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Defining the trials nurses' role in operationalising a medicinal cannabis clinical trial

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ABSTRACT

Background: With increasing use of medicinal cannabis for symptom management, clinical trials nurses need to consider the various legal, social, ethical, and interdisciplinary care issues of implementing these clinical trials, especially in a palliative care population.
Aim: To define the trials nurses' role in operationalising a medicinal cannabis pharmacokinetic inpatient trial in an advanced cancer population.
Methods: A qualitative, descriptive design incorporating case study methodology was used. Data were collected from minuted meetings, field notes, telephone, and email discussions involving trials nurses at two palliative care sites. Data were integrated and synthesised to identify the key considerations required to operationalise the trial and define the trials nurses' role.
Findings: Three key considerations were identified: (i) Normalising the trial, (ii) Creating the environment to undertake the trial, and (iii) Managing the complexity. The trials nurses' role was explored through subthemes of these considerations including: their understanding of the purpose of the research and training in the protocol; organising inpatient resources, pharmacy requirements and managing the external scrutiny; participant recruitment, staffing requirements, safety, and supporting caregivers.
Discussion: This study emphasises the multifactorial role of the trials nurses in managing a complex palliative care trial, and the importance of their early involvement and recognition as the vital link between all parties.
Conclusion: Defining the trials nurses' role, within the confines of the protocol, the context of efficient nursing processes and ensuring a patient-centred approach enabled the operationalisation of a Phase I/II medicinal cannabis trial which will have global impact.

Summary of relevance

Problem

Little is known about the role of clinical trials nurses in operationalising a medicinal cannabis clinical trial in a palliative population.

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What is already known

People with palliative diagnoses need to be well supported to consider, consent and complete Phase I/II trials, which makes the trials nurses' role critical for enhancing scientific knowledge.

What this paper adds

This study demonstrates that executing a complex trial requires trials nurses to be at the forefront of the protocol implementation processes. Acknowledging their multifaceted role and link to all parties is crucial for the successful completion of a trial with international attention.

1. Introduction

Although the use of cannabis as a medicine dates to around 2700 BC, its acceptance in mainstream medicine has been restricted, largely due to concerns around the drug's psychoactive effects thus, making its possession illegal (Zuardi, 2006). Anecdotal evidence for broad symptom management has led to global lobbying for its approval, and a socio-political shift toward a more legitimate medicinal use, especially in palliative care. With the Australian Government acknowledging the lack of quality data relating to medicinal cannabis use in humans and the need for more clinical trials in this area (Australian Government Department of Health Therapeutic Goods Administration, 2018), this fostered the commitment of funding for a "Phase I/II dose ranging study of the pharmacokinetic dose response parameters, and feasibility of vaporised botanical cannabis flower bud in advanced cancer" clinical trial (ACTRN12616000516482) (Australian New Zealand Clinical Trials Registry, 2019). From the onset, this clinical trial presented several issues including: (i) a prohibited plant product; (ii) advanced cancer participant population; (iii) pharmacokinetic study with frequent blood sampling; (iv) conducting the trial within inpatient facilities and; (v) community stigma, especially regarding vaporisation.

Social, political, and legal/policy pressures surrounding the supply and handling of a restricted drug, within the scrutiny and high expectations of the public eye, adds to the macro methodological complexities of conducting medicinal cannabis clinical trials (Fig. 1). This poses greater demands on hospitals and staff at the meso level, particularly clinical trials nurses (hereafter trials nurses), to undertake these clinical trials with a palliative care population, whilst working within the jurisdiction of the regulatory authorities, capability of their sites and timeframes upheld by the funding bodies. Trials nurses working in palliative care require considerable knowledge, interpersonal and practical skills to manage the micro level, namely the patient's care and caregiver needs, whilst working with the investigator team to fulfil the obligations of the clinical trial (Wilkes, Jackson, Miranda, & Watson, 2012).

2. Literature review

Palliative care research is challenging to undertake and presents many practical and moral dilemmas. Managing the palliative participant's physical decline, other comorbidities, polypharmacy and limited life expectancy may restrict their capacity to be enrolled in and complete clinical trials (Eagar, Watters, Currow, Aoun, & Yates, 2010). Yet, many people with palliative diagnoses welcome the opportunity and indeed benefit from contribution to well-designed studies and trials, which are vital to building the evidence-base for improving care outcomes (White & Hardy, 2010).

Fundamental pharmacodynamic and pharmacokinetic analyses are critical for learning more about a drug's behaviour in the body and its effects on the body in any population. However, people with palliative diagnoses need to be well supported to consider, consent and complete these trials, which makes the trials nurses' role a critical success factor (Hosie et al., 2011; Wilkes et al., 2012). Although there are many studies reporting the results of early phase trials in the literature, there are few studies that outline the role of the trials' nurses. Previously, the trials nurses' role was examined in an industry-sponsored trial but no context was provided regarding the purpose of the research, drug, patient population, site selection, or challenges (Poston & Buescher, 2010). In particular, there is no study of the trials nurses' role in providing an inpatient trial of a highly vulnerable population using a highly controversial, unapproved drug. This is even more relevant for medicinal cannabis as most pharmacokinetic studies have been conducted in healthy participants (Abrams et al., 2007; Ahmed et al., 2014; Vandrey et al., 2017).

Hence, it was important to report the trial's implementation from a nursing perspective. Thus, the purpose of this study was to define the trials nurses' role in operationalising a botanical medicinal cannabis pharmacokinetic trial in an advanced cancer population.

3. Methods

3.1. Participants

Dedicated senior trials nurses (n = 5) (from an inpatient palliative care unit in a public metropolitan hospital (Site 1) and an inpatient cancer ward in a public, regional hospital (Site 2) in New South Wales (NSW), Australia) were invited to participate in weekly multidisciplinary trial management committee meetings. This committee consisted of research and clinical academic staff (with expertise in palliative care, clinical pharmacology, plant medicine, drug and addiction medicine, psychology, clinical trials) and project staff. Formal onsite meetings were undertaken throughout the year involving the trials nurses and ward nurses working in palliative care (n = 5-10) at each site.

3.2. Study design

Case study methodology was used because it allowed for the in-depth examination of real-life contemporary phenomenon (in this case the trial) through the integration of multiple sources of evidence which are not always quantifiable (Yin, 2009). A retrospective qualitative descriptive approach using multiple sources was employed to consolidate the case, the goal and the context in which they occurred (Taylor & Thomas-Gregory, 2015). This study is reported according to the *Reporting Standards for Organisational Case Studies* whereby the case is the trial and the organisation is the trials nurses (Rodgers et al., 2016). This study was reviewed by the human research ethics committee (HREC) overseeing the trial at the site and formal ethics approval was deemed unnecessary.

3.3. Data collection and analysis

Data were collected from August 2015 to March 2020 from weekly trials management committee teleconference meetings, monthly site teleconferences, onsite meetings, field notes, telephone and email discussions including the nurses involved in the trial from the two sites. These secured data sources provided an audit trail for the decision-making. Published local and national legal regulatory documents (Australian Government Department of Health Therapeutic Goods Administration, 2020; New South Wales Government Health, 2019) and pharmacy policy were referred to.

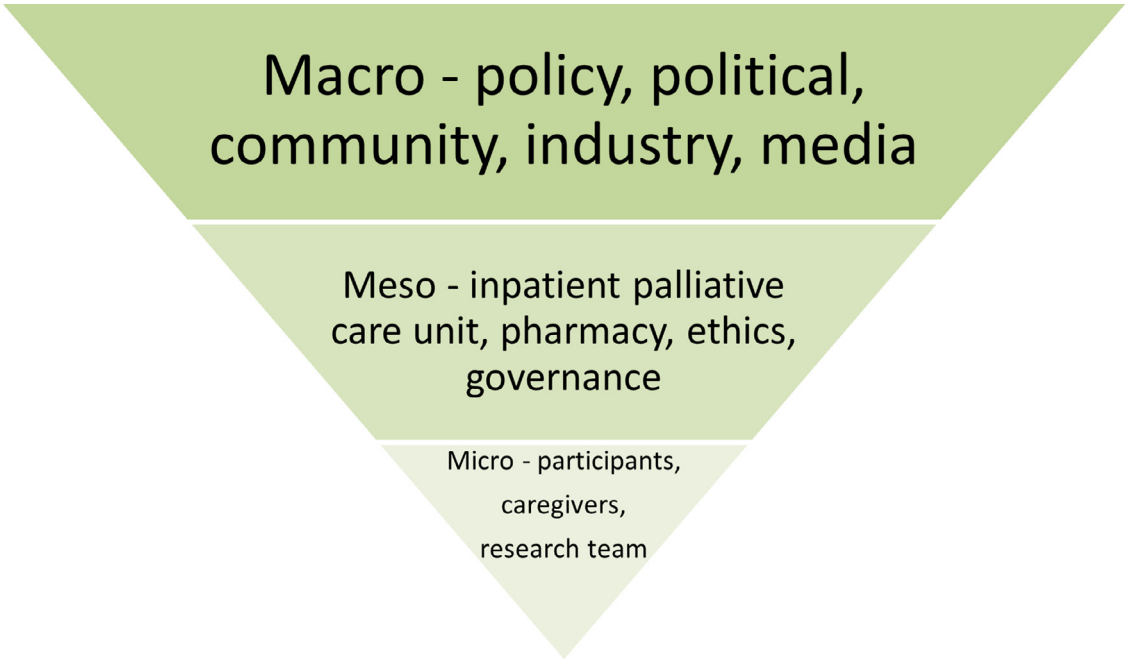

Fig. 1. Overview of the macro, meso and micro factors influencing the conduct of the medicinal cannabis trial.

Data were collated by the trials' coordinator (VR-N) and integrated and synthesised (by VR-N, JP, PW, FB, NB, DB) to identify the key considerations required to operationalise the trial. These considerations were analysed by VR-N and arranged into subthemes (with input from all authors) to define the trials nurses' role in operationalising the processes.

3.4. Rigour

The rigour of the data was addressed using Lincoln and Guba's trustworthiness criteria (Lincoln & Guba, 1986). Credibility was maintained through (i) documented notes (minuted meetings, emails etc.) which are securely kept for auditing purposes and (ii) sustained engagement with the nursing and investigator team throughout the trial. Author checking of the key considerations and subthemes contributed to the credibility of the findings. The "thick descriptive" narrative of this study outlines the considerations and principles that can be used to inform future clinical trials involving medicinal cannabis and/or palliative care populations. The processes and triangulation, which are documented for the external auditing as for any clinical trial, support dependability and confirmability. Trial investigators and the trials nurses who are involved in the running of the trial, have extensive clinical and/or research experience in palliative care. They have contributed to the writing of the article and have agreed to be listed as co-authors, thus confirming authenticity.

4. Findings

The data integration and synthesis revealed three key considerations from a trials nursing perspective required to operationalise the inpatient, pharmacokinetic trial with a palliative care population including: (i) Normalising the trial, (ii) Creating the environment to undertake the trial, and (iii) Managing the complexity. The subthemes aligned to the key considerations are shown in Fig. 2.

4.1. Normalising the trial

As the world's first medicinal cannabis trial using a vaporised botanical product involving a palliative population, the trials nurses had little prior experience to draw upon. Normalising the trial required trials nurses to understand that processes were like other clinical trials through:

4.1.1. Understanding the purpose of the research

The trials nurses offered a realistic perspective when reviewing the protocol for execution at their site. This was coupled with their knowledge of the patient population, patient care and site processes. Thus, understanding the purpose of the research provided the basis for the trial's implementation. Therefore, the trials nurses' role was to familiarise themselves with the required background knowledge and voice their questions early in the planning stages to the investigator team and consolidate this with the practical challenges that may be faced during the trial at their site. Specifically, this allowed trials nurses to articulate the research to other nursing staff to facilitate site readiness, and to potential participants to foster recruitment. Table 1 outlines the initial research questions posed by the trials nurses regarding the purpose of the research and their prior knowledge, the protocol sections that answered the questions, along with the sources of information accessed and the immediate onsite challenges.

4.1.2. Training in the protocol (product, vaporising, pharmacokinetic blood sampling)

Meticulous adherence to protocols is crucial for addressing the outcomes of any clinical trial. Fig. 3 summaries the trial and demonstrates the intensity of the daily trials nursing activities, which included 5 days of pharmacokinetic blood sampling over an 8-day, inpatient stay. Thus, the trials nurses' role was to familiarise themselves with the protocol's procedures and, subsequently, requested training in the protocol. Trials nurses attended a university's clinical simulation room fitted out as a typical hospital ward to examine the timing of the protocol requirements in practice. In addition, yearly refresher training at the sites (organised and run by the chief investigator, trial coordinator, national project officer and senior trials nurses) trained existing and new nurses in the protocol.

Several aspects of the trial that were new to the trials nurses was the drug form and vaporisation device. The vaporiser had

Fig. 2. Three key considerations (Normalising the trial, Creating the environment to undertake the trial, and Managing the complexity) and subthemes to address the operationalisation of the medicinal cannabis pharmacokinetic clinical trial in a palliative care population.

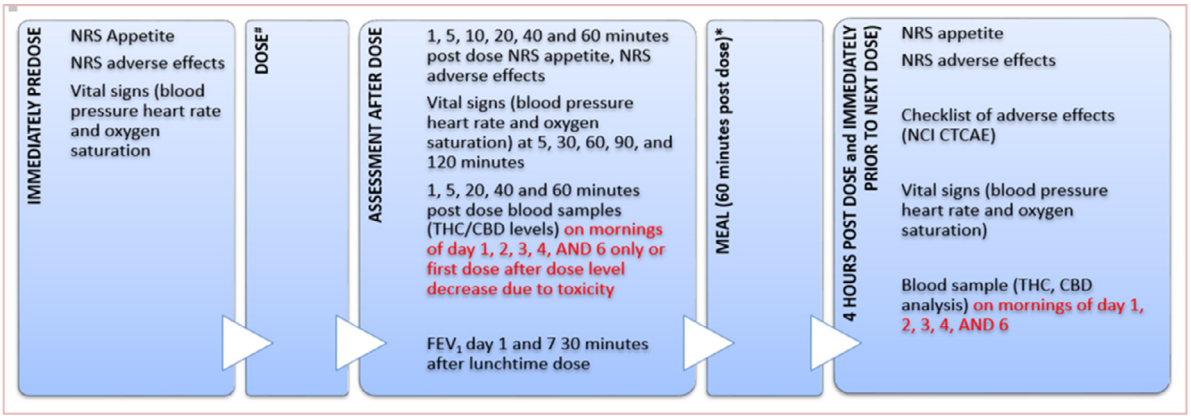

Fig. 3. Summarised Phase I/II clinical trial design[2]. FEV_1 = Forced expiratory volume in 1 second; NRS = Numerical Rating Scale; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; THC = Δ-9-Tetrahydrocannabinol; CBD = Cannabinoid.

never been used in this population and background information was limited. The trials nurses' role was to understand the workings of the device and to educate the participants on how to use the vaporiser and administer the drug, assess the safety and practicality of delivery, whilst troubleshooting. With the guidance of the trial coordinator and the vaporiser supplier, the trials nurses created a step-by-step inhalation procedure for the participant.

Their role extended to taking frequent time-specific blood samples to track the pharmacokinetics of the drug in this population, complete staff and patient-reported assessments at specified times, whilst simultaneously caring for the palliative participant and their family. To consolidate the procedures, the trials nurses from both sites drew up a "daily activity" sheet for the blood sampling, patient-reported outcomes, vital signs and meal timings.

One major concern of the trials nurses were reduced venous access in this population and the possibility of bruising and infections. The trials nurses sought the assistance of the oncology clinical nurse educator and accreditations were updated for venous access and sampling. Managing the intensity of the 5 days of blood sampling required the trials nurses to discuss with the participant their preferred venous access that would best meet their needs and limit their distress. After completing the first few participants, peripherally inserted central catheters and portacaths were preferred to venous cannulation as they proved to be a more reliable method for collecting multiple samples of blood in the tight time frame.

4.2. Creating the environment to undertake the trial

It was vital that the sites had a well-equipped and supportive infrastructure, practical experience in and a collaborative environment for running trials and some anonymity due to the nature of

Table 1
Initial research questions posed by the trials nurses to the investigator team (knowledge described as some, limited and none), sources of information accessed and immediate trial challenges.

Question (knowledge)	Protocol response	Source(s)	Challenges
What is the issue?	It is known that up to 90% of advanced cancer sufferers are affected by anorexia, affecting quality of life and mortality rates.	Protocol; cancer-anorexia literature	Finding advanced cancer patients with anorexia; number of inpatient participants at any given time
(Limited)			
What are the limitations of the drugs used for this symptom?	Current medications such as progestins and corticosteroids provide short-term improvements in appetite, weight or food enjoyment and are limited by side effects.	Protocol; cancer-anorexia literature	Population may be currently using these drugs thus, recruitment may be difficult
(Some)			
Why are we doing the research?	To explore whether medicinal cannabis will provide symptom relief to advanced cancer sufferers experiencing anorexia.	Protocol	Stigma and media attention around drug may affect recruitment
(None)			
What is the drug used in the study?	Plant product: dried cannabis female flower buds of the *Cannabis sativa* strain.	Investigator brochure, product website	Never used plant material in a clinical trial; how would it be administered
(None)[a]			
What is the main component(s)?	Delta-9-tetrahydrocannabinol (Δ-9-THC), the main psychoactive component of cannabis, essential oils.	Protocol; analytical literature	Safety of participant/staff/other patients
(Limited to none)			
What is the mechanism of action?	Effects on appetite through the cannabinoid receptors in the brain.	Protocol; pharmacology literature	Safety of participant
(Limited to none)			
Why are we doing a clinical trial?	- Synthetic formulation of Δ-9-THC (dronabinol) approved overseas for anorexia in HIV-AIDS.	Clinical trials' literature	Sample size, frailty of the population, dosages, timing, outcome measures; inclusion/exclusion criteria;
(Some)	- Results of Phase III trials in anorexia remain inconclusive.		
Why an inpatient, pharmacokinetic study?	-Limited early phase (pharmacokinetic) studies of vaporised cannabis in the advanced cancer population.	Protocol	Intensity of the pharmacokinetic schedule; inpatient resources; staffing requirements; family/carer concerns; access to other health care services
(Limited to none)	- To understand dosing and blood quantities of the compounds and correlate to outcome measures.		
What is the delivery mechanism?	Commercially-available vaporiser	Device information, emails from the supplier relayed to the trials nurses	Not registered as a medical device; assembling; instructing patient to use correctly; practicality; product support
(None)			
Why vaporisation?	Vaporisation provides a direct pathway to the blood stream, bypassing liver metabolism. Smoking is not ideal due to many carcinogenic by-products.	Protocol; literature	No experience in clinical trials involving vaporisation; safety of participants, staff, other patients
(None)			
How will the drug be packed?	Study intervention will be pre-packed and labelled into weighed aliquots in tamper proof packaging	Protocol; product information	Loading drug into the vaporiser; pharmacy procedures for controlled drug.
(Some)			

the study drug as this would drive the successful completion of the trial. Thus, site selection for the trial was driven by the presence of an engaged and supportive hospital executive, and experienced trials nurses and clinical team. In particular, the trials nurses' role was to:

4.2.1. Organise in-patient resources

Once site-specific approval was granted, the trials nurses' role was to organise in-patient resources, including bed availability, blood sampling equipment and ongoing support of the participant.

At Site 1, the trials nurses discussed the in-patient requirements of the trial with the nurse unit manager (NUM), recognising that a single room would not be adequate to host the participant and two or more nurses if required. Subsequent negotiations resulted in a two-bedded room being made available for the trial, depending on ward activity levels on the scheduled commencement dates.

Site 2 planned to admit participants into a standalone palliative care unit; however, this was not feasible due to the blood sampling requirements. Discussions undertaken by the trials nurses with the hospital management resulted in the participant admitted to a single room on the acute oncology ward.

Trials nurses were fully aware of their onsite capacity which was influenced by acute bed requirements. If there were patients with greater clinical need, the trial would be postponed. This made coordination and management of the admission process challenging, and the trials nurses decided that one participant would be on the trial at any one time. Trials nurses allocated a 2-week timeframe between participants to enter the data and prepare for the next participant.

Blood sampling equipment (blood collection tubes, saline, safe-sharp needles, syringes, gauzes, swabs, portable cooler and test request form) were checked by the trials nurses a week before participant admission. Trials nurses transported blood collections to pathology twice daily for immediate spinning, aliquoting of plasma, and storage.

Another important role of the trials nurses was ensuring ongoing communication between other HPs (physiotherapists and dietitians) who supported the participant's care. To adhere to the protocol's timelines, trials nurses confirmed the ordering and delivery

time of the meals with hospital catering. The trials nurses organised external food purchases to suit the needs and requests of the participant (e.g., vegetarian, gluten-free, snacks etc.).

4.2.2. Organise pharmacy procedures

During trial planning, the cannabis classification changed from a Schedule 9 (prohibited substance), to a Schedule 8 (S8 - controlled drug) product (Australian Government Department of Health Therapeutic Goods Administration, 2020; New South Wales Government Health, 2019) which required trials nurses' adherence to the correct storage, handling and disposal of the drug at the pharmacy and on the ward. The trials nurses' role was to notify the trials pharmacy staff of the participant's pending admission date so that the drug was ready to be dispensed. Trials nurses collected the drug (which was dispensed for up to 3 days at a time and stored in the locked drug cupboard on the ward at room temperature) and returned the cannabis remnants and unused product to the pharmacy.

4.2.3. Manage the external scrutiny

As the drug was the focus of political, community and media interest, the trial was vulnerable to social media breaches. With much misinformation regarding medicinal cannabis in the media and community, the trials nurses' role was to discuss the participant's expectations on the trial, with the focus remaining on clinical and trial-related issues. Trials nurses asked participants (and their families) not to post themselves on social media platforms whilst on the trial.

4.3. Managing the complexities

In clinical trials with an advanced cancer population, the trials nurses' role is to find the balance between the complexities of care and trial requirements. This was explored through:

4.3.1. Participant recruitment

The trials nurses' role was to implement the recruitment strategy at each site. The recruitment criteria specified people with advanced cancer and poor appetite, no mental illness with good respiratory function required for inhalation, who were not currently using cannabis and were agreeable to an 8-day hospital stay to participate in the trial. Trials nurses engaged the support of the local cancer charity to present the trial at their group meetings. Both sites had recruitment pools comprising inpatient and community-based palliative care and oncology units. Trials nurses regularly visited oncology waiting rooms and placed recruitment cards to promote the study. Trials nurses received referrals from oncology departments, community palliative care team and allied health. If an individual met the initial screening criteria (done by the site investigator), they were given a participant information sheet, time to consider participating in the trial and to discuss with their caregivers. Trials nurses followed up referrals via the telephone which helped to gauge interest for participation. Participants were invited to attend a hospital clinic visit with caregivers so that they could meet with the trials team to discuss the trial and undertake the required eligibility assessment. If needed, trials nurses organised an interpreter a week prior to the meeting to ensure that informed consent was possible for all. If the prospective participant met the inclusion criteria, the trials nurse would organise consent form signing with the participant and site investigator. The trials nurse would then coordinate an admission date with the NUM. For every 14 participants screened, one would be enrolled onto the trial.

4.3.2. Staffing requirements

The simulation training determined that three nurses would be required during the day for blood sampling days and two nurses for non-blood sampling days. On the weekdays, Site 1 had two trials nurses working 8 hours and one ward nurse, who was trained in the trial, working 12 hours. On the weekends, one nurse worked 8 hours and one nurse worked 12 hours. Ward nurses covered the evening shift (7 pm onwards) and ensured one evening assessment was completed by the participant and monitoring overnight. Site 2 worked around three 8-hour shifts. This ensured adequate nursing coverage for the participant during the trial. Trials nurses would file a request to the NUM to roster ward nurses (trained in the trial) over the participant's admission period. Hence, trial staffing included clinical nurses from the inpatient facility seconded to work on the trial with training, and the units dedicated clinical trials nurses working in partnership. Negotiations with the NUM and casual nursing pool resulted in recruiting, via expressions of interest, from the existing inpatient unit staff, to fill in for the trial outside the trials nurses' existing hours. At Site 1, seven expressions of interest were received, providing ample staff to draw from, with the inpatient unit staff to be backfilled with nurses from the existing casual pool. At Site 2, six expressions of interest were received initially, with three staff already working full-time, which posed problems with rostering. An expression of interest recruited seven additional staff.

Another important role for the trials nurses was to minimise overtime/time in lieu so that trial costs were within budget. Trials nurses and the NUM at both sites considered several options, including employing staff from the hospital's casual pool, recruiting from existing permanent ward staff or employing specialised pharmacokinetics-trained staff from a nursing agency. As the trial continued, more nurses were regularly trained in the protocol due to staff turnover. Trials nurses were required to have updated International Conference on Harmonisation Good Clinical Practice (ICH GCP) training to work on the trial.

For each participant, the trials nurses entered the staff and patient-reported questionnaires into the research management system for processing and organised the trial documents for monitoring. Trials nurses also presented the trial at inhouse and local forums to educate other HPs.

4.3.3. Safety of participants, staff, and other inpatients

In Phase I trials, drug and/or device safety is the primary outcome. However, the added risk of staff and other patients' second-hand exposure to cannabis vapour was unknown. Trials nurses coordinated the participant's admission to a separate room. Trials nurses reassured the participant that they were being observed during the inhalation process (through either a window on the door (Site 1) or closed-circuit television monitoring from the nursing station (Site 2)).

4.3.4. Supporting caregivers

Trials nurses included the caregivers in all stages of the trial process at the site and their role was to explain difficult trial concepts (organising an interpreter service to facilitate communication if required) and clarify what they can expect to happen to their loved one and reassurance that the participant would be well cared for and symptoms/side effects managed, access to a multidisciplinary team to support the ongoing participant's care and how they could help with the trial, e.g., getting their loved one to appointments, ideal times to visit, participating in an interview.

5. Discussion

This study provided an in-depth examination of the trials nurses' role in operationalising an early phase, pharmacokinetic medicinal cannabis clinical trial in a palliative care population. There are no studies that explore their roles in detail, especially within the context of a trial with complex legal, ethical, social and

interdisciplinary care considerations. The three key considerations that emerged from this case study included: (i) Normalising the trial, (ii) Creating the environment to undertake the trial, and (iii) Managing the complexity.

This study revealed the multifaceted roles undertaken by the trials nurses in managing the trial, and the researcher, administrator and clinician capabilities required from them (Green, 2011; Kunhunny & Salmon, 2017; McEvoy, Cannon, & MacDermott, 1991; Poston & Buescher, 2010; Rath, Hitchcock, Oakley, & Graham, 2003). This was explored through subthemes which incorporated their understanding of the purpose of the research and training in the protocol; organising inpatient resources, pharmacy requirements and managing the external scrutiny; and navigating the complexities of participant recruitment, staffing requirements, safety and supporting caregivers.

Trials nurses are in a position to provide a unique perspective when marrying protocol requirements and site feasibility which is central for normalising the trial (Poston & Buescher, 2010). In one study investigating the trials nurses' role, protocol planning was regarded as an important activity. However, their involvement in protocol planning was lacking and this may ultimately influence care processes within the trial and trial outcomes (Catania et al., 2012). Our study revealed that involving trials nurses early in the development of the protocol and understanding the trial's purpose was not only vital for executing the procedures, but also to explain the protocol in terms that could be easily understood to potential participants to ascertain their interest and to also train other nursing staff (Chan et al., 2013).

A previous study uncovered the management challenges for the trials nurses, whereby nurses felt a lack of recognition or respect (Mueller & Mamo, 2002). Engaging them with the investigators at frequent meetings recognised them as an essential member of the research team (Berthelsen & Hølge-Hazelton, 2018). One study showed that recognising that nurses responsibility for undertaking a myriad of different roles in clinical trials is crucial to their successful completion (Nagel, Gender, & Bonner, 2010). Another study discussed the issues with training and the support that is required to meet the multiple demands of the role (Spilsbury et al., 2008). This clinical trial was particularly complex and recognised that the trials nurses needed early training in the protocol to administer the investigational product, undertake blood sampling and complete patient-reported questionnaires whilst managing challenges without delay, along with the usual standard of care and ensuring high-quality data (Hernon, Dalton, & Dowling, 2020). Unlike other trials, trials nurses were required to follow governmental legislation on medicinal cannabis which was central to the legitimacy of the trial.

An important role of the trials nurses is establishing the environment for the trial to transition from start to finish (Rath et al., 2003). In this trial, trials nurses were integral to the finite planning and implementation of the practicalities of the Phase I/II design at their respective sites and were the vital link between all parties. This is in agreement with Poston and Buescher (2010) which outlines the trials nurses link between principal investigator, participant, site, clinical staff, ethics and governance, ancillary departments such as pharmacy and sponsor requirements (Poston & Buescher, 2010). It is stipulated that Phase I investigators and palliative care clinicians need to work together to optimise care for the participant (Kapo & Casarett, 2002).

One aspect that is often questioned is the ethical considerations of a palliative care population (Dean & McClement, 2002). This is coupled with the challenge of recruiting people with palliative diagnoses to Phase I/II clinical trials due to the frailty of the population (health status changing rapidly), concomitant therapies and medications (possible increase in the side effects and interactions of the drug), infection, vein access (for pharmacokinetic studies) and stringency of eligibility. Trials nurses in this study were vigilant in approaching and screening participants that could complete the trial however, it was the participant's decision to decide whether they were well enough and willing to partake in the trial.

The limited time participants may have would make hospital stays less appealing especially for pharmacokinetic studies (Ling, Rees, & Hardy, 2000). However, a pharmacokinetic study of cannabis in a healthy population noted that, "*the in-patient setting permitted us to measure plasma THC concentration over time and to rigorously assess the primary and secondary outcome variables in a controlled clinical environment*" (Abrams et al., 2007). A review showed that low attrition rates were attributed to inpatient versus outpatient scenarios in palliative oncology clinical trials (Hui, Glitza, Chisholm, Yennu, & Bruera, 2013). Our study showed that the inpatient setting allowed trials nurses to successfully balance the clinical care of the participants whilst concurrently addressing the research needs of the trial and minimising associated risks. A recent study disclosed that nurse-led palliative care intervention supported participants' well-being in Phase I trials (Ferrell et al., 2021).

Another aspect that was revealed in this study that has not been discussed previously was how timing proved to be a crucial factor in recruitment to the trial: once the participant's preferred date was considered, immediate onsite planning by the trials' nurses included allocating staff rosters, bed and resources, drug availability and notifying the trials pharmacist of the participant's pending admission date. Moreover, the participant's health condition was delicate and could change at any time. If any of these processes/situations were not in sync, the participant could not enrol in the trial. This is another challenge for the trials nurses above and beyond the common difficulties associated with other trials. Their input early in the protocol refinement allowed solutions to be implemented as soon as problems arose.

As trials nurses were responsible for recruitment, they involved caregivers early in the process, enabling a sense of trust through ensuring consistency of information relayed, answering questions and addressing any concerns regarding the procedures. In a recent study, caregivers were shown to have an increased burden compared to the patient on a clinical trial and ongoing support would need to be addressed (Rezash et al., 2020). Another study has showed that caregivers involved in palliative care research reported positive experiences (Hudson, 2003). As an inpatient trial, this provided the caregiver with an opportunity for respite, and they were reassured by the trials nurses that their loved ones were well taken care of.

Thus, trials nurses with clinical, administrative and research skills are an asset to a health organisation to promote a safe, clinical environment (McCabe & Lawrence, 2007). Without these attributes, complex, inpatient trials would not have successful outcomes. Due to their involvement in the trial, ward nurses changed the culture of the palliative care ward to become less of a "gatekeeper" to palliative care studies, and some nurses have gone on to become trials nurses in palliative care.

6. Strengths and limitations

Trials nurses have the arduous task of combining holistic patient care with the demands of governance, management and protocol implementation of a clinical trial, coupled with risks and benefits, which makes this trial no different to any other study (Gibbs & Lowton, 2012). Good clinical practice is fundamental to all clinical trials, and trials nurses play a critical role in adhering to these guidelines. Furthermore, this study allowed the in-depth exploration of the processes and challenges posed to trials nurses when implementing an inpatient, pharmacokinetic clinical trial which is generalisable to other Phase I studies. Protocols,

staffing, participants and the nature of the drug and its availability affect all clinical trials, albeit some details may vary. However, this study provided unique insight into the trials nurses' role in operationalising a clinical trial encompassing a myriad of social, political and scientific attributes, especially with regards to an illicit drug in the form of plant material. Thus, trials examining oral, single pharmaceuticals in an outpatient setting may require different design and implementation processes, especially if there are no external scrutinies or restrictions. The limitations of this study include no quantitative data and that it was only possible to report data from the audit trail of secured notes.

7. Conclusion

Defining the trials nurses' role, within the confines of the protocol, the context of efficient nursing processes and ensuring a patient-centred approach, is vital for operationalising an inpatient Phase I/II botanical medicinal cannabis pharmacokinetic trial in an advanced cancer population. Trials nurses' early involvement and collaboration with nursing management, hospital executive, supporting departments and investigators is integral for examining the quality, safety and efficacy of medicinal cannabis in the palliative care setting and the drug's future world translation into policy and clinical practice. Future clinical trials should address and acknowledge the trials nurses' role which will provide insight into the underlying logistics of conducting clinical trials in an advanced cancer population.

Author contributions

Valentina Razmovski-Naumovski: Conceptualisation, Formal analysis, Investigation, Writing – Original Draft, Writing – Review and Editing, Project administration; Penny West: Resources, Writing – Original Draft, Project administration; Frances Bellemore: Resources, Writing – Original Draft, Writing – Review and Editing, Project administration; Naomi Byfieldt: Resources, Writing – Original Draft, Project administration; Douglas Bellamy: Resources, Writing – Original Draft, Writing – Review and Editing, Project administration; Richard Chye: Resources, Writing – Review and Editing, Supervision, Project administration, Funding acquisition; Katherine Clark: Resources, Writing – Review and Editing, Supervision, Project administration, Funding acquisition; Jennifer H. Martin: Writing – Review and Editing, Funding acquisition; Belinda Fazekas: Writing – Review and Editing; Jane Phillips: Methodology, Writing – Review and Editing, Funding acquisition; Meera Agar: Conceptualisation, Writing – Review and Editing, Supervision, Project administration, Funding acquisition.

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Ethical statement

This study was reviewed on the 8 May 2020 by the St Vincent's Hospital Research Office overseeing the trial protocol at the site and, as there is no patient data, no secondary use of data, no testing of protocol/equipment and no targeting of minority groups, formal ethics committee approval was deemed unnecessary. The trials nurses involved in the running of the trial have contributed to the writing of the article and have agreed to be listed as co-authors.

Conflict of interest

None.

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