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Recruitment of patients into head and neck clinical trials: acceptability of studies to patients from perspective of the research team

Abstract

We reviewed longitudinal recruitment data to assess recruitment into head and neck cancer trials, and to identify factors that could influence this and affect their acceptability to patients. We retrieved data from the prospective computerised database (2009-2016) to measure acceptability to patients using the recruitment:screening ratio, and compared observational with interventional studies, single specialty (or site) with multispecialty (or site) studies, and "step-up" randomisation with "non-inferiority" randomisation designs. A total of 1283 patients were screened and 583 recruited. The recruitment:screening ratio for all the studies combined was 0.47 (486/1133). Studies that involved treatment by several specialties or at several sites had a significantly adverse impact on acceptability ($p = 0.01$). Recruitment into non-inferiority randomised controlled studies was lower than that into step-up randomised studies ($p = 0.06$). The complexity of the study's design did not compromise recruitment. Treatment across several specialties or several sites and perceived non-inferiority designs, reduced the acceptability of some trials.

Keywords: Clinical trials; Head and Neck research; Trial recruitment; Acceptability clinical trials; Trial design

Introduction

Recruitment into head and neck clinical trials can be impeded by insufficient resources or logistical support, and poor acceptability to patients. Known barriers include patients' preferences for the type of treatment, aversion to randomisation, lack of equipoise amongst clinicians, and the complexity of the trial's design and the information provided.[1,2] The Specialty Clinical Studies Group at the National Cancer Research Institute has identified key areas of need for research or clinical trials, but the success of a study depends on the ability of the local head and neck trials team to recruit suitable patients, ideally within the projected trajectory of accrual. The head and neck team at the Bradford Institute for Health Research with the Bradford Teaching Hospitals head and neck multidisciplinary team support the National Institute for Health Research (NIHR) portfolio of clinical trials.

The team supports a catchment of around 1.25 million residents of West Yorkshire, England, where about 150 patients each year are diagnosed with cancer of the head and neck. Recruitment into trials is reviewed annually (measured primarily by recruitment to projected targets) by the Yorkshire and Humber Clinical Research Network to secure continued funding of the head and neck trials team at the Bradford Institute for Health Research (0.1 whole-time equivalent head and neck surgeon and 1.5 whole-time equivalent clinical research nurses). Most studies on recruitment into clinical trials have been qualitative[1] or cross-sectional,[2] or consisted of the opinions of clinicians.[3,4]

We have therefore reviewed longitudinal recruitment data from a head and neck clinical trials team (since its inception) at a district teaching hospital to assess recruitment into head and neck clinical trials, and to identify factors that influence this and indicate their acceptability to patients.

Patients and methods

We used the computerised prospective database of the head and neck team at the Bradford Institute for Health Research to retrieve data on projected recruitment targets, the number of patients screened and recruited for each NIHR portfolio observational trial, and every interventional study from 1 April 2009 to 30 May 2016. Patients who agreed to donate to the ethical tissue bank at the University of Bradford were excluded.

The acceptability of a study to patients (or relative success of recruitment into a clinical trial) is measured by the recruitment:screening ratio. The complexity of a trial or the acceptability of a NIHR portfolio trial to patients is reflected by the recruitment:projected recruitment target ratio. We compared observational with interventional, single specialty (or site) with multispecialty (or site), and step-up randomisation with non-inferiority, trials. The objective of non-inferiority trials is to compare a new treatment with an active treatment to show that it is not clinically worse with regards to a specified endpoint. It is assumed that the comparator treatment has a significant clinical effect compared with placebo. We used the Student's *t* test to compare the mean of the ratios (GraphPad QuickCalcs 7, GraphPad Software Inc). Probabilities of less than 0.05 were considered significant.

Results

Sixteen observational and interventional studies were opened to recruitment by the head and neck multidisciplinary team at Bradford Teaching Hospitals during the study period (Table 1). Overall, 1283 eligible patients were screened by the clinical trials team, and 583

recruited. The recruitment:screening ratio for all the studies combined was 0.47 (486/1133). The recruitment:target ratio for all NIHR portfolio studies combined was 1.22 (486/397).

Non-NIHR portfolio studies or trials did not have specified recruitment targets, as they were not included in the Yorkshire and Humberside Clinical Research Network's annual projection for recruitment. The recruitment targets and the figures for screening and recruitment for all the studies have been summarised in Table 2. The mean recruitment:screening and recruitment:target ratios were lower for observational studies than for interventional studies, but not significantly so (Table 3A and B). Comparison of the mean recruitment:screening ratios showed a significant preference for studies that involved a single specialty or site compared with those that involved several, but differences in the mean recruitment:target ratios were not significant (Table 4A and B). When randomised controlled trials were assessed separately, the mean recruitment:screening ratios were significantly lower in non-inferiority studies than in those that randomised patients to standard treatment, or to step-up or additional treatment groups, for example, LIHNCS and NIMRAD (Table 5).

Discussion

To our knowledge, this study is one of the first to compare recruitment and screening data (over roughly eight years) from a district teaching hospital with a wide portfolio of clinical trials (most of which have been endorsed by the NIHR) to objectively assess the acceptability to patients of head and neck clinical trials. The trials team, which is led by the head and neck or maxillofacial surgical team, is strongly supported by members of the head and neck multidisciplinary team, particularly the visiting clinical oncologists.

Our main findings suggest that two factors have led to poorer recruitment into head and neck clinical trials in Bradford: the need to coordinate several specialties across different sites, and the use of randomised controlled trials with a non-inferiority design. In Bradford, patients with cancer of the head and neck have access to the full scope of cancer surgery with allied health support, and treatment involves a journey of 10 miles to Leeds for non-surgical treatment (primary and adjuvant). Whilst this distance is relatively small, the difficulties involved in the coordination of patients across different sites and organisations could have contributed to poorer recruitment. In relation to the HOPON and DAHANCA-21 trials, the duration and frequency of travel that the protocols in both require (the nearest hyperbaric treatment centre is 60 miles away in Hull) will probably have made participation less attractive. Some clinicians and patients could also have formed personal views on the value of the treatment, which would challenge the concept of equipoise.[5,6]

The difficulties involved in recruiting patients when the intention is to de-escalate treatment or the trial is perceived to be of a non-inferiority design, were reflected in the lower recruitment:screening ratios, although the difference was not significant. The publication of outcomes of several previous studies such as PARSPORT[7] and PET-NECK[8] would reassure patients that governance in the design of NIHR portfolio trials is robust and safe, and would highlight the fact that quality of life is as important as cure. The involvement of a patient-led support group might encourage newly-diagnosed patients to take part, but this could add to the burden of a new diagnosis, and would need to be approached carefully and tactfully. On several occasions patients have told the trials team that the anxiety and stress associated

with their diagnosis led them to decide not to participate. Although interventional and randomised controlled trials potentially require more effort from the team and engagement from patients, this has not significantly hindered recruitment.

The sustainability of the head and neck trials team depends on continued support and funding from the Yorkshire and Humber Clinical Research Network, and in the climate of austerity within the National Health Service, it is necessary to recruit enough patients to justify continued investment. The experience of the trials team in Bradford is exemplified by the recruitment:screening ratio, which indicates that one patient is recruited for every two that are screened. Projected research activity might have been more ambitious given the recruitment:target ratio of 1.22, but it highlights the degree of care and consideration taken in the governance and operation of the team. Projected recruitment, which is set arbitrarily by the local team at the beginning of each study, often falls short or is comfortably exceeded, with no implication that there are any concerns about performance. If a trial recruits its target number despite low screen:randomisation rates, it would be considered broadly successful.

Ideally, from the perspective of a trials team, a strategically planned portfolio that allows several active studies or trials with different designs and target groups (for example, a combination of prevention or early detection, HPV and non-HPV cancers, carcinomas with unknown primaries, and survival and management of late toxicity) to run concurrently, would ensure that trials were available to more patients. This would reduce competition for a specific group, and the diversity of studies in the portfolio would ensure that the head and neck trials team had plenty to do, which is vital for successful recruitment.

Nationally, the relative strength of support for trials from surgical (Oral and Maxillofacial Surgery or Otorhinolaryngology) and oncological (Clinical Oncology or Medical Oncology) teams could be relevant to studies such as PET-NECK and DeESCALaTE, in which many patients would initially be referred to surgeons. This can also reflect local compared with national recruitment, so issues about the generalisability of the findings in this study must be taken into consideration.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

Not applicable

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Table(s)

Table 1.

Brief description of observational and interventional trials opened to recruitment in Bradford Teaching Hospitals NHS Foundation Trust (1 April 2009 – 30 May 2016).

Trial	Subject	Current status	Design
Brush Biopsy	Dielectrophoretic analysis of brush biopsy specimen	Closed	Observational
DeteQT	Determination of QoL instrument most preferred by patients with thyroid cancer	Closed	Observational
Determin	Determination of quality of life instrument most preferred by head and neck patients	Closed	Observational
Head & Neck 5000	Clinical cohort study of 5000 patients with Head and Neck Cancer UK	Closed	Observational
PREDICTR	Molecular biomarkers: study in stratification of the management of individual patients with oropharyngeal cancer	Closed	Observational
PANDORA	Point-of-care Analysis by Non-invasive Dielectrophoresis for ORAl cancer diagnosis	Closed	Observational
TCUK	Thyroid cancer genetic investigation in the UK	Closed	Observational
EURECA	European research on electrochemotherapy in head and neck cancer	Closed	Interventional
DeESCALaTE	Determination of Epidermal growth factor receptor-inhibitor (cetuximab) versus Standard Chemotherapy (cisplatin) early And Late Toxicity Events in Human Papillomavirus-positive oropharyngeal squamous cell carcinoma	Open	Interventional
NIMRAD	A phase III trial to investigate the modified use of nimorazole hypoxia with intensity-modulated radiotherapy in head and neck cancer	Open	Interventional
LiDCO Rapid	LiDCo Rapid optimization in major head & neck cancer surgery	Closed	Interventional
LIHNCS	The effectiveness of Lugol's Iodine to assist excision of marginal dysplasia at resection of oral and oropharyngeal squamous carcinoma	Closed	Interventional
TITAN	Trial of induction TPF therapy in advanced head & neck cancer	Closed	Interventional
PET Neck	A multicentre randomised phase III trial comparing PET-CT-guided watch-and-wait policy compared with planned neck dissection for the management of locally advanced (N2/N3) nodal metastases in patients with head and neck squamous cancer	Closed	Interventional
LEONIDAS 2	Long-term Evaluation of the effectiveness Of a Novel Intraoral electrostimulator for the treatment of raDiotherapy-ASsociated dry mouth	Closed	Interventional
HOPON	Hyperbaric oxygen in prevention of mandibular osteonecrosis	Open	Interventional
DAHANCA 21	Hyperbaric oxygen treatment of mandibular osteonecrosis	Open	Interventional

Table 2.

Overall target, total number of eligible patients screened and recruited, recruitment: screening and recruitment:target ratios for observational and interventional head and neck trials. Bradford Institute for Health Research 1 April 2009 – 30 May 2016.

	Type of study	Total target	Total screened	Total recruited	Recruitment: screen ratio	Recruitment: target ratio
PET Neck	Interventional	15	26	1	0.04	0.07
DETEQT	Observational	30	50	4	0.08	0.13
DeESCALaTE	Interventional	25	118	17	0.14	0.68
TITAN	Interventional	4	19	4	0.21	1
Head & Neck 5000	Observational	50	382	85	0.22	1.7
HOPON	Interventional	14	30	7	0.23	0.5
LEONIDAS 2	Interventional	42	42	20	0.48	0.48
DAHANCA 21	Interventional	2	2	1	0.5	0.5
NIMRAD	Interventional	2	8	4	0.5	2
LIHNCS	Interventional	45	139	80	0.58	1.78
PREDICTR	Observational	50	62	43	0.69	0.86
Determin	Observational	43	108	89	0.82	2.07
PANDORA	Observational	35	64	54	0.84	1.54
TCUK	Observational	20	49	43	0.88	2.15
LiDCO Rapid	Interventional	*	95	87	0.92	*
Brush Biopsy	Observational	20	34	34	1	1.7
EURECA	Interventional	*	10	10	1	*
Total			1238	583		

*non-portfolio studies

Table 3A.

Comparison of recruitment:target ratios between observational and interventional studies (1 April 2009 – 30 May 2016).

Study	Recruitment:target ratio
Observational studies:	
Determin	2.07
TCUK	2.15
Brush Biopsy	1.7
DETEQT	0.13
Head & Neck 5000	1.7
PANDORA	1.54
PREDICTR	0.86
Mean (SD)	1.45 (0.72)
Interventional studies:	
HOPON	0.5
PET Neck	0.07
TITAN	1
LEONIDAS 2	0.48
LIHNCS	1.78
DeESCALaTE	0.68
DAHANCA 21	0.5
NIMRAD	2
Mean (SD)	0.875 (0.24)
Two-tailed *t* test: p = 0.136 (t = 1.5898; df = 13)	
Overall mean difference: 0.574	
95% CI: -0.2059 to 1.3534	

Table 3B.

Comparison of recruitment:screening ratios between observational and interventional studies (1 April 2009 – 30 May 2016).

Study	Recruitment:screening ratio
Observational studies:	
Determin	0.82
TCUK	0.88
Brush Biopsy	1
DETEQT	0.08
Head & Neck 5000	0.22
PANDORA	0.84
PREDICTR	0.69
Mean (SD)	0.65 (0.35)
Interventional studies:	
LiDCO Rapid	0.92
HOPON	0.23
PET Neck	0.04
TITAN	0.21
LEONIDAS 2	0.48
LIHNCS	0.58
DeESCALaTE	0.14
DAHANCA 21	0.5
NIMRAD	0.5
EURECA	1
Mean (SD)	0.46 (0.32)
Two-tailed *t* test: p = 0.273 (t = 1.1391; df = 15)	
Overall mean difference: 0.187	
95% CI: -0.1630 to 0.5373	

Table 4A.

Comparison of recruitment:target ratios between single-specialty (site) and multispecialty (multisite) studies (1 April 2009 – 30 May 2016).

Study	Recruitment:target ratio
Multispecialty/site:	
HOPON	0.5
PET Neck	0.07
TITAN	1
DeESCALaTE	0.68
DAHANCA 21	0.5
NIMRAD	2
Mean (SD)	0.79 (0.67)
Single specialty/site:	
Determin	2.07
TCUK	2.15
Brush Biopsy	1.7
DETEQT	0.13
LEONIDAS 2	0.48
LIHNCS	1.78
Head & Neck 5000	1.7
PANDORA	1.54
PREDICTR	0.86
Mean (SD)	1.38 (0.71)
Two-tailed *t* test: p = 0.134 (t = 1.5993; df = 13)	
Overall mean difference: 0.587	
95% CI: -1.3804 to 0.2060	

Table 4B.

Comparison of recruitment:screening ratios between single specialty (site) and multispecialty (multisite) studies (1 April 2009 – 30 May 2016).

Study	Recruitment: screening ratio
Multispecialty/site:	
HOPON	0.23
PET Neck	0.04
TITAN	0.21
DeESCALaTE	0.14
DAHANCA 21	0.5
NIMRAD	0.5
Mean (SD)	0.27 (0.19)
Single specialty/site:	
LiDCO Rapid	0.92
Determin	0.82
TCUK	0.88
Brush Biopsy	1
DETEQT	0.08
LEONIDAS 2	0.48
LIHNCS	0.58
Head & Neck 5000	0.22
PANDORA	0.84
PREDICTR	0.69
EURECA	1
Mean (SD)	0.68 (0.31)
Two-tailed *t* test: p = 0.01 (t = 2.937; df = 15)	
Overall mean difference: 0.413	
95% CI: -0.7123 to -0.1132	

Table 5.

Comparison of recruitment:screening ratio between step-up and non-inferiority randomised controlled trials (1 April 2009 – 30 May 2016).

Study	Recruitment: screening ratio
Step-up randomisation:	
LiDCO Rapid	0.92
HOPON	0.23
TITAN	0.21
LEONIDAS 2	0.48
LIHNCS	0.58
DAHANCA 21	0.5
NIMRAD	0.5
Mean (SD)	0.49 (0.24)
Non-inferior randomisation:	
PET Neck	0.04
DeESCALaTE	0.14
Mean (SD)	0.09 (0.07)
Two-tailed *t* test: p = 0.06 (t = 2.2415; df = 7) Overall mean difference: 0.399 95% CI: -0.0219 to 0.8190	