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Rogers, SN, Lowe, D, Highet, V et al. (4 more authors) (2022) Patient characteristics and refusal to participate in a head and neck cancer intervention trial: experience of two tertiary UK head and neck cancer centres. Annals of The Royal College of Surgeons of England, 104 (2). pp. 121-124. ISSN 0035-8843

https://doi.org/10.1308/rcsann.2021.0166

Patient characteristics and refusal to participate in a head and neck cancer intervention trial – Experience of two tertiary UK head and neck cancer (HNC) centres.

Rogers SN, Lowe D, Highet V, Dukanovic G, Lowies C, Thomas S and Kanatas A

Professor Simon N Rogers, Faculty of Health and Social Care, Edge Hill University, Ormskirk, L39 4QP and Liverpool Head and Neck Centre, Liverpool University Hospital Aintree, Liverpool, UK
simonn.rogers@aintree.nhs.uk ORCID: 0000-0002-5989-6142

Mr Derek Lowe, Medical Statistician, Director, Astraglobe Ltd, Congleton, Cheshire. astraglobeltd@btconnect.com

Ms Victoria Highet, Liverpool Head and Neck Centre, Liverpool University Hospital Aintree, Liverpool, UK

Ms Gillian Dukanovic Dental Translational Clinical Research Unit (DenTCRU), Leeds Dental Institute, University of Leeds, UK
g.dukanovic@leeds.ac.uk

Miss Cher Lowies, Liverpool Head and Neck Clinical Trials, Clinical Sciences Building, University Hospital Aintree, Liverpool, UK cher.lowies@gmail.com

Professor S Thomas University of Bristol, University Hospital Bristol and Weston NHS Trust, Bristol, UK

Professor Anastasios Kanatas, Leeds Teaching Hospitals and St James Institute of Oncology, Leeds Dental Institute and Leeds General Infirmary, Leeds, UK anastasios.kanatas@nhs.net

Corresponding author
Anastasios Kanatas, FRCS (OMFS), MD, SFHEA. Consultant Surgeon / Professor, Leeds Teaching Hospitals and St James Institute of Oncology, Leeds Dental Institute and Leeds General Infirmary, LS1 3EX.

Tel: 00447769946105 e-mail: anastasios.kanatas@nhs.net

Abstract

Randomised Clinical Trials are an essential component for robust clinical evaluation. They are expensive to deliver but can fail to deliver the required outcomes. The aim of this paper is to report details regarding trial recruitment in a head and neck Patient Concerns Inventory (PCI) intervention trial from two UK head and neck tertiary centres.

Method

Data was collected for a pragmatic cluster preference randomised control trial with 15 consultants recruiting patients treated with curative intent after a diagnosis of head and neck cancer (all sites, disease stages, treatments). Ethical approval was given to report on those non-recruited by the following characteristics: trial site, trail arm, age, gender, tumour site, overall stage, IMD quintile, timeframe.

Results

There were 368 patients approached who remained eligible and 22% (80) declined to participate**.** Logistic regression suggested that age group (p=0.008) and IMD quintile group (p=0.003) were independent predictors; refusal rate by age and IMD quintile.

Conclusions

Although recruitment to the trial was very good it raised the issue of lower recruitment in the more deprived older group and lower social economic strata. Innovative ways need to be explored in order to facilitate the 'hard to reach' group contributing and benefiting from clinical trials.

Keywords: Head and neck cancer recruitment; intervention; prompt list; health related quality of life; Patient Concerns Inventory; Randomised Clinical Trail

Introduction

Randomised controlled trials (RCT's) are an effective way to evaluate healthcare interventions and several involving head and neck cancer patients have been published. Many RCTs struggle to recruit to target and to time and result in underpowered studies of limited clinical value (1,2). Data relevant to recruitment issues in HNC is limited (3-7). Reasons explaining poor recruitment included methodological issues (6), logistical issues, poor recruiter training, clinicians not accepting the primary trial outcome, poor identification of eligible patients (6) and inappropriate design (3). Often patients do not provide a reason and a poor understanding will result in recruitment barriers affecting future trials. Head and neck cancer diagnosis and treatment often have detrimental effects on patients and carers. Concerns are often multiple and can be missed in busy clinics (8). The details of the treatment can be overwhelming during a difficult time for patients and support from clinical teams is essential. Although cancer research is important it may be seen as an 'unnecessary burden' to families. In centres with multiple available trials patients may be confused to identify what is more suitable for them. For some time (9) clinical teams have been aware of a strong association between survival and participation in interventional clinical studies. Despite this, there are many practical difficulties encountered that hinder patient participation in trials and attempts have been made to improve recruitment levels (10). Previous reports suggest that the main barrier to recruitment of head and neck patients is preference for one arm of the trial (3,5).

In this work we analysed case mix details of patients recruited to an interventional trial involving the Patient Concerns Inventory (PCI) (11) alongside details of all those patients approached for the trial and eligible at that time but who for one reason or another decided not to participate. The trial itself evaluated the effectiveness of using the PCI at routine outpatient clinics for one year after treatment, on health-related QOL (HRQOL). The aim of this current work is to report the overall refusal rate to the trial and to determine any patient characteristics that relate to this. In so doing it is hoped that conclusions can be drawn that can benefit those contemplating trials involving head and neck cancer patients.

Methods

The methods relating to this trial have been published in full (11). The study was a pragmatic cluster-controlled trial conducted at two UK Cancer Centres in Aintree and Leeds, with 15 consultants (clusters) randomised to 'using' or 'not using' an intervention incorporating the PCI prompt list at all their trial clinics. Individual patient randomisation was ruled out because of the likely sensitization of consultants to using the PCI, which could lead to carry over effects when seeing control group patients. Patients that satisfied the trial criteria were identified by the clinical team at the multidisciplinary team meeting (MDT). In the trial itself the baseline trial clinic was a median (IQR) of 194 (125-249) days after diagnosis, 103 (71-162) days after the end of treatment, and the time when patients finalised their consent before baseline varied according to patient circumstance. Patients were given written information about the trial and willing participants were asked to provide written consent when they next attended hospital. Patients consented to their clinical data being used and to completing research questionnaires before each post-treatment consultation, information from which could be used in their consultation. Fishers exact test was used to compare patient subgroups in regard to the percentage of eligible patients who refused to participate in the trial when approached. Logistic regression was performed with age and IMD to assess whether each variable predicted refusal to participate independent of the other. Statistical significance was taken as $p<0.05$. The patient subgroups used were as described in Table 2. Index of Multiple Deprivation (IMD 2019) ranks were derived from patient postcodes using publicly available data (12) for 32,844 small areas within England. The IMD 2019 measures relative deprivation, i.e. how deprived one area is compared with another and for this study IMD rank quintile categories ranging from the 20% of most deprived areas in England to the 20% least deprived were used. Additional ethical approval was sought and given to use case mix of non-participants: REC reference:16/NW/0465 IRAS project ID: 189554.

Results

Patients first thought to be eligible for the trial were discussed at MDT meetings between January 2017 and December 2018. During the trial recruitment phase, trial staff approached 265 patients at Aintree and 172 at Leeds. Many of these patients could not be considered for recruitment because they had become ineligible after they were approached at the MDT (Table 1). Reasons for being ineligible were patient related for 32: recurrence/new disease/palliation/death (23), no HNC (2), in another trial (2), memory issues (1), unknown (4). Other non-eligibility for 24 was related to site or consultant: site changes (17), hospital late in

entering trial patients (2), consultant request to exclude patient (5). There were 368 patients approached who remained eligible and 22% (80) declined to participate, 25% (59/237) at Aintree and 16% (21/131) at Leeds. Trial refusal rates by patient subgroups are shown in Table 2. There was a statistically significant difference in regard to patient age (p=0.02) by which the refusal rate was higher in older patients; 17% (38/225) if aged under 65 years and 29% (42/143) if aged 65 years and above. Patients living in more deprived neighbourhoods were also more likely to refuse to participate (p=0.003). The refusal rate was 31% for those living in the most deprived quintile of neighbourhoods, compared with 6% for those living in the most affluent quintile, and 15-18% for the intermediate quintiles. Logistic regression suggested that age group (p=0.008) and IMD quintile group (p=0.003) were independent predictors; refusal rate by age and IMD quintile is summarised in Table 3.

Discussion

Recruiting patients to trials is challenging. Head and neck research has moved forwards in the last 10 years with many published trials, data related to recruitment issues in HNC is still scarce. Trials often end up being underpowered with conclusions that don't withstand scrutiny. The main results from this cluster preference randomised controlled trial were recently published (13). Despite meticulous planning, expenses and effort this trial (13) was ultimately underpowered. Limitations of this work included the limited numbers of the centres involved, that may not be representative of all UK units, in terms of resources and manpower. There is limited data people who were eligible but not recruited and in particular why they declined to participate. This lack of data may occur because the clinical teams may overlook recruitment failure issues, at the study design stage.

The reasons for poor recruitment are several. This research is often undertaken in busy NHS clinics with several trials recruiting at the same time. Appropriate trained research nurses are not always available, and their numbers are limited due to years of underfunding. This trial involved Ear Nose and Throat and Oral and Maxillofacial consultants with clinics taking place simultaneously in different buildings. Staff availability between clinics and consultants, in order to try and talk to patients, is always difficult. One way to address those issues may be meticulous patient screening for eligible patients prior to the clinic. Although the trial recruitment was high 78% (13), the trial was still underpowered. Such a high recruitment rate is rare in clinical trials especially when considering the group of patients, their age, life-style,

socio-economic background, distance travelled and of course the inherited difficulties of the cancer journey. In our experience, recruitment to clinical trials will improve if the trial is integrated in clinical care and the outpatient clinics. The broad eligibility criterea for this trial (13) may have contributed to the relatively high recruitment rate and that patients were not individually randomised reducing the complexity of the study.

Logistically trials have changed over the years with the introduction of technology. However, patients are approached at a difficult time which can make the additional burden of participation in a trial challenging. Often they are eligible for several different trials an expectation that involvement would mean longer wait times /extra visits. The role of the trial team in recruitment is crucial . More patients refused to participate in this trial in the Liverpool centre where two sites shared recruitment whereas in Leeds they were recruited in the same building in shared specialty clinics. Fifteen clinicians were involved in this study. Each consultant developed their own method for the patient approach which related to patient numbers at the clinic. Some consultants introduced the research to the patient and then the research staff took over. In other clinics the research staff informed the consultant that patient was eligible and took the patient post diagnosis/appointment. Occasionally the research staff approached the patient independently and then informed the relevant consultant of their eligibility. Trial recruitment was different to many trials in that there was a time lag between MDT and baseline clinic, during which eligible patients could become ineligible, with approaches and consent obtained at different times post MDT depending on treatment circumstances. Due to this lag, we noticed that some patients with early-stage cancers thought that the trial wasn't for them, or they didn't need it. Patients with advanced stage disease were more difficult to track contact for recruitment as they were required to be seen multiple teams in order to begin their treatment. Cancer is a disease of the elderly and this is true in head and neck cancer yet this group of patients are underrepresented in clinical trials (14). We found there were higher refusal rates among people over the age of 65 years . This may be due to the current research infrastructure not easily accommodating the needs of older adults. For example, they may need carers, they may have parking concerns or have to fit the day around hospital transport arrangements. Many older adults have other uncommunicated and unaddressed aging-related conditions that are associated with morbidity and early mortality (15). Older adults have physical symptoms such as fatigue due to multiple comorbidities which may act as barriers to participation in trials and may be unfamiliar with technology used to collect the data.

Patient populations with historically lower financial resources are often underrepresented in cancer clinical trials whereas patients with higher socioeconomic status to take part in cancer clinical trials more readily (16). Deprivation was an issue in recruitment in this trial. This is particularly important as patients with head and neck cancer often come from more deprived backgrounds (ref). similar to other cancer sites. Their need should be addressed by ensuring transport and a convenient location and understanding the competing priorities of the low-income patients that we are looking to recruit.

From this work it is obvious that we need to increase participation of people with head and neck cancer in trials, especially those hard-to-reach groups who are older and more deprived. More research into enabling these peole to participate should be a priority. Innovative ways to support people to engage in trials may include increasing awareness through social media campaigns. Lessons learnt from this work may help clinical teams to recruit more patients into head and neck cancer-relating trials and by so doing to improve the generalisability of trial results.

Declaration of Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0215-36047). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

The authors wish express sincere gratitude to all the patients, trials team and consultants involved in this study.

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Table 1 Trial eligibility and participation in those approached

	Aintree	Leeds
No or no longer eligible - patient factors	15	17
No or no longer eligible – site factors	5	19
Eligible - declined	59	21
Eligible - participated	178	110
Lost to follow-up – not known if still eligible	8	5

Table 2 Refusal rate in eligible patients who were approached for the trial

		Patients	Refusal: %	Refusal: n	P Value**
	Total	368	22	80	
Trial group*	No PCI	183	19	35	0.26
	PCI	185	24	45	
Location	Aintree	237	25	59	0.05
	Leeds	131	16	21	
Age	<55	90	21	19	0.02
	55-64	135	14	19	
	65-74	97	31	30	
	≥75	46	26	12	
Gender	Male	254	22	56	0.89
	Female	114	21	24	
Tumour site	Oral cavity	163	18	29	0.17
	Oropharynx	116	22	25	
	Larynx	56	27	15	
	Other	33	33	11	
Overall stage	Early 0-2	154	19	30	0.44
	Advanced 3-4	214	23	50	
IMD 2019 quintile	1 most deprived	159	31	49	0.003
	2	48	17	8	
	3	60	18	11	
	4	65	15	10	
	5 Least deprived	36	6	2	
MDT	Jan-Jun 2017	59	22	13	0.97
	Jul-Dec 2017	104	20	21	
	Jan-Jun 2018	113	22	25	
	Jul-Dec 2018	92	23	21	

*For patients who refused, their intended trial group (PCI or no PCI) was derived from knowing who their consultants were.
** Fishers exact test

Table 3 Refusal rate by age and IMD 2019

IMD 2019 quintile(Q)	Age	Refusal: %	Refusal: n
Most deprived (Q1)	≥65	37	20/54
	<65	28	29/105
Intermediate (Q2-Q4)	≥65	28	20/72
	<65	9	9/101
Least deprived (Q5)	≥65	12	2/17
	<65	0	0/19