BMJ Open

Experiences of cancer immunotherapy with immune checkpoint inhibitors (ExCIm): Insights of people affected by cancer and healthcare professionals: A qualitative study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043750
Article Type:	Protocol
Date Submitted by the Author:	12-Aug-2020
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Keywords:	QUALITATIVE RESEARCH, ONCOLOGY, EDUCATION & TRAINING (see Medical Education & Training), IMMUNOLOGY, Adult oncology < ONCOLOGY

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Experiences of cancer immunotherapy with immune checkpoint inhibitors (ExCIm): Insights of people affected by cancer and healthcare professionals: A qualitative study protocol

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ABSTRACT

Introduction

There is global interest in cancer immunotherapy. Clinical trials have found that one group, immune checkpoint inhibitors (ICIs), have demonstrated clinical benefit across various cancers. However, research focused on the experiences of people affected by cancer of this treatment using qualitative methodology is currently limited. Moreover, little is known about the experiences and education needs of healthcare staff supporting people receiving these immunotherapies. This study therefore seeks to explore both people affected by cancer and healthcare professionals' experiences of ICIs, and use the findings to make recommendations for ICI supportive care guidance development, cancer immunotherapy education materials for healthcare professionals, cancer policy and further research.

Methods and Analysis

Patient participants (*n*= up to 30) will be recruited within the United Kingdom. The sample will incorporate a range of perspectives, socio-demographic factors, diagnoses and treatments, yet share some common experiences. Healthcare professionals (*n*= up to 15) involved in supporting people receiving immunotherapy will also be recruited from across the UK. Data will be generated through in-depth semi-structured interviews. Reflexive thematic analysis will be used to obtain thorough understanding of individuals' perspectives on, and experiences of, immunotherapy.

Ethics and Dissemination

The research will be carried out in accordance with the UK Policy for Health and Social Care Research and [University name redacted] Research Integrity and Governance Code of Practice (2018). The study received favourable ethical opinion from the West Midlands and Black Country REC in October

2019. Health Research Authority (HRA) and Health and Care Research Wales (HCRW) approvals were confirmed in December 2019. All participants will provide informed consent electronically. Findings will be published in peer reviewed journals, non-academic platforms, the Macmillan Cancer Support website, disseminated at relevant national and international conferences and presented via webinar to participants. The study is listed on the NIHR Clinical Research Network Central Portfolio.

Word count: 300 (abstract); 3,464 (full paper)

Keywords: QUALITATIVE RESEARCH; ONCOLOGY; EDUCATION AND TRAINING; IMMUNOLOGY; ADULT ONCOLOGY

Article Summary

Strengths and limitations of the study

1. Few qualitative studies have explored people's experiences of immunotherapy and its associated supportive care, with no studies exploring these experiences known to be reported in the UK context.
2. This original qualitative study has been designed to build on existing knowledge derived predominantly from clinical trials and capture rich, detailed insight into aspects of individuals' experiences of cancer immunotherapy in the United Kingdom, to develop suggestions for improving person-centred care from those receiving, prescribing and supporting treatment.
3. This work samples healthcare professionals from within and outside specialist oncology, and as a result explores the unique experiences of professionals who are expected to have knowledge and experience of managing ICI toxicities and providing safe and effective person-centred supportive care.
4. The sample size is appropriate given that qualitative research does not search for a representative sample but to give breadth, depth and rich information for analysis. However, there is the possibility of selection bias in that as participants are self-selecting they may be particularly motivated to participate in the study.
5. The study coincided with the global COVID-19 pandemic and the introduction in the UK of physical distancing measures which may have an impact on the data generated.

INTRODUCTION

Globally, the rapidly evolving field of cancer immunotherapy [1] is substantially transforming outcomes for some people with advanced solid and haematological cancers. As populations age and grow, cancer detection improves and treatments advance, more people will live with cancer [2,3]. This, together with the increasing use of some immunotherapies earlier in disease trajectories as the standard of care, means more people will receive these treatments as part of their management pathway. Yet, immunotherapies are not without risk. Indeed, there is real potential for treatment-related adverse events, some of which can be severe and even life-threatening.

Arguably, immune checkpoint inhibitors (ICIs), one type of cancer immunotherapy, constitute one of the most significant developments in cancer therapeutics in recent years, bringing enhanced survival hope to patients with advanced cancer and transforming the standard of care [4,5]. ICIs include the anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) (e.g. Ipilimumab), anti-programmed cell death 1 (PD-1) (e.g. Nivolumab, Pembrolizumab) and anti-programmed cell death 1 ligand 1 (PD-L1) (e.g. Atezolizumab, Durvalumab), and monoclonal antibodies (mAbs), which revive anti-tumour immune responses and restore anti-cancer immunity by targeting immune checkpoints and blocking specific proteins in cancer cells which turn the immune system off [4,6].

Clinical trials of ICIs in people with advanced cancers, including for example, non-small cell lung cancer, metastatic and unresectable melanoma and recurrent or metastatic head and neck cancer, have demonstrated clinical benefit [7-17]. Indeed, when evaluated against traditional comparator treatments, for example, chemotherapy, consistent improvements in progression free, treatment free and overall survival have been reported in both treatment-naïve and previously treated patients [7-14]. Furthermore, Pembrolizumab and Nivolumab maintained or even improved quality-of-life (QoL) to a greater degree than comparators [15-17].

ICIs are usually delivered intravenously within an oncology day hospital setting in treatment cycles ranging between two to six weeks and lasting for up to two years. As the targeting of immune cells generates an autoimmune response, immune-related adverse events (irAEs) are not uncommon. When used alone (e.g. Ipilimumab) and in combination (e.g. Ipilimumab and Nivolumab), ICIs have also produced severe and unique treatment-related adverse events [18-20], which are very different to those associated with traditional cancer therapies and can generate a considerable negative impact on individuals' quality of life [21,22]. Indeed, patients have reported a range of irAEs including endocrine, gastrointestinal, respiratory, dermatological and musculoskeletal problems [23,24]. Furthermore, by the end of 2018, in excess of 13,000 cancer immunotherapy irAEs in 18 countries had been reported, with more than two thirds of recorded cases connected with ICIs [25].

Compared with the effects of some chemotherapy regimens, irAEs may be relatively minor, manageable and reversible with timely administration of immune-modulating interventions such as corticosteroids. However, irAEs can also be unpredictable, severe and challenging to manage, arise months after treatment initiation [26], persist once treatment has ended and even arise several months and years after treatment has been completed [27-29]. Furthermore, whilst uncommon, fatalities due to the toxic effects of ICIs have been reported [30]. Indeed, whilst recognising the limitations of the World Health Organisation pharmacovigilance database (Vigilyze), a comprehensive analysis of entries between 2009 and 2018 identified 613 fatalities due to ICI irAEs. Most frequently, deaths were due to colitis (70% of the anti-CTLA-4 deaths [*n*=193] and 37% of combination therapy [*n*= 87]) and pneumonitis (35% of the anti-PD-1/PD-L1 monotherapy deaths [*n*=333]) [30].

Prioritising the enhancement of peoples' experiences of care, treatment and support, together with meeting individuals' needs during treatments and recovery, are central to the cancer policy commitments of the UK's central and devolved governments [31-33]. In phase III cancer

trials, patient-reported outcomes, notably health-related quality-of-life, have provided invaluable insights into treatment impact on individuals [see, for example, 34-36]. Health-related quality-of-life assessment has been prominent in multiple ground-breaking international phase III randomized controlled trials of checkpoint inhibitors [15,37-40]. Yet, notwithstanding the positive results from many randomized trials, treatment experiences of patient populations in real world settings, as opposed to trial settings, may be different. Certainly, given the potentially prolonged nature of immunotherapy treatment delivery, together with the possibility of unique immune-related adverse events in the short, medium and long term, there is potential for a substantial burden of treatment and 'collateral damage' which may adversely impact on individuals' lives, health and wellbeing.

While the use of ICIs in clinical practice is in its infancy, several ICIs have now been approved for treating a range of cancers and are used across cancer centres in the UK and beyond. The emergence of exciting, new and 'cutting edge' ICI therapies as standard care outside of clinical trials has been shown to engender hope and optimism amongst people with advanced cancers [24,26,41,42]. In addition, these perceptions may outweigh much of the perceived risk of undergoing treatment. Some recipients feel sufficiently well and motivated to resume a degree of normalcy in their everyday lives [23]. However, findings from international studies have also highlighted the lasting and profound existential, social, financial, treatment and disease related uncertainty, adverse effects on physical and emotional health and wellbeing, and a perceived need amongst some for enhanced informational support and guidance [23,24,26,41,42].

To the best of our knowledge, there has been no published empirical investigation of people's experiences of the ICI treatment journey from a UK perspective. Moreover, the experiences of healthcare professionals' who deliver cancer immunotherapy and support people receiving these treatments, both within specialist oncology settings and beyond, appear to be absent from the

literature, as are their education and training needs. The paucity of existing research is a concern for it is a barrier to the effective planning and delivery of high-quality person-centred care and support across the cancer immunotherapy treatment journey and beyond, particularly as patients experiencing irAEs may present to acute medical or emergency department admissions rather than to oncology services. Further investigation of patients' experiences of immunotherapy treatment and support, as well as healthcare professionals' experiences of associated care delivery and training needs, is therefore imperative to identify gaps in knowledge, improve understanding and enhance patient health outcomes and experiences across care settings, and strengthen healthcare professionals' cancer immunotherapy education and training.

Aim and research questions

This study aims to comprehensively investigate the experience of ICI treatment by people affected by cancer and healthcare professionals' experiences of delivering and caring for people receiving this treatment. Specifically, it seeks to address the following research questions:

1. What are the decision-making experiences of people receiving ICI immunotherapy treatment?
2. What are the concerns, information and support needs of people receiving ICI treatment?
3. What are healthcare professionals' experiences of caring for and supporting patients receiving cancer immunotherapy?
4. What are healthcare professionals' cancer immunotherapy education, training and support needs?

METHODS

Design

To obtain a thorough understanding of individuals' perspectives on and experiences of cancer immunotherapy as standard care, there is a need to generate rich data that has the power to account for and explain context and complexity. Thus, an exploratory, qualitative approach comprising in-depth interviews and thematic, interpretive analysis [43,44] will be used. The use of qualitative research will facilitate in-depth exploration of individuals' personal and unique views, capturing rich and detailed insight into hitherto unexplored aspects of individuals' experiences. Furthermore, qualitative research is valuable in the investigation of situations that are not yet fully understood [45], complex and sensitive.

Research setting and study participants

A purposive sample of up to 30 people affected by cancer who are being or have been treated with ICIs will be identified from two oncology treatment centres in the UK by clinicians during routine consultations. Purposive sampling will be utilised to represent a range of socio-demographic (i.e. age, gender), cancer diagnoses (i.e. lung, melanoma, head and neck, renal) and treatment related variables (i.e. ICIs used as first and second line treatment).

In view of the COVID-19 physical distancing requirements to reduce infection risk, and following HRA guidance [46], if interested, individuals will be provided with a study information pack comprising of a letter of invitation, participant information sheet and expression of interest researcher contact form, featuring the primary researcher's phone number and e-mail address so as to enable the potential participant to respond directly to the researcher. Individuals who decide to participate will be asked to contact the primary researcher directly either by e-mail or telephone as detailed on the expression of interest researcher contact form. The researcher will subsequently reply to the individual directly either by e-mail or by telephone to address any further questions.

If the individual is still interested in participating, study documents (participant information sheet, consent form and letter of invitation) will again be e-mailed to ensure patients have the correct information, and consent will be accepted via electronic completion and signature as recommended by the latest NHS Health Research Authority guidance [46] updated in response to Covid-19. Following this, a mutually convenient day, time, place and format (face-to-face, by telephone or via a secure video conferencing platform (e.g. Microsoft Teams), for the interview will be agreed.

Following two pilot interviews, a combination of purposive and snowball sampling will be used to recruit up to 15 registered nurses, pharmacists and physicians from oncology services, primary and secondary care (acute oncology) who have experience of caring for and supporting people receiving immunotherapy. The sample will include a diverse range of healthcare professionals including clinical nurse specialists (oncology and immunotherapy), oncologists, advanced nurse practitioners, nurse consultants, pharmacists and primary care practitioners. Services outside specialist oncology centres, including primary care, are considered important as patients often present to these services for toxicity management and late onset irAEs, including those which arise post-treatment.

Participants will be recruited via targeted online social media, specifically Twitter, initially using existing project networks, and advertising within society newsletters and bulletins including the United Kingdom Oncology Nursing Society (UKONS). Interested healthcare professionals will contact the researcher directly by e-mail. If willing to participate, a convenient time and preferred interview format (i.e. telephone or secure, university approved and encrypted video-conferencing software such as Microsoft Teams) will be arranged. All documents will be e-mailed and consent will be accepted via electronic completion and signature.

Individuals' suitability for inclusion will be assessed against criteria outlined in Table 1.

Table 1: Inclusion/exclusion criteria for participants

Healthcare professionals		**People affected by cancer**	
Inclusion criteria	Exclusion criteria	Inclusion criteria	Exclusion criteria
• Are registered practitioners (nurses, doctors and pharmacists) with permanent or regular bank contracts • Have experience of working with people affected by cancer treated with immune checkpoint inhibitor immunotherapy • Are willing and able to give informed consent	• Are not registered practitioners, or do not have permanent or regular bank contracts • Do not have experience of working with people affected by cancer treated with immune checkpoint inhibitor immunotherapy	• Have a confirmed cancer diagnosis • Are currently being, or have been treated with immune checkpoint inhibitor immunotherapy in the last six months • Are over 18 • Able to participate in a spoken interview in English • Are not participating in a clinical trial • Are able and willing to give informed consent	• Are participating in a current clinical trial • Demonstrate cognitive or psychological difficulties that would preclude study participation • Unable to participate in a spoken interview in English

Data collection

All data will be generated through in-depth, semi-structured, digitally, audio-recorded interviews. In view of COVID-19 physical distancing requirements, to prevent infection and following Health Research Authority guidance [46], interviews will be conducted either by telephone or secure video conferencing software (only the audio of video interviews will be recorded in order to protect participant anonymity). Semi-structured interviews allow core topics to be raised for discussion, while leaving space and scope for the identification and exploration of unforeseen issues that may emerge [47,48]. All interviews will take place in accordance with participants' preferences and, in the case of patients, when they are not undergoing treatment or investigations. It is anticipated that interviews will last up to an hour, although they could be longer.

Before commencing interviews, information about the study will be confirmed. Participants will have an opportunity to ask questions and will be informed of their right to withdraw at any time without reason or prejudice. If a companion is present during an interview, this will be respected and facilitated, as this may be advantageous in terms of support. Companions' informed consent will be sought and obtained electronically.

Interviews will be conducted by trained researchers [author initials redacted] and will commence with open questions to develop rapport. Loose interview guides for patients and healthcare professionals, developed by the research team, derived from the literature review, practice and personal knowledge and scrutinised by the project management team's PPI member, will act as aide memoires. The interview guides will use mainly open-ended questions [49]. To elicit further responses, enrich the description and illuminate experiences, prompts will be made and clarifications sought when necessary. Prior to closing the interview, participants will be given the opportunity to reflect and add any additional relevant information to ensure important aspects not included in the interview guide are addressed.

Data analysis

Data collection and analysis will occur simultaneously. All interviews will be fully transcribed verbatim by a university-approved external transcriber. Files will be securely sent via the [university name redacted] *FastFile* application. The software package *NVivo* 12 for Windows/Mac will be used to facilitate the organisation, analysis and presentation of data. Transcribed data will be analysed using the framework for reflexive thematic analysis devised by Braun and Clarke [43,44]. This inductive, systematic, analytic approach involves searching across the dataset for repeated patterns of meaning: data familiarisation, noting early analytical observations; generating initial codes, collating codes and relevant data extracts; identifying meaningful relationships between initial codes and developing themes; refining, defining and naming themes and sub-themes in relation to the research aim and objectives.

Within a constructionist, reflexive approach to thematic analysis [44], the process of generating central organizing concepts and themes is influenced by the researcher. Indeed, the development and identification of themes is based on the researcher's interpretations and positionality (i.e. experience, background, characteristics and assumptions). It is therefore important within this approach to outline the process of theme generation. Accordingly, a comprehensive coding framework will be developed as the analysis progresses and explanations of how central organizing concepts and themes were created will be provided for greater transparency. Furthermore, to ensure rigour, all core research team members [initials redacted for publication] will contribute to data analysis to ensure consistency in interpretation and a reflective research diary detailing the researcher's role and impact on the study will be maintained.

Patient and public involvement

Following NIHR guidance for involving people in research [50,51], this study has been developed through consultation and active collaboration with members of [name redacted] University's Patient Experience and Evaluation in Research (PEER) and [name redacted] Patient and Public Involvement

(PPI) group, who have been personally affected by cancer. Initially, members of the PEER group provided constructive feedback on the research idea and question, study population and design. PEER group representation on the project management team ensures continuing, active patient and public involvement at all stages of the research, including dissemination. Examples to date include offering feedback on the research protocol and ethics applications, acceptability of participant information sheets and interview schedules and contributing to project team meetings. PPI membership of the project's advisory group will contribute to strategic decisions including disseminating findings and routes to impact.

Ethics and dissemination

The proposed research will be carried out in accordance with the UK Policy for Health and Social Care Research and [University name redacted] Research Integrity and Governance Code of Practice (2018). The project was reviewed by the West Midlands and Black Country Research Ethics Committee in October 2019 and received a favourable opinion (REC ref: 19/WM/0299). The study is listed on the NIHR Clinical Research Network Central Portfolio Management System (study ID: 43946).

The dignity, rights, safety and wellbeing of participants will be the primary ethical considerations. Potential participants will be given sufficient time to read and consider study information and ask any questions. All participants who decide to participate will be asked to provide informed consent prior to taking part in the audio-recorded interview. Consent will be accepted via electronic completion and signature, and following Seymour [52], the researcher will use phrases such as '*would it be okay if I asked about . . .*' to reaffirm consent during the interview. The participant's willingness to continue will also be checked at regular intervals.

Data collected from participants will be stored securely at [University name redacted]. Completed consent forms will be stored on the University's password protected secure server in a location which is only accessible to the Chief Investigator [author initials redacted] and project researcher [author initials redacted]. The interview audio recordings will be uploaded onto the password-protected secure server at [University name redacted]. Only the core research team [author names redacted] will be able to access the recordings. Once interview transcripts have been checked against corresponding audio-recordings, all identifiable information will be redacted and pseudonyms ascribed to all participants. All data will be securely stored after this study in accordance with [University name redacted] policies, the General Data Protection Regulation (GDPR) (2016/679) and the Data Protection Act 2018.

Participants may benefit from knowing that their experiences will be used to help inform service developments at individual and organisational levels and healthcare professional education, and thus potentially enhance the quality of person-centred care for people receiving cancer immunotherapy. The study findings may also facilitate knowledge transfer across different treatment sites, potentially benefiting wider patient groups. Knowledge transfer processes include outreach and collaboration, with the study team developing collaborations with cancer centres in order to enhance the practitioner-focused relevance of the educational and training recommendations arising from analysis of data.

While the research involves people affected by cancer, some of whom may have advanced disease, their participation in the study is unlikely to cause physical harm. However, there is an element of risk related to emotional distress. If this occurs, the researcher will stop recording immediately. Only if the participant is certain they would like to resume will the interviewer continue. After interviews, a 'debrief' space will mean that all participants will have the opportunity to talk to the researcher about the interview. For patient interviews, if any upsetting or unsettling feelings arose or are

disclosed at this point, they will be signposted to local cancer support services. With permission, the person's cancer key worker [53] and consultant will be informed. Likewise, healthcare professional participants will be asked if they would like information about local NHS employee wellbeing support systems. Any signposting events will be logged in the study file.

Findings will be reported in relevant, peer-reviewed and professional journals using accepted reporting criteria such as COREQ-32 [54] to ensure transparency. A policy briefing highlighting key findings will be prepared and webinars facilitated to disseminate findings to participants. The findings will be presented at relevant local, national and international conferences and healthcare professional education meetings.

Discussion

The findings from this research will provide novel insights and in-depth, contextualised knowledge of cancer immunotherapy decision-making, the impact of treatments on people's everyday lives, their needs and concerns and how they feel they might best be prepared and supported during treatment and beyond. It will explore healthcare professionals' confidence and preparedness to provide safe, effective, proactive immunotherapy care and identify their support, education and training needs. Understanding people's experiences may ultimately assist in the co-design of appropriate, effective supportive interventions to optimise the delivery of safe, effective, person-centred immunotherapy care. Furthermore, study findings may be used to inform and support the co-production of educational materials related to cancer immunotherapy and associated supportive care for healthcare professionals.

Current status of the study

Data collection commenced at the end of May 2020.

Data statement

Research data are not shared due to sensitivity of topic.

Affiliations, Contributors, Funding and Competing Interests

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Author contributions

The first draft of the manuscript was written by Stephen Jennings and Tessa Watts. Sally Anstey, Janet Bower, Alison Brewster, John Buckman, Deborah Fenlon and Deborah Fitzsimmons are co-applicants on the grant that funds this study. The study was conceived and designed by Tessa Watts, John Buckman and Janet Bower. John Buckman is a Patient and Public Involvement (PPI) representative who contributed to the study design. Every author contributed to the drafting of this manuscript.

Funding

This work was supported by Macmillan Cancer Support (FO = 7165318).

Competing Interests

The research team includes individuals from various organisations, including Cardiff University, Swansea University, Hywel Dda University Health Board and Swansea Bay University Health Board. Deborah Fenlon reports an honorarium from Roche.

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Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

Please note: the study has been submitted as a protocol paper, therefore many of the questions are not relevant due to the stage of project. These have been marked as 'N/A', however the research team are aware of the importance of submitting the checklist in full when reporting study results.

Domain 1: Research team and reflexivity

Personal Characteristics

1. **Interviewer/facilitator**: Which author/s conducted the interview or focus group?
SJ/SA/TW

2. **Credentials**: What were the researcher's credentials? E.g. PhD, MD
MA (SJ); PhD (SA); PhD (TW)

3. **Occupation**: What was their occupation at the time of the study?
Research Assistant (SJ); Senior Lecturer (SA;TW)

4. **Gender**: Was the researcher male or female?
Male (SJ); Female (SA;TW)

5. **Experience and training**: What experience or training did the researcher have?
Qualitative research via PhD programme and workplace based training/experience (SJ: in the process of submitting thesis; TW; SA)

Relationship with participants

6. **Relationship established**: Was a relationship established prior to study commencement?
No

7. **Participant knowledge of the interviewer**: What did the participants know about the researcher? e.g. personal goals, reasons for doing the research.
Job title, university affiliation, reasons for doing the research (documented on participant information sheet)

8. **Interviewer characteristics** What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic
N/A. Interviewer characteristics will be reported upon submission of findings papers, and will be based on the reflexive diary (see below).

Domain 2: study design

Theoretical framework

9. **Methodological orientation and Theory:** What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis
Reflexive thematic analysis (Braun and Clarke, 2019; 2006)

Participant selection

10. **Sampling**: How were participants selected? e.g. purposive, convenience, consecutive, snowball
Patients: Purposive sampling will be utilised to represent a range of socio-demographic (i.e. age, gender), cancer diagnoses (i.e. lung, melanoma, head and neck, renal) and treatment related variables (i.e. ICIs used as first and second line treatment). Healthcare professionals: combination of purposive and snowball.

11. **Method of approach:** How were participants approached? e.g. face-to-face, telephone, mail, email
Healthcare professionals were approached via social media (Twitter). Patient participants were initially approached by clinicians during routine consultations.

12. **Sample size**: How many participants were in the study?
Healthcare professionals (*n*=up to 15); Patients (*n*=up to 30).

13. **Non-participation**: How many people refused to participate or dropped out? Reasons?
None to date – non-participation will be reported in relevant findings papers at a later date.

Setting

14. **Setting of data collection:** Where was the data collected? e.g. home, clinic, workplace
Home (remote interviewing due to Covid-19 and physical distancing requirements)

15. **Presence of non-participants**:
Was anyone else present besides the participants and researchers?
Healthcare professionals: No; Patient participants: Potentially (companions will be invited to join the participant if the participant wishes)

16. **Description of sample**:
What are the important characteristics of the sample? e.g. demographic data, date
N/A

Data collection

17. **Interview guide**: Were questions, prompts, guides provided by the authors? Was it pilot tested?
Yes – SJ, TW, SA, AB and JBu. Interview guides were piloted twice.

18. **Repeat interviews** Were repeat interviews carried out? If yes, how many?
N/A

19. **Audio/visual recording:** Did the research use audio or visual recording to collect the data?
Interviews were/ will be audio recorded.

20. **Field notes**: Were field notes made during and/or after the interview or focus group?
Interviewers kept a reflective diary throughout the interview process to enhance researcher reflexivity and transparency.

21. **Duration**: What was the duration of the interviews or focus group?
Data collection with healthcare participants has commenced, with a mean duration of 54 minutes.

22. **Data saturation** Was data saturation discussed?
N/A. Data saturation will be discussed by the core research team (SJ, TW and SA)

23. **Transcripts returned**: Were transcripts returned to participants for comment and/or correction?
No, however participants will be given opportunity at the end of interviews to clarify responses.

Domain 3: analysis and findings

Data analysis

24. **Number of data coders**: How many data coders coded the data?
N/A. 3 data coders will code (core research team – SJ, TW and SA).

25. **Description of the coding tree**: Did authors provide a description of the coding tree?
N/A. A description of the coding tree will be presented upon publication of findings papers.

26. **Derivation of themes:** Were themes identified in advance or derived from the data?
Both. Data collection and analysis are/will be running concurrently. Key themes generated from initial analysis of data collected will/have influence(d) future interviews and the continual adaptation of interview schedules based on data collected and analysed.

27. **Software** What software, if applicable, was used to manage the data?
NVivo for Mac/Windows

28. **Participant checking** Did participants provide feedback on the findings?
Participants will be given the opportunity to provide feedback on study findings. Findings will be communicated to participants via a webinar with a Q&A section. Participants will be encouraged to stay in touch with core research team throughout the study and are encouraged to feedback on the study as a whole as well as findings.

Reporting

29. **Quotations presented** Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. participant number
N/A. Participant quotations will be presented to illustrate findings and each quotation will be given a unique identification number ascribed to individual participants.

30. **Data and findings consistent:** Was there consistency between the data presented and the findings?
N/A - protocol paper

31. **Clarity of major themes** Were major themes clearly presented in the findings?
N/A - protocol paper

32. **Clarity of minor themes** Is there a description of diverse cases or discussion of minor themes?
N/A - protocol paper

BMJ Open

Experiences of cancer immunotherapy with immune checkpoint inhibitors (ExCIm): Insights of people affected by cancer and healthcare professionals: A qualitative study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043750.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Mar-2021
Complete List of Authors:	Jennings, Stephen; Cardiff University, School of Healthcare Sciences Anstey, Sally; Cardiff University, School of Healthcare Sciences Bower, Janet; Hywel Dda University Health Board, Chemotherapy Day Unit Brewster, Alison; Swansea Bay University Health Board, South West Wales Cancer Centre Buckman, John Fenlon, Deborah; Swansea University, Department of Nursing, College of Human and Health Sciences Fitzsimmons, Deborah; Swansea University, Swansea Centre for Health Economics, College of Human and Health Sciences Watts, Tessa; Cardiff University, School of Healthcare Sciences
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Qualitative research, Health services research, Medical education and training, Nursing
Keywords:	QUALITATIVE RESEARCH, ONCOLOGY, EDUCATION & TRAINING (see Medical Education & Training), IMMUNOLOGY, Adult oncology < ONCOLOGY

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Experiences of cancer immunotherapy with immune checkpoint inhibitors (ExCIm): Insights of people affected by cancer and healthcare professionals: A qualitative study protocol

Authors: Stephen Jennings, Sally Anstey, Janet Bower, Alison Brewster, John Buckman, Deborah Fenlon, Deborah Fitzsimmons, Tessa Watts

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ABSTRACT

Introduction

There is global interest in cancer immunotherapy. Clinical trials have found that one group, immune checkpoint inhibitors (ICIs), have demonstrated clinical benefit across various cancers. However, research focused on the experiences of people affected by cancer of this treatment using qualitative methodology is currently limited. Moreover, little is known about the experiences and education needs of healthcare staff supporting people receiving these immunotherapies. This study therefore seeks to explore both people affected by cancer and healthcare professionals' experiences of ICIs, and use the findings to make recommendations for ICI supportive care guidance development, cancer immunotherapy education materials for healthcare professionals, cancer policy and further research.

Methods and Analysis

Patient participants (*n*= up to 30) will be recruited within the United Kingdom. The sample will incorporate a range of perspectives, socio-demographic factors, diagnoses and ICI treatments, yet share some common experiences. Healthcare professionals (*n*= up to 15) involved in supporting people receiving immunotherapy will also be recruited from across the UK. Data will be generated through in-depth, semi-structured interviews. Reflexive thematic analysis will be used to obtain thorough understanding of individuals' perspectives on, and experiences of, immunotherapy. Study dates: December 2019-May 2021.

Ethics and Dissemination

The research will be carried out in accordance with the UK Policy for Health and Social Care Research and Cardiff University's Research Integrity and Governance Code of Practice (2018). The study

received ethical approval from the West Midlands and Black Country REC in October 2019. Health Research Authority and Health and Care Research Wales approvals were confirmed in December 2019. All participants will provide informed consent. Findings will be published in peer-reviewed journals, non-academic platforms, the Macmillan Cancer Support website, disseminated at relevant national and international conferences and presented via a webinar. The study is listed on the NIHR Clinical Research Network Central Portfolio.

Word count: 299 (abstract); 3,958 (full paper)

Keywords: QUALITATIVE RESEARCH; ONCOLOGY; EDUCATION AND TRAINING; IMMUNOLOGY; ADULT ONCOLOGY

Article Summary

Strengths and limitations of the study

1. Few qualitative studies have explored people's experiences of immunotherapy and its associated supportive care, with no studies exploring these experiences known to be reported in the UK context.
2. This original qualitative study has been designed to build on existing knowledge derived predominantly from clinical trials and capture rich, detailed insight into aspects of individuals' experiences of cancer immunotherapy in the United Kingdom, to develop suggestions for improving person-centred care from those receiving, prescribing and supporting treatments.
3. This work samples healthcare professionals from within and outside oncology, and as a result explores the unique experiences of professionals who are expected to have knowledge and experience of managing ICI toxicities and providing safe and effective person-centred supportive care.
4. The sample size is appropriate given that qualitative research does not search for a representative sample but to give breadth, depth and rich information for analysis. However, there is the possibility of selection bias in that as participants are self-selecting they may be particularly motivated to participate in the study.
5. The study coincided with the global COVID-19 pandemic and the introduction in the UK of physical distancing measures which may have an impact on the data generated.

INTRODUCTION

Globally, the rapidly evolving field of cancer immunotherapy [1] is substantially transforming outcomes for some people with advanced solid and haematological cancers. As populations age and grow, cancer detection improves and treatments advance, more people will live with cancer [2,3]. This, together with the increasing use of some immunotherapies earlier in disease trajectories as the standard of care, means more people will receive these treatments as part of their management pathway. Yet, immunotherapies are not without risk. Indeed, there is real potential for treatment-related adverse events, some of which can be severe and even life-threatening [4-6].

Arguably, immune checkpoint inhibitors (ICIs), one type of cancer immunotherapy, constitute one of the most important developments in cancer therapeutics in recent years, bringing enhanced survival hope to patients with advanced cancer and transforming the standard of care [7,8]. ICIs include the anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) (e.g. Ipilimumab), anti-programmed cell death 1 (PD-1) (e.g. Nivolumab, Pembrolizumab) and anti-programmed cell death 1 ligand 1 (PD-L1) (e.g. Atezolizumab, Durvalumab), and monoclonal antibodies (mAbs), which revive anti-tumour immune responses and restore anti-cancer immunity by targeting immune checkpoints and blocking specific proteins in cancer cells which turn the immune system off [7,9].

Clinical trials of ICIs in people with advanced cancers, including for example, non-small cell lung cancer, metastatic and unresectable melanoma and recurrent or metastatic head and neck cancer, have demonstrated clinical benefit [10-20]. Indeed, when evaluated against traditional comparator treatments, for example, chemotherapy, consistent improvements in progression free, treatment free and overall survival have been reported in both treatment-naïve and previously treated patients [10-17]. Furthermore, Pembrolizumab and Nivolumab maintained or even improved quality-of-life (QoL) to a greater degree than comparators [18-20].

ICIs are usually delivered intravenously within an oncology day hospital setting in treatment cycles ranging between two to six weeks and lasting for up to two years. As the targeting of immune cells generates an autoimmune response, immune-related adverse events (irAEs) are not uncommon. When used alone (for example, Ipilimumab) and in combination (for example, Ipilimumab and Nivolumab), ICIs have also produced severe and unique treatment-related adverse events [4-6], which are very different to those associated with traditional cancer therapies and can generate a considerable negative impact on individuals' quality of life [21,22]. Indeed, patients have reported a range of irAEs including endocrine, gastrointestinal, respiratory, dermatological and musculoskeletal problems [23,24]. Furthermore, by the end of 2018, in excess of 13,000 cancer immunotherapy irAEs in 18 countries had been reported, with more than two thirds of recorded cases connected with ICIs [25].

Compared with the effects of some chemotherapy regimens, irAEs may be relatively minor, manageable and reversible with timely administration of immune-modulating interventions such as corticosteroids. However, irAEs can also be unpredictable, severe and challenging to manage, arise months after treatment initiation [26], persist once treatment has ended and even arise several months and years after treatment has been completed [27-29]. Furthermore, whilst uncommon, fatalities due to the toxic effects of ICIs have been reported [30]. Indeed, whilst recognising the limitations of the World Health Organisation pharmacovigilance database (Vigilyze), a comprehensive analysis of entries between 2009 and 2018 identified 613 fatalities due to ICI irAEs. Most frequently, deaths were due to colitis (70% of the anti-CTLA-4 deaths [*n*=193] and 37% of combination therapy [*n*= 87]) and pneumonitis (35% of the anti-PD-1/PD-L1 monotherapy deaths [*n*=333]) [30].

Prioritising the enhancement of peoples' experiences of care, treatment and support, together with meeting individuals' needs during treatments and recovery, are central to the cancer policy

commitments of the UK's central and devolved governments [31-33]. In phase III cancer trials, patient-reported outcomes, notably health-related quality-of-life, have provided invaluable insights into treatment impact on individuals [see, for example, 34-36]. Health-related quality-of-life assessment has been prominent in multiple ground-breaking international phase III randomized controlled trials of checkpoint inhibitors [18,37-40]. Yet, notwithstanding the positive results from many randomized trials, treatment experiences of patient populations in real world settings, as opposed to trial settings, may be different. Certainly, given the potentially prolonged nature of immunotherapy treatment delivery, together with the possibility of unique immune-related adverse events in the short, medium and long term, there is potential for a substantial burden of treatment and 'collateral damage' which may adversely impact on individuals' lives, health and wellbeing.

While the use of ICIs in clinical practice is in its infancy, several ICIs have now been approved for treating a range of cancers and are used across cancer centres in the UK and beyond. The emergence of exciting, new and 'cutting edge' ICI therapies as standard care outside of clinical trials has been shown to engender hope and optimism amongst people with advanced cancers [24,26,41,42]. In addition, these perceptions may outweigh much of the perceived risk of undergoing treatment. Some recipients feel sufficiently well and motivated to resume a degree of normalcy in their everyday lives [23]. However, findings from international studies have also highlighted the lasting and profound existential, social, financial, treatment and disease related uncertainty, adverse effects on physical and emotional health and wellbeing, and a perceived need amongst some for enhanced informational support and guidance [23,24,26,41,42].

Shared decision-making (SDM), where clinicians support patients to share responsibility for decisions, based on the best available evidence and considering the strengths and risks of various treatment options [43], positively affects patients' treatment experiences [44] and quality of life [45]

in cancer care. However, it has been noted that existing cancer decision-making pathways for some patients focus on clinical management of disease rather than patients' preferences and priorities for cancer treatment [46]. Limited literature examines the immunotherapy decision-making process, for patients across all tumour sites and at various stages of disease. In one study very few patients communicated a good understanding of immunotherapy, particularly the potential effectiveness of treatment and the possibility of experiencing treatment-related side effects [41]. Patients receiving immunotherapy and their informal carers have also experienced uncertainty related to communication and treatment decision-making [24,47]. Indeed, patients reported feeling hampered by a lack of clear information [23], and carers experienced unclear communication regarding immunotherapy treatment [47]. Findings from a recent study [48] indicated that most recommendations for ICI treatment were made by physicians, though patients generally preferred to have the final say regarding treatment commencement. Further enquiry is therefore required to explore both patients' and healthcare professionals' experiences of immunotherapy treatment decision-making in the context of the UK.

To the best of our knowledge, there has been no published empirical investigation of people's experiences of the ICI treatment journey from a UK perspective. Moreover, the experiences of healthcare professionals' who deliver cancer immunotherapy and support people receiving these treatments, both within and outside specialist oncology settings in the UK, appear to be absent from the literature, as are their education and training needs. The paucity of existing research within the UK context is a concern, for it is a barrier to the effective planning and delivery of high-quality safe and effective person-centred care and support across the cancer immunotherapy treatment journey and beyond, particularly as patients experiencing irAEs may present to acute medical or emergency department admissions rather than oncology services.

Further investigation of patients' experiences of immunotherapy treatment and support, as well as healthcare professionals' experiences of associated care delivery and training needs, is therefore imperative to identify gaps in knowledge, improve understanding and enhance patient health outcomes and experiences across care settings, and strengthen healthcare professionals' cancer immunotherapy education and training. Furthermore, data from a UK perspective are required to ensure contextually-relevant immunotherapy education and training interventions are developed.

Aim and research questions

This study aims to investigate people's experiences of ICI treatment and associated supportive care and healthcare professionals' experiences of delivering and caring for people receiving this treatment. Specifically, it seeks to address the following research questions:

1. What are the decision-making experiences of people receiving ICI immunotherapy treatment?
2. What are people's experiences of ICI immunotherapy treatment? What are their expectations, concerns, information and support needs?
3. What are healthcare professionals' experiences of caring for and supporting patients receiving ICI immunotherapy for cancer?
4. What are healthcare professionals' cancer immunotherapy education, training and support needs?

METHODS

Design

To obtain a thorough understanding of individuals' perspectives on and experiences of cancer immunotherapy as standard care, there is a need to generate rich data that has the power to account for and explain context and complexity. Thus, an exploratory, qualitative approach comprising in-depth interviews and thematic, interpretive analysis [49,50] will be used. The use of qualitative research will facilitate in-depth exploration of individuals' personal and unique views, capturing rich and detailed insight into hitherto unexplored aspects of individuals' experiences. Furthermore, qualitative research is valuable in the investigation of situations that are not yet fully understood [51], complex and sensitive.

Research setting and study participants

A purposive sample of up to 30 people affected by cancer who are being treated with ICIs will be identified from two oncology treatment centres in the UK. The oncology treatment centres were selected based on convenience sampling, notably existing academic and clinical collaborations and networks between Cardiff University and an NHS University Health Board and a University Hospital Trust, where it was known that immunotherapies were widely-delivered, and where patients could be recruited reflecting the above variables. The sites reflect both urban and rural socio-geographic contexts and different treatment settings. Based on expert knowledge, it was suggested that these characteristics are largely consistent across the immunotherapy treatment context in the other UK nations.

Purposive sampling will be utilised to represent a range of socio-demographic (for example, age, gender), cancer diagnoses (for example, lung, melanoma, head and neck, renal) and treatment related variables (for example, ICIs used as first and second line treatment). Purposive sampling and

recruitment by clinicians during routine consultations will ensure representation of people affected by cancer regarding their performance status and experience of irAEs.

In view of the COVID-19 physical distancing requirements to reduce infection risk, and following HRA guidance [52], if interested, individuals who meet the inclusion criteria (Table 1) will be provided with a study information pack comprising a letter of invitation, participant information sheet and expression of interest researcher contact form, featuring the primary researcher's phone number and e-mail address so as to enable the potential participant to respond directly to the researcher. Individuals who decide to participate will be asked to contact the primary researcher directly either by e-mail or telephone as detailed on the expression of interest researcher contact form. The researcher will subsequently reply to the individual directly either by e-mail or by telephone to address any further questions.

PLEASE INSERT TABLE 1 HERE

Table 1: Inclusion/exclusion criteria for people affected by cancer

Inclusion criteria	Exclusion criteria
• Have a confirmed cancer diagnosis • Are currently being, or have been treated with immune checkpoint inhibitor immunotherapy in the last six months • Are over 18 • Able to participate in a spoken interview in English • Are not participating in a clinical trial • Are able and willing to give informed consent	• Are participating in a current clinical trial • Demonstrate cognitive or psychological difficulties that would preclude study participation • Unable to participate in a spoken interview in English

If the individual is still interested in participating, study documents (participant information sheet, consent form and letter of invitation) will again be e-mailed to ensure patients have the correct information, and consent will be accepted via electronic completion and signature as recommended by the latest NHS Health Research Authority guidance [52] updated in response to Covid-19.

Following this, a mutually convenient day, time, place and format (by telephone or via a secure video conferencing platform, e.g. Microsoft Teams), for the interview will be agreed.

Following pilot interviews and to ensure our participants have appropriate insights, recruitment of up to 15 registered nurses, pharmacists and physicians from oncology services, primary and secondary care (acute oncology) with direct experience of caring for and supporting people receiving cancer immunotherapy will proceed using a combination of purposive and snowball sampling. The sample will include a range of healthcare professionals including clinical nurse specialists (oncology and immunotherapy), oncologists, advanced nurse practitioners, nurse consultants, pharmacists and primary care practitioners. Services outside specialist oncology centres are considered important as patients often present to these services for toxicity management and late onset irAEs, including those which arise post-treatment.

While the sample size of 15 relevant healthcare professionals is not large, it will be the in-depth, semi-structured interview that will enable the team to generate rich data, providing meaningful insights into these experiences across various professional groups. In-depth qualitative interviews have been considered to be an appropriate methodology when looking to generate rich, meaningful data based on experiences, and the success of this methodology in doing so requires close proximity to the human experience under study [53]. The term 'information power' was conceptualised [54] as a way to guide adequate sample size for qualitative research: the more relevant information that the sample holds, the fewer participants required. For this study, it is the relevance of healthcare professionals' experience in supporting patients undergoing immunotherapy within the sample that is considered the key marker of meaning making within the qualitative approach [53-54].

Due to COVID-19 physical distancing regulations, physicians, registered nurses and pharmacists supporting people receiving immunotherapy will initially be recruited via targeted online social media, specifically Twitter, using existing project networks, and advertising within society newsletters and bulletins including the United Kingdom Oncology Nursing Society (UKONS). Interested healthcare professionals will contact the researcher directly by e-mail. If willing to participate and eligible based on the inclusion criteria (Table 2), a convenient time and preferred interview format (telephone or secure, university approved and encrypted video-conferencing software such as Microsoft Teams) will be arranged. To facilitate snowball sampling, interview participants will be asked if they could identify known healthcare professionals (physicians, nurses and pharmacists) who are directly involved in supporting patients undergoing immunotherapy, forward the project flyer to these individuals and ask them to contact the project researcher by e-mail or telephone if they are interested in taking part. Individuals who contact the researcher via this sampling method will be also screened using the inclusion/exclusion criteria documented in Table 2. All documents will be e-mailed and consent will be accepted via electronic completion and signature.

PLEASE INSERT TABLE 2 HERE

Table 2: Inclusion/exclusion criteria for healthcare professionals

Inclusion criteria	Exclusion criteria
• Are registered practitioners (nurses, doctors and pharmacists) with permanent or regular bank contracts • Have experience of working with people affected by cancer treated with immune checkpoint inhibitor immunotherapy • Are willing and able to give informed consent	• Are not registered practitioners, or do not have permanent or regular bank contracts • Do not have experience of working with people affected by cancer treated with immune checkpoint inhibitor immunotherapy

Data collection

All data will be generated through in-depth, semi-structured, digitally, audio-recorded interviews. In view of COVID-19 physical distancing requirements, to prevent infection and following Health Research Authority guidance [52], interviews will be conducted either by telephone or secure video conferencing software (only the audio of video interviews will be recorded in order to protect participant anonymity). Semi-structured interviews allow core topics to be raised for discussion, while leaving space and scope for the identification and exploration of unforeseen issues that may emerge [55,56]. All interviews will take place in accordance with participants' preferences. It is anticipated that interviews will last up to an hour, although they could be longer.

Before commencing interviews, information about the study will be confirmed. Participants will have an opportunity to ask questions and will be informed of their right to withdraw at any time without reason or prejudice. If a companion is present during an interview, this will be respected and facilitated, as this may be advantageous in terms of support. Companions' informed consent will be sought and obtained electronically.

Interviews will be conducted by trained researchers [author initials redacted] and will commence with open questions to develop rapport. Loose interview guides (please see supplementary file) for patients and healthcare professionals, developed by the research team, derived from the literature review, practice and personal knowledge and scrutinised by the project management team's PPI member, will act as aide memoires. The interview guides will use mainly open-ended questions [57]. To elicit further responses, enrich the description and illuminate experiences, prompts will be made and clarifications sought when necessary. Prior to closing the interview, participants will be given the opportunity to reflect and add any additional relevant information to ensure important aspects not included in the interview guide are addressed.

Data analysis

Data collection and analysis will occur simultaneously. All interviews will be fully transcribed verbatim by a university-approved external transcriber. Files will be securely sent via the Cardiff University *FastFile* application. Transcribed data will be analysed using the framework for reflexive thematic analysis devised by Braun and Clarke [49,50]. This inductive, systematic, analytic approach involves searching across the dataset for repeated patterns of meaning: data familiarisation, noting early analytical observations; generating initial codes, collating codes and relevant data extracts; identifying meaningful relationships between initial codes and developing themes; refining, defining and naming themes and sub-themes in relation to the research aim and objectives. This approach to thematic analysis was chosen to enhance the transparency and detail of the analysis and to best ensure that key patterns and areas of participants' experiences are captured, relative to the study research questions. The approach also provides researchers with flexibility regarding theoretical approaches that can be applied to the data. Table 3 documents how Braun and Clarke's [49,50] six-step approach to thematic analysis will be applied in this study:

INSERT 3 TABLE HERE

Table 3: Application of Braun and Clarke [49,50] six-step approach to thematic analysis

Step	Description	Example of application of TA step
1	**Familiarising yourself with the data**: Transcribing data, reading and re-reading the data, noting down initial ideas	Each interview will be transcribed, anonymised and subsequently read by all members of the core research team (initials redacted). During this process initial notes regarding how the data might address the various study research questions will be made. At this stage, members of the core research team will meet to discuss initial impressions of the data.
2	**Generating initial codes:** Coding interesting features of the data in a systematic fashion	The project researcher will generate initial codes based on the aforementioned discussions. The project researcher will draft an initial coding tree with examples

	across the entire data set, collating data relevant to each code	of categories and codes. A recoding process will subsequently be undertaken, to ensure relevant data can be collated effectively and concisely.
3	**Searching for themes:** Collating codes into potential themes, gathering all data relevant to each potential theme	Categories and codes developed in the previous step will be discussed in meetings between members of the core research team. Codes will be altered and streamlined, and collated into potential themes.
4	**Reviewing themes:** Checking if the themes work in relation to the coded extracts and the entire data set, generating a thematic 'map' of the analysis	A comprehensive coding framework will be developed, with clear themes generated from the previous stage. These themes will be reviewed in discussions with the core research team. A thematic map will centre around the coding framework and illustrative data extracts.
5	**Defining and naming themes:** Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells, generating clear definitions and names for each theme.	Key themes central to the analysis will be defined and named.
6	**Producing the report:** The final opportunity for analysis. Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back the analysis to the research question and literature, producing a scholarly report of the analysis	Chapters will be constructed around the key themes developed in Step 5. Data extracts will be chosen carefully to support claims made.

Within a constructionist, reflexive approach to thematic analysis [50] the process of generating codes, categories and themes is influenced by the researcher. Indeed, the development and

identification of themes is based on the researchers' interpretations and positionality (i.e. experience, background, characteristics and assumptions). It is therefore important within this analytic approach to outline the process of theme generation. Furthermore, to ensure rigour, all core research team members [initials redacted for publication] will contribute to data analysis to ensure consistency in interpretation and a reflective research diary detailing the researcher's role and impact on the study will be maintained.

Patient and public involvement

Following NIHR guidance for involving people in research [58,59], this study has been developed through consultation and active collaboration with members of Swansea University Patient Experience and Evaluation in Research (PEER) and Cardiff University Patient and Public Involvement (PPI) group, who have been personally affected by cancer. Initially, members of the PEER group provided constructive feedback on the research idea and question, study population and design. PEER group representation on the project management team ensures continuing, active patient and public involvement at all stages of the research, including dissemination. Examples to date include offering feedback on the research protocol and ethics applications, acceptability of participant information sheets and interview schedules and contributing to project team meetings. PPI membership of the project's advisory group will contribute to strategic decisions including disseminating findings and routes to impact.

Ethics and dissemination

The proposed research will be carried out in accordance with the UK Policy for Health and Social Care Research and Cardiff University Research Integrity and Governance Code of Practice (2018). The project was reviewed by the West Midlands and Black Country Research Ethics Committee in October 2019 and received a favourable opinion (REC ref: 19/WM/0299). The study is listed on the NIHR Clinical Research Network Central Portfolio Management System (study ID: 43946).

The dignity, rights, safety and wellbeing of participants will be the primary ethical considerations. Potential participants will be given sufficient time to read and consider study information and ask any questions. All participants who decide to participate will be asked to provide informed consent prior to taking part in the audio-recorded interview. Consent will be accepted via electronic completion and signature, and following Seymour [60], the researcher will use phrases such as '*would it be okay if I asked about . . .*' to reaffirm consent during the interview. The participant's willingness to continue will also be checked at regular intervals.

Data collected from participants will be stored securely at Cardiff University. Completed consent forms will be stored on the University's password protected secure server in a location which is only accessible to the Chief Investigator [author initials redacted] and project researcher [author initials redacted]. The interview audio recordings will be uploaded onto the password-protected secure server at Cardiff University. Only the core research team [author names redacted] will be able to access the recordings. Once interview transcripts have been checked against corresponding audio-recordings, all identifiable information will be redacted and pseudonyms ascribed to all participants. All data will be securely stored after this study in accordance with Cardiff University policies, the General Data Protection Regulation (GDPR) (2016/679) and the Data Protection Act 2018.

Participants may benefit from knowing that their experiences will be used to help inform service developments at individual and organisational levels and healthcare professional education, and thus potentially enhance the quality of person-centred care for people receiving cancer immunotherapy. The study findings may also facilitate knowledge transfer across different treatment sites, potentially benefiting wider patient groups. Knowledge transfer processes include outreach and collaboration, with the study team developing collaborations with cancer centres in order to enhance the practitioner-focused relevance of the educational and training recommendations arising from analysis of data.

While the research involves people affected by cancer, some of whom may have advanced disease, their participation in the study is unlikely to cause physical harm. However, there is an element of risk related to emotional distress. If this occurs, the researcher will stop recording immediately. Only if the participant is certain they would like to resume will the interviewer continue. After interviews, a 'debrief' space will mean that all participants will have the opportunity to talk to the researcher about the interview. For patient interviews, if any upsetting or unsettling feelings arose or are disclosed at this point, they will be signposted to local cancer support services. With permission, the person's cancer key worker [61] and consultant will be informed. Likewise, healthcare professional participants will be asked if they would like information about local NHS employee wellbeing support systems. Any signposting events will be logged in the study file.

Findings will be reported in relevant, peer-reviewed and professional journals using accepted reporting criteria such as COREQ-32 [62] to ensure transparency. A policy briefing highlighting key findings will be prepared and webinars facilitated to disseminate findings to participants. The findings will be presented at relevant local, national and international conferences and healthcare professional education meetings.

Discussion

There are a number of factors to consider relative to the study design. For instance, there are potential implications for the sample characteristic of using purposive and snowball sampling, as participating healthcare professionals are more likely to be self-selecting, engaged participants, and may even have more years of experience and seniority. However, it is feasible that this approach will ensure that the intended study population is recruited to produce data which will enable us to address the research questions. As snowball sampling will likely lead to professionals identifying colleagues and known networks, this will potentially lead to some degree of bias in terms of work

setting, level of experience. Patient participants will also likely to be affected by self-selection bias, even though they are to be identified and approached by clinicians. Self-selection bias in this instance might possibly be related to performance status, overall health and stage of disease, with patients who are generally more well and able to participate electing to participate in the interviews.

Differences in recruitment strategy will also potentially affect analysis of data. The healthcare professionals' population is feasibly more likely to represent a UK-wide perspective compared with patients, who are likely to be resident within travelling distance of the two oncology treatment centres, situated in Wales. The possible implications for the analysis are that findings from healthcare professionals are potentially more applicable to a UK-wide context. Experiences of immunotherapy treatment, the decision-making processes, associated treatment-related side effects are however likely to be translatable across regions within the UK. Within the analysis of data, the limitations of the variable recruitment strategies and resulting differences between population samples will be discussed.

The findings from this research will provide novel insights and in-depth, contextualised knowledge of cancer immunotherapy decision-making, the impact of treatments on people's everyday lives, their needs and concerns and how they feel they might best be prepared and supported during treatment and beyond. It will explore healthcare professionals' confidence and preparedness to provide safe, effective, proactive immunotherapy care and identify their support, education and training needs. Understanding people's experiences may ultimately assist in the co-design of appropriate, effective supportive interventions to optimise the delivery of safe, effective, person-centred immunotherapy care. Furthermore, study findings may be used to inform and support the co-production of educational materials related to cancer immunotherapy and associated supportive care for healthcare professionals.

Current status of the study

Data collection commenced at the end of May 2020 and is ongoing.

Data statement

Research data are not shared due to sensitivity of topic.

Affiliations, Contributors, Funding and Competing Interests

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Author contributions

The first draft of the manuscript was written by Stephen Jennings and Tessa Watts. Sally Anstey, Janet Bower, Alison Brewster, John Buckman, Deborah Fenlon and Deborah Fitzsimmons are co-applicants on the grant that funds this study. The study was conceived and designed by Tessa Watts, John Buckman and Janet Bower. John Buckman is a Patient and Public Involvement (PPI) representative who contributed to the study design. Every author contributed to the drafting of this manuscript.

Funding

This work was supported by Macmillan Cancer Support (FO = 7165318).

Competing Interests

The research team includes individuals from various organisations, including Cardiff University, Swansea University, Hywel Dda University Health Board and Swansea Bay University Health Board. Deborah Fenlon reports an honorarium from Roche.

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SUPPLEMENTARY FILE – INTERVIEW GUIDES: HEALTHCARE PROFESSIONALS AND PEOPLE AFFECTED BY CANCER

Appendix 1: Healthcare professionals' interview guide

Section 1: Background to role

- Please could you clarify your current role (all) and Agenda for Change grade (Nurses/Pharmacists only)?
- How long have you worked in your role?
- What was your formal educational preparation for the role – e.g. first degree/ higher degree?
- Have you been on a prescribing course and if so which one?
- How do you keep up to date with prescribing given how new immunotherapy is as a pathway?

Section 2: Understandings of immunotherapy

- To start, please could you tell me in your own words what your understanding of cancer immunotherapy treatment is and how it works?

Section 3: Supporting immunotherapy care

- What does your role in supporting cancer immunotherapy entail?
- Please could you tell me a bit about your experience of caring for/ supporting people being treated with cancer immunotherapy with immune checkpoint inhibitors?

Section 4: Information giving, support and patient expectations

- What do you think are patients' priorities and expectations of treatment?
- How do patients respond to support?
- How is information about immunotherapy treatment communicated to patients?
- Do you have training on how to help patients make decisions? Do you have training on how to explore patients' unmet needs?
- What psychological support is offered to patients?

Section 5: Delivery of effective care/support

- How do you define effective care/ support?

- How is treatment/support delivered out of hours?
- How do you support patients' self-management?
- Do professionals experience uncertainty in prescribing/delivering treatment and support for immunotherapy?

Section 6: Knowledge, skills and education

- What would you say has particularly prepared you for prescribing or supporting immunotherapy treatment/care?
- What knowledge and skills do healthcare professionals (doctors/nurses/pharmacists) need to provide safe and effective high-quality care and support for people being treated with cancer immunotherapy?
- What aspects of cancer immunotherapy would you like to know more about and why?
- How might your ongoing immunotherapy education and training needs be best addressed?
- What are the challenges for you of accessing education and training?
- Why is it important that healthcare professionals working in other care settings, for example, emergency admissions, general practice, primary care and acute hospital settings know about and understand cancer immunotherapy treatment regimes?
- What education is available to patients?
- How is knowledge disseminated across multi-professional teams?
- What are your thoughts on certification for immunotherapy?

Section 7: Final thoughts

- Overall, how would you describe your experience providing immunotherapy treatment to date?
- What has been the influence of COVID-19?
- Is there anything else you would like to add?

Appendix 2: People affected by cancer interview guide

Section 1: Life/illness history

1. To start, please could you tell me a little bit about your experiences living with cancer and your treatment for it?

Section 2: Understandings of immunotherapy treatment

2. Could you please tell me in your own words what your understanding of immunotherapy treatment is?

3. What is your understanding of the difference between chemotherapy and immunotherapy?

4. What did you know about immunotherapy before it was proposed as a treatment option? Did you research it?

Section 3: Communication and treatment decision-making processes

5. Could you tell me about how the decision to have immunotherapy was made?

6. How would you describe the quality of communication with your care team about the decision to have immunotherapy?

7. Can you think of anything that can be done to improve consultations about commencing immunotherapy treatment?

Section 4: Information about immunotherapy

8. What can you remember about the information you were given regarding immunotherapy?

9. Were you told about what immunotherapy treatment involved?

10. Did the information you have been given about immunotherapy meet your needs?

Section 5: Expectations and concerns about immunotherapy

11. What did you expect to happen on immunotherapy before you started treatment?

12. Did you have any concerns about immunotherapy? If so, what were they and how were these dealt with?

Section 6: Immunotherapy treatment experience

13. Can you tell me about your immunotherapy treatment experience?

14. What has your experience been like between each treatment cycle?

15. Have you experienced any side effects? If so, how have these been handled/addressed by your care team?

16. Have you experienced a financial impact from your treatment?

17. How would you describe the quality of care and support offered by healthcare professionals in your care team?

18. Have you required or wanted to access psychological or emotional support from your care team? If you're willing to share your experiences, please can you tell me a little bit about this?

19. What is your understanding of what you need to do to take care of yourself?

20. What advice would you give to patients just about to start immunotherapy treatment?

21. Overall, how would you describe your immunotherapy treatment experience to date?

Section 7: Final thoughts

22. Is there anything else you would like to add before we finish the interview?

23. Has COVID-19 had an impact on your treatment experience? If so, please could you share how.

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

Please note: the study has been submitted as a protocol paper, therefore many of the questions are not relevant due to the stage of project. These have been marked as 'N/A', however the research team are aware of the importance of submitting the checklist in full when reporting study results.

Domain 1: Research team and reflexivity

Personal Characteristics

1. **Interviewer/facilitator**: Which author/s conducted the interview or focus group?
SJ/SA/TW

2. **Credentials**: What were the researcher's credentials? E.g. PhD, MD
MA (SJ); PhD (SA); PhD (TW)

3. **Occupation**: What was their occupation at the time of the study?
Research Assistant (SJ); Senior Lecturer (SA;TW)

4. **Gender**: Was the researcher male or female?
Male (SJ); Female (SA;TW)

5. **Experience and training**: What experience or training did the researcher have?
Qualitative research via PhD programme and workplace based training/experience (SJ: in the process of submitting thesis; TW; SA)

Relationship with participants

6. **Relationship established**: Was a relationship established prior to study commencement?
No

7. **Participant knowledge of the interviewer**: What did the participants know about the researcher? e.g. personal goals, reasons for doing the research.
Job title, university affiliation, reasons for doing the research (documented on participant information sheet)

8. **Interviewer characteristics** What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic
N/A. Interviewer characteristics will be reported upon submission of findings papers, and will be based on the reflexive diary (see below).

Domain 2: study design

Theoretical framework

9. **Methodological orientation and Theory:** What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis
Reflexive thematic analysis (Braun and Clarke, 2019; 2006)

Participant selection

10. **Sampling**: How were participants selected? e.g. purposive, convenience, consecutive, snowball
Patients: Purposive sampling will be utilised to represent a range of socio-demographic (i.e. age, gender), cancer diagnoses (i.e. lung, melanoma, head and neck, renal) and treatment related variables (i.e. ICIs used as first and second line treatment). Healthcare professionals: combination of purposive and snowball.

11. **Method of approach:** How were participants approached? e.g. face-to-face, telephone, mail, email
Healthcare professionals were approached via social media (Twitter). Patient participants were initially approached by clinicians during routine consultations.

12. **Sample size**: How many participants were in the study?
Healthcare professionals (*n*=up to 15); Patients (*n*=up to 30).

13. **Non-participation**: How many people refused to participate or dropped out? Reasons?
None to date – non-participation will be reported in relevant findings papers at a later date.

Setting

14. **Setting of data collection:** Where was the data collected? e.g. home, clinic, workplace
Home (remote interviewing due to Covid-19 and physical distancing requirements)

15. **Presence of non-participants**:
Was anyone else present besides the participants and researchers?
Healthcare professionals: No; Patient participants: Potentially (companions will be invited to join the participant if the participant wishes)

16. **Description of sample**:
What are the important characteristics of the sample? e.g. demographic data, date
N/A

Data collection

17. **Interview guide**: Were questions, prompts, guides provided by the authors? Was it pilot tested?
Yes – SJ, TW, SA, AB and JBu. Interview guides were piloted twice.

18. **Repeat interviews** Were repeat interviews carried out? If yes, how many?
N/A

19. **Audio/visual recording:** Did the research use audio or visual recording to collect the data?
Interviews were/ will be audio recorded.

20. **Field notes**: Were field notes made during and/or after the interview or focus group?
Interviewers kept a reflective diary throughout the interview process to enhance researcher reflexivity and transparency.

21. **Duration**: What was the duration of the interviews or focus group?
Data collection with healthcare participants has commenced, with a mean duration of 54 minutes.

22. **Data saturation** Was data saturation discussed?
N/A. Data saturation will be discussed by the core research team (SJ, TW and SA)

23. **Transcripts returned**: Were transcripts returned to participants for comment and/or correction?
No, however participants will be given opportunity at the end of interviews to clarify responses.

Domain 3: analysis and findings

Data analysis

24. **Number of data coders**: How many data coders coded the data?
N/A. 3 data coders will code (core research team – SJ, TW and SA).

25. **Description of the coding tree**: Did authors provide a description of the coding tree?
N/A. A description of the coding tree will be presented upon publication of findings papers.

26. **Derivation of themes:** Were themes identified in advance or derived from the data?
Both. Data collection and analysis are/will be running concurrently. Key themes generated from initial analysis of data collected will/have influence(d) future interviews and the continual adaptation of interview schedules based on data collected and analysed.

27. **Software** What software, if applicable, was used to manage the data?
NVivo for Mac/Windows

28. **Participant checking** Did participants provide feedback on the findings?
Participants will be given the opportunity to provide feedback on study findings. Findings will be communicated to participants via a webinar with a Q&A section. Participants will be encouraged to stay in touch with core research team throughout the study and are encouraged to feedback on the study as a whole as well as findings.

Reporting

29. **Quotations presented** Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. participant number
N/A. Participant quotations will be presented to illustrate findings and each quotation will be given a unique identification number ascribed to individual participants.

30. **Data and findings consistent:** Was there consistency between the data presented and the findings?
N/A - protocol paper

31. **Clarity of major themes** Were major themes clearly presented in the findings?
N/A - protocol paper

32. **Clarity of minor themes** Is there a description of diverse cases or discussion of minor themes?
N/A - protocol paper