, the need to prioritize and invest in health care professionals' immunotherapy education was a common thread across participants' accounts. The dearth of formal cancer immunotherapy education available was highlighted, mostly by nurses.

*There isn't a national training program or educational program for immunotherapy. There's... as far as I'm aware, and I might be wrong, there's a lot of chemotherapy modules out there. I haven't seen many university-based immunotherapy ones.* (PI16, immunotherapy CNS)

Yet across participants' accounts, informal workplace learning opportunities, often sponsored by the pharmaceutical industry and facilitated in collaboration with professional organizations, were well received.

Recognizing the complexity and continuously evolving nature of cancer immunotherapy and to optimize patients' safety and health outcomes, participants across professional groups were mindful of the need to continually enhance their own knowledge and understanding of immunotherapy, particularly IRAEs.

*It's all-changing world with the immunotherapy and it is certainly a lot different now than what it was when I first started the role, so and I think it's just going to get a lot bigger. So... It's essential to keep learning.* (PI8, acute oncology, CNS)

*We're constantly being challenged at a specialist level to think of, you know, "Could these be immune mediated?" So, it's education ongoing.* (PI1, oncologist)

Yet enhancing knowledge and understanding of immunotherapy extended beyond those employed in oncology services. Participants recognized that some patients who experienced acute problems while on treatment presented to their general practitioners for unscheduled and emergency care.

*People phone GP practices with side effects and they're meant to be phoning us and, they've been phoning 111 when they're meant to be phoning us.* (PI18 pharmacist)

Participants' accounts indicated that there was a pressing need for nononcology health care professionals to better understand the profile of IRAEs and their management to enable them to recognize and respond appropriately to actual and potential IRAEs and thereby ensure the right care was given the first time.

*For our ED and AMU colleagues, it's about toxicity management and recognizing that a patient coming in with immune, diarrhea when they're on immunotherapy is completely different to a patient coming in with diarrhea that's on chemotherapy. Time is of the essence. There is a sense of urgency there.* (PI7, acute oncology ANP)

*I had to say to a few medics, "If you are going to treat this patient as having chemotherapy-related toxicity and they've actually had immunotherapy-related toxicity, you can end up killing them because you're treating them for the wrong type of toxicity."* (PI4, acute oncology, CNS)

In addition, several participants drew attention to the fact that on treatment completion, there was still potential for late-onset IRAEs.

*Side effects can continue for 12/18 months after treatment; that's another one of the big challenges around immunotherapy. It's not just something that finishes three or four weeks after you've finished your treatment; you can develop the problems way down the line. So, as a consequence, it might well be that patients could have almost forgotten they'd had immunotherapy and then turn up to the GP with a problem, which could be diagnosed as irritable bowel, for example, and that's actually late-onset colitis.* (PI14, acute oncology, CNS)

Thus equipping nononcology health care professionals with firm foundational knowledge in immune-oncology, IRAEs and their management, and the potential for chronic and late treatment effects were priority areas for action.

*We need to think outside of oncology when we think of education that we need to be providing that support to our other colleagues who will see these side effects much more infrequently but will often be at the sharp end of it. So, I think it's just reiterating that, we spend a lot of time thinking about educating oncology teams, but actually the real education is the people who aren't using these treatments all the time.* (PI9, oncologist)

## DISCUSSION

As set out in the introduction to this paper, ICIs are transforming the landscape of care for many people affected by cancer. Through in-depth individual interviews, this unique qualitative study explored practice experiences from the perspective of oncology health care professionals who supported people treated with ICIs. The significance of the results reported here rests on the fact that, to our knowledge, this was the first study to investigate ICIs from the perspective of oncology health care professionals. This is important given the expanding use of ICIs internationally.

Our results resonate with the theoretical notion of health care being a complex adaptive system,<sup>39-41</sup> the nature of which means that change, in the case of this research expansion and diversification of ICI treatment regimens, presents certain challenges. As seen in our results, complex systems are comprised of individual agents who react, interact, and adapt to each other's actions, rendering these systems as dynamic and changing over time. These systems are also likely to have informal, bottom-up rules and arrangements, creating further unpredictability.<sup>41</sup> This means that attempts to introduce new innovations, including new therapies such as ICIs, can experience different responses to the same input. In this respect, frontline oncology health care professionals are key and are essential in supporting such innovation.

The data revealed that the rapid expansion of ICIs into everyday practice was accepted, welcomed and supported. This was firmly connected with the positive impact of ICIs on disease progression for many people with advanced cancers. Simultaneously, expanding and diversifying the use of ICIs disrupted service organization and everyday professional practices in terms of the frequency and duration of patient contact and care processes and pathways, particularly when compared with "business as usual" associated with established known and understood traditional SACT. To some extent, this connects with and supports findings reported by Aguiar-Ibanez et al,<sup>42</sup> who documented the substantial time oncologists and oncology nurses in the United States spent with patients during monotherapy and combined immunotherapy treatment cycle visits and for up to 2 years.

ICI unpredictability compounded organizational and practice disruption. Their idiosyncrasies, particularly compared with established SACT, meant that participants occupied a space imbued with uncertainty regarding treatment impact on disease and the occurrence, nature, duration, and potential severity of IRAEs. Faced with unpredictability and needing to be proactive and responsive to

optimize patient safety and enhance cancer and health outcomes, active surveillance, pharmacovigilance, and adverse event management all generated additional work.

In delivering and supporting people receiving ICIs, participants were actually doing more with less and voiced concerns about insufficient capacity in the oncology workforce to meet current and future demands. Given the intensive, complex nature of these treatment regimes, associated monitoring, and IRAE management, this is not surprising, especially when set against substantial, persisting shortages in the multidisciplinary oncology workforce globally.<sup>43,44</sup> Yet with anticipated increased patient flow associated with the steady expansion of ICIs, especially in the context of more clinical trials in new cancer sites, implementation of new indications, earlier use of ICIs as the standard of care, and the rising incidence and prevalence, and thus burden of cancer, there is an urgent need to bolster and extend the specialist oncology workforce, invest in infrastructure and explore innovative models of care. Indeed, failure to do so may exacerbate workload strain and contribute to excessive workplace stress.

Our data revealed that proactive monitoring for early detection of potentially serious IRAEs was privileged. Here patients were perceived to have important roles. Between scheduled pretreatment assessments and equipped with information and monitoring resources, patients were expected to actively embrace self-management roles by assuming responsibility for identifying and reporting treatment-related symptoms in an appropriate, timely manner. The active engagement of people living with chronic conditions, including cancer, in self-managing problems that may result from their conditions and associated treatments is widely accepted across health care. Nonetheless, this presumes that all patients have the capacity to comprehend complex information and the capability, motivation, resources, and self-efficacy to engage in appropriate self-management behaviors.

This study has highlighted that underreporting or delayed reporting, symptom self-management, and patients' health beliefs meant that self-management of IRAEs could be inadequate. Given that enhancing the quality of proactive self-management support for TRAEs is a strategic priority in cancer care,<sup>45</sup> this finding may not be so surprising, particularly when it is recognized that many of these people are living in the shadow of possible relapse, disease recurrence, and even death. However, this finding is notable and concerning as suboptimal reporting of IRAE effects and early treatment cessation due to these IRAEs may leave these patients vulnerable to poorer cancer and survival outcomes and quality of life.

Sharing information with patients about monitoring and reporting potential IRAEs is undoubtedly necessary as part of the patient education process. Yet it is not sufficient. Our results may also signal that patients' success as self-managers is contingent on more than sharing information. It also requires acceptable, accessible, appropriate, and theoretically informed, co-produced patient education interventions, together with access to timely, acceptable proactive professional self-management support that is embedded within treatment pathways throughout the ICI treatment trajectory. In this context patient education is vital. The optimal design, content, format, and implementation of theoretically informed patient education interventions, which empower patients to identify potential IRAEs with a degree of confidence and take positive action in terms of reporting should be explored in collaboration with patients and those important to them, and interventions coproduced and tested.

The data also revealed that the disruptive impact of ICIs on care delivery extended beyond specialist oncology settings. Several participants articulated that when experiencing treatment-related problems, patients often directly accessed primary, unscheduled, and emergency care services rather than using oncology triage helplines. It has been recognized that some patients receiving ICIs present to acute general hospitals for emergency care, particularly when specialist acute oncology care is not readily available or accessible.<sup>46,47</sup>

In this study participants recognized that particular expertise notwithstanding, health care professionals outside of oncology were often unfamiliar with ICIs and insufficiently experienced or equipped with the requisite knowledge to identify, diagnose, and appropriately manage IRAEs. This further heightened the risk of delayed or inappropriate toxicity management, hospital admissions, new co-morbidities, and even death. To ensure appropriate, timely IRAE management this signals the need for and importance of upskilling the primary and emergency care workforce and encouraging and enabling health care professionals outside of oncology to actively liaise with specialist oncology services.

Our results begin to render visible, for the first time, the vital, complex, and multifaceted contribution to optimal IRAE management of acute oncology CNSs. In the United Kingdom, these advanced practice nurses specialize in acute, rather than site-specific, oncology and work mostly in general hospital settings. Our data indicated that in acute hospital settings, nurses often worked in time-critical situations, and thus under considerable pressure, to ensure serious IRAEs were effectively and appropriately managed. The research highlighted that while these nurses saw themselves as members of wider multidisciplinary teams, their practice was shaped by an idiosyncratic professional nursing gaze at the heart of which was a keen focus on individual patients.

Data highlighted that these expert specialist nurses accomplished their work through focusing on patients and exercising clinical nursing judgment: gathering patient information from a range of sources, interpreting information, and responding proactively. To ensure safe, effective, and timely interventions, by the right professional, the data also revealed that acute oncology CNSs drew on their expert immunotherapy knowledge and specialist guidelines to advise specialist medical teams and orchestrated care across professional and specialist boundaries. This was not without challenge. Providing advice and orchestrating care across professional boundaries could be disruptive forces, especially when concerning aspects of work beyond physicians' routine everyday specialty work. Yet, to mitigate disruption, they exercised leadership and worked hard to reach out, facilitate, and sustain positive, trusting, and collaborative working relationships within and between multidisciplinary teams.

The importance of and need to ensure health care professionals are adequately prepared to support people during and beyond ICI treatment journeys is well documented.<sup>48,49</sup> Furthermore, various high-quality, accessible consensus guidelines are available.<sup>50,51</sup> Nonetheless, our data highlighted that the complexity of supporting people receiving ICIs and experiencing IRAEs was often set against a background of insufficient ICI knowledge among both generalist and specialist oncology health care professionals. Among study participants, this knowledge gap related specifically to the scope and temporal patterns of potential IRAEs and the knowledge and confidence to identify the characteristics and appropriate course of action, particularly in the case of new treatments and combination therapies, for example, ICIs and TKIs and ICIs and chemotherapy. Understanding toxicity profiles of IRAEs is central to the delivery of safe and effective care and therefore this finding was unexpected. Yet, with regard to combination treatments particularly, this finding may not be surprising for this is a rapidly emerging field. Indeed, a recent systematic review and meta-analysis found that compared with ICI monotherapy, combination ICI therapies had a significantly different adverse event profile.<sup>52</sup>

Given the importance of enhancing patient safety and care experiences, the results from this study raise important questions about health care professionals' ICI educational preparation particularly, but not exclusively, among those employed in unscheduled and emergency care. These are important results. To some extent our results align with those reported in international studies where an immunotherapy knowledge and confidence gap has been identified among physicians and medical students.<sup>53,54</sup> Expanding use of ICIs

across different cancer sites, new treatments, and treatment combinations must be supported by appropriate, accessible education and continuing professional development, particularly of the generalist health care professional workforce. Since cancer is predominantly a disease of older adults and prevalence of cancer among this population is rising, age related co-morbidities, frailty, polypharmacy, insufficient social support, and comprehensive geriatric assessment must also be included in ICI education, not least because some associations are emerging between these factors, notably frailty, and immunotherapy tolerance.<sup>55</sup> Furthermore, immune-modulating interventions such as systemic corticosteroids, which are used to manage serious IRAEs, may have adverse consequences in the shape of iatrogenic effects for older people with existing co-morbidities.<sup>56</sup> Yet in itself, while enhancing professional education is undoubtedly necessary, this may not be sufficient, not least because of well-documented resources and time constraints in health care services internationally, which may negatively impact engagement in ongoing education. Arguably specialist oncology health care professionals have a vital and central role in cultivating and leading cross-sector collaborative partnerships which focus on developing, testing, and implementing innovative, multidisciplinary, evidence-based, immunotherapy education for health care professionals through the lens of co-production.

#### Strengths and limitations

This study adds to the growing literature on ICI experiences in the context of cancer. The strength of this work is that it focused on experiences from an unexplored group, namely senior oncology health care professionals, and unusually, included experiences of oncology pharmacists. A further strength was the generation of extensive, rich data which covered a breadth of experience from three professions across diverse geographical locations. Nonetheless these strengths must be balanced against the study's limitations. All participants were self-selecting and may therefore have had their own motivation when agreeing to take part. While we had hoped to recruit participants from primary care settings, we were unfortunately unable to do so. Data were also generated during the COVID-19 pandemic. It is possible that this shaped participants' experiences and thus their accounts. Physical distancing regulations necessitated a switch to electronic and telephone processes for recruitment, consenting, and interviewing. Telephone interviewing may not provide the same opportunities to develop rapport and yield rich data.

#### CONCLUSION

This research has provided important knowledge for understanding the inherent complex adaptive systems challenges associated with supporting people treated with ICIs. Our results show that healthcare professionals voiced that ICIs offered a genuine possibility of improved survivorship outcomes. Yet this was balanced against the disruption generated by specific and associated organizational and workforce challenges. These challenges were inextricably connected with profound uncertainties regarding disease response and the diagnosis and management of complex IRAEs. Direct care focused on IRAE management and was contingent on nurses' expert orchestration of cross-boundary multi-professional care. Yet the complexity of supporting people receiving ICIs was set against a background of inadequate ICI knowledge.

Given that rising numbers of people with cancer may be treated with ICIs there is an urgent need for proactive, acceptable supported self-management to be embedded within ICI treatment pathways. Supported self-management is important to ensure early detection of IRAEs through comprehensive real time assessment by the right health care professional with the aim of optimizing patients' health and cancer outcomes and preventing, where possible the escalation

of symptoms experienced to serious adverse events and acute hospital admissions. In addition, given the continually evolving ICI treatment landscape and thus the potential for the existing knowledge gaps to grow, ICI and IRAE educational preparation of health care professionals in primary and secondary care must be prioritized and appropriate educational interventions co-developed.

#### Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Tessa Watts reports financial support was provided by Macmillan Cancer Support. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### CRediT authorship contribution statement

**Tessa Watts:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Stephen Jennings:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Formal analysis, Data curation. **Sally Anstey:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Dominic Roche:** Writing – review & editing, Writing – original draft.

#### Funding

This work was supported by Macmillan Cancer Support [grant number [7165318, 2019](#)]

#### Acknowledgments

We wish to acknowledge Macmillan Cancer support for funding this study, and extend thanks to the participants who generously offered their time and insights

#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.soncn.2024.151745](https://doi.org/10.1016/j.soncn.2024.151745).

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