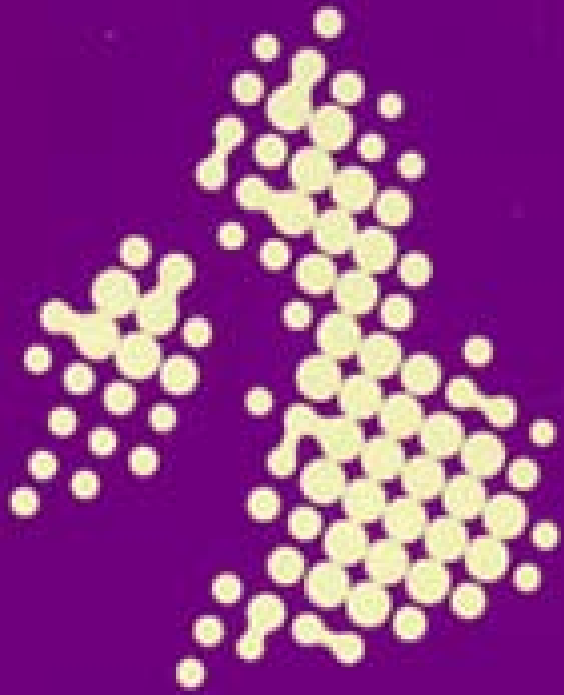


Practical difficulties with
undertaking prognostic research
in palliative care patients: lessons
from the PiPS study

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St George's University of London

What is PiPS?



NCRI

National
Cancer
Research
Institute

Palliative Care Clinical
Study Group

The Prognosis in
Palliative Care Study

CANCER RESEARCH UK





PCS
2006

Original Article

Elevated Serum Vitamin B12 Levels Associated With CRP as a Predictive Factor of Mortality in Palliative Care Cancer Patients: A Prospective Study Over Five Years

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Universitaires de Genève, Genève, Switzerland; Center for Bioethics (C.-H.R.), IRCM, University of
Montreal, Montreal, Canada; and Centre Intefacultaire de Gérontologie (C.-H.R.), University of
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Abstract

The relationship between vitamin B12 levels and survival was studied in a group of 161 terminally ill cancer patients who were recruited consecutively between 1988 and 1989. Their average age was 74.7 years. The length of survival decreased with the increase in serum vitamin B12 levels ($P = 0.0015$, Cox model). In multivariate analyses, C-reactive protein (CRP) was the most important prognostic factor in this population, and vitamin B12 provided information independent of CRP in predicting survival. These data indicate that an elevated serum vitamin B12 level is a predictive factor for mortality in patients with cancer, independent of CRP or other factors. Multiplying it by the CRP makes it possible to create a new, easy-to-use prognostic index, which can distinguish different levels of mortality risk at three months. J Pain Symptom Manage 2000;20:93–103. © U.S. Cancer Pain Relief Committee, 2000.

The B₁₂/CRP index as a simple prognostic indicator in patients with advanced cancer: a confirmatory study

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Received 15 December 2006; revised 16 March 2007; accepted 23 March 2007

Background: The vitamin B₁₂/C-reactive protein Index (BCI) has been proposed as a prognostic indicator in patients with advanced cancer. The purpose of this study was to confirm the utility of the BCI in palliative care patients.

Patients and methods: Patients with advanced cancer provided a blood specimen for analysis. Demographic and disease-related variables were recorded. Patients were followed up for at least 90 days or until death.

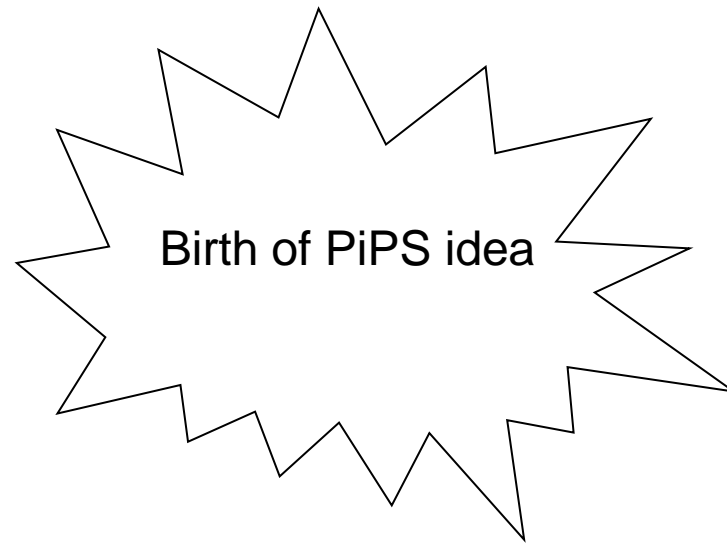
Results: Patients ($n = 329$) were divided into three groups according to their BCI score. Patients in group 3 (BCI >40 000; median survival 29 days) had a significantly ($P < 0.01$) worse survival than patients in group 2 (BCI 10 001–40 000; median survival 43 days) and patients in group 1 (BCI ≤10 000; median survival 71 days). However, patients in group 1 did not have a significantly better prognosis than those in group 2 ($P = 0.091$). The point estimates for 90-day mortality for each of the three risk groups were different from the figures previously reported during the development phase of the BCI (group 1, 58.9% versus 47.2%; group 2, 64.0 versus 72.5%; group 3, 78.9% versus 90.6%).

Conclusions: An elevated BCI (>40 000) predicts poor survival in patients with advanced cancer.

Key words: C-reactive protein, neoplasms, palliative care, prognosis, survival, vitamin B₁₂

First meeting of
PiPS collaborators

15th January 2004



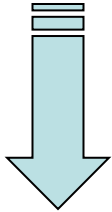
First meeting of
PiPS collaborators

15th January 2004



Second meeting of
PiPS collaborators

4th March 2004



Seventh meeting of
PiPS collaborators

21st October 2004

Methodological issues

- What is the primary aim?
 - Lesson learnt from BCI study
 - Need to compare against “gold standard”

PIPS

- Primary Aim
 - To develop a novel prognostic index that is significantly more accurate than doctor estimates of survival alone in palliative care patients

PIPS

- Subsidiary aims
 - To determine whether a repeated prognostic assessment is more accurate than a single assessment at predicting survival in advanced cancer patients.
 - To determine whether patient self-reported symptom severity provides better prognostic accuracy than observer-rated symptom severity in competent palliative care patients

Methodological issues

- What is a palliative care patient?
- How to define the inception cohort?
 - Need to reflect a real-world “palliative care” situation
 - Need for some homogeneity in sample

PIPS

- Population
 - Consecutive patients referred to participating palliative care services
- Inclusion criteria
 - Locally advanced or metastatic cancer in whom no further disease modifying treatment is planned
 - Adult
- Exclusion criteria
 - Patients currently receiving chemotherapy or radiotherapy
 - Patients who have undergone a change in anti-cancer therapy in the previous 4 weeks

Methodological issues

- How to ensure a consecutive series?
- Is consent necessary?
 - Even if study is purely observational?
 - What about incompetent patients?
 - Do the patients need to know the study is about prognosis?
- How to measure clinician estimates of survival?
 - Absolute number of days? weeks? months?
 - Probability of survival?

PIPS

- Process
 - Keep record of all patients referred to service
 - Identify eligible patients
 - Document reasons why patients not eligible, not approached or refused consent
 - If competent seek consent
 - If incompetent seek approval of relative/carer

Methodological issues

- Which variables to measure?
 - The same in all patients?
- How to assess chosen variables?
 - Interviews
 - Questionnaires
 - Scales

PIPS

- Procedures
 - In all patients collect **core data-set**, in competent patients collect **extended data-set**
 - Repeat procedures one week later

PIPS - core data-set

- Demographic details
- AMTS
- Disease-related variables
- Medication
- Blood results (if known)
- Pulse rate
- Oedema
- Ascites
- Performance status
- Observer-rated symptom checklist
- Observer-rated global health status
- Clinician estimate of survival
- Clinician descriptors

PiPS - additional data-set

- Blood tests
- Anthropometric details
- Patient-rated performance status
- Patient-rated symptom checklist
- Patient-rated global health status
- Patient estimate of survival

Methodological issues

- How to collect, store and manage data?
- How to manage the project?

PIPS - staffing

- Project manager
 - 3 years full-time, I-grade nurse, registered for PhD
- Data collectors
 - 2.5 w.t.e. F-grade research nurses
 - 1 w.t.e. each at Derby and Manchester
 - 0.5 w.t.e. at Surrey
 - 2 years full-time

PiPS staffing

- Administrative support
 - 0.2 w.t.e. secretarial support
 - 3 years
- Statistical support
 - 1.0 w.t.e. statistician
 - 9 months
- Steering committee
 - lead researchers, statistician, user representative, independent chair

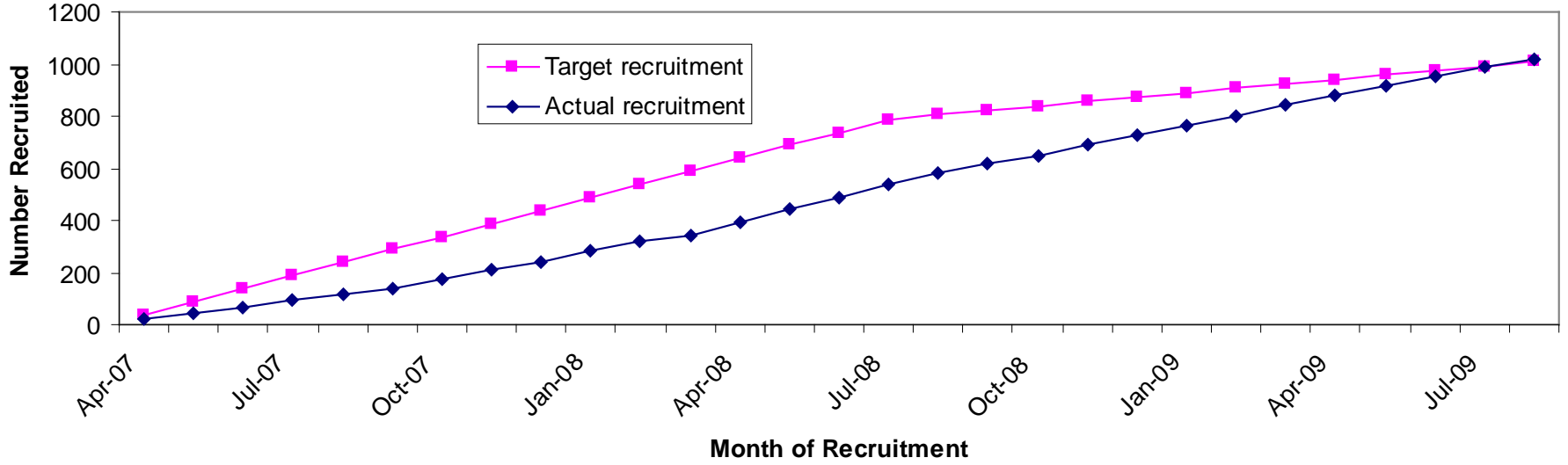
PIPS Timelines

- Application to CRUK
 - 9th Feb 2005
- CRUK funding awarded
 - 10th Aug 2005
- Application to Ethics
 - 12th October 2005
- PIAG
 - 8th Feb 2006

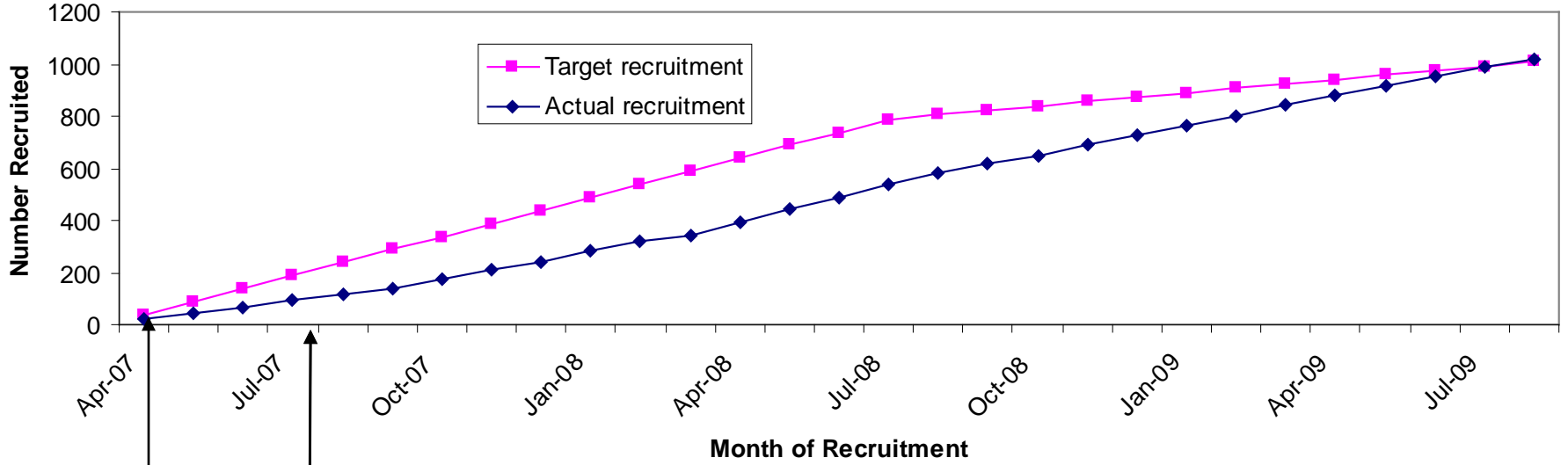
PIPS Timelines

- Ethics approval
 - 10th Feb 2006
- R and D approval
 - 10th May 2006
- PIAG approval
 - 28th September 2006
- Bridget Gwilliam starts
 - 30th October 2006

Timeline for Total Recruitment August 2009

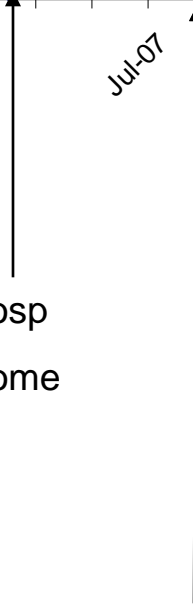


Timeline for Total Recruitment August 2009

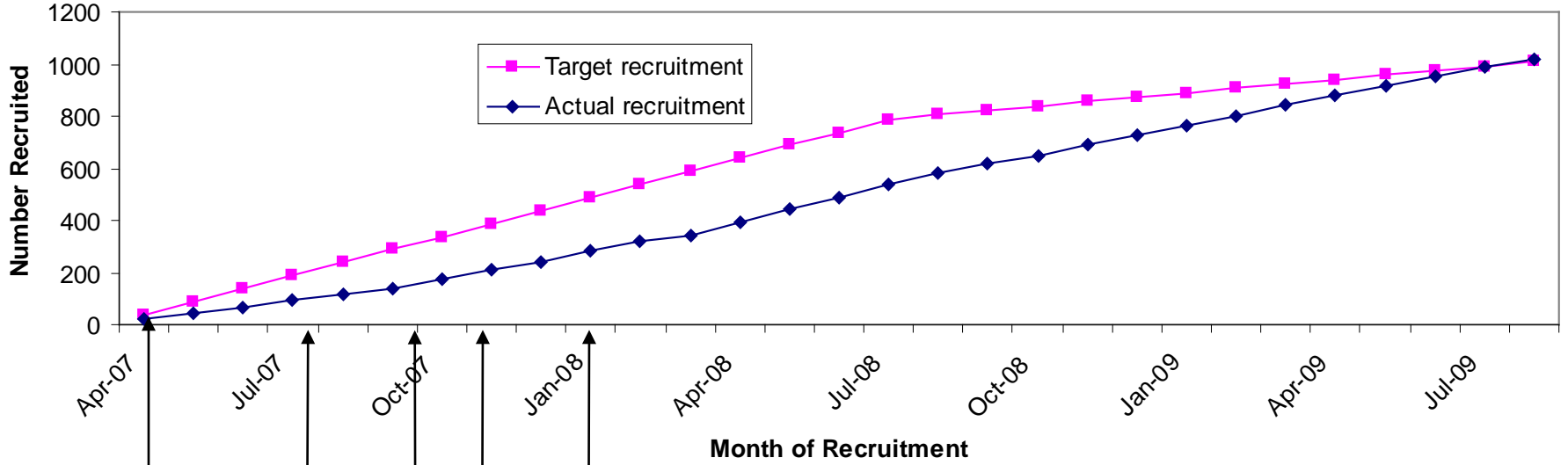


Trinity Hosp
 Trinity Home
 LH
 ESH
 Derby
 Christie

LH Day-care



Timeline for Total Recruitment August 2009



Trinity Hosp
 Trinity Home
 LH
 ESH
 Derby
 Christie

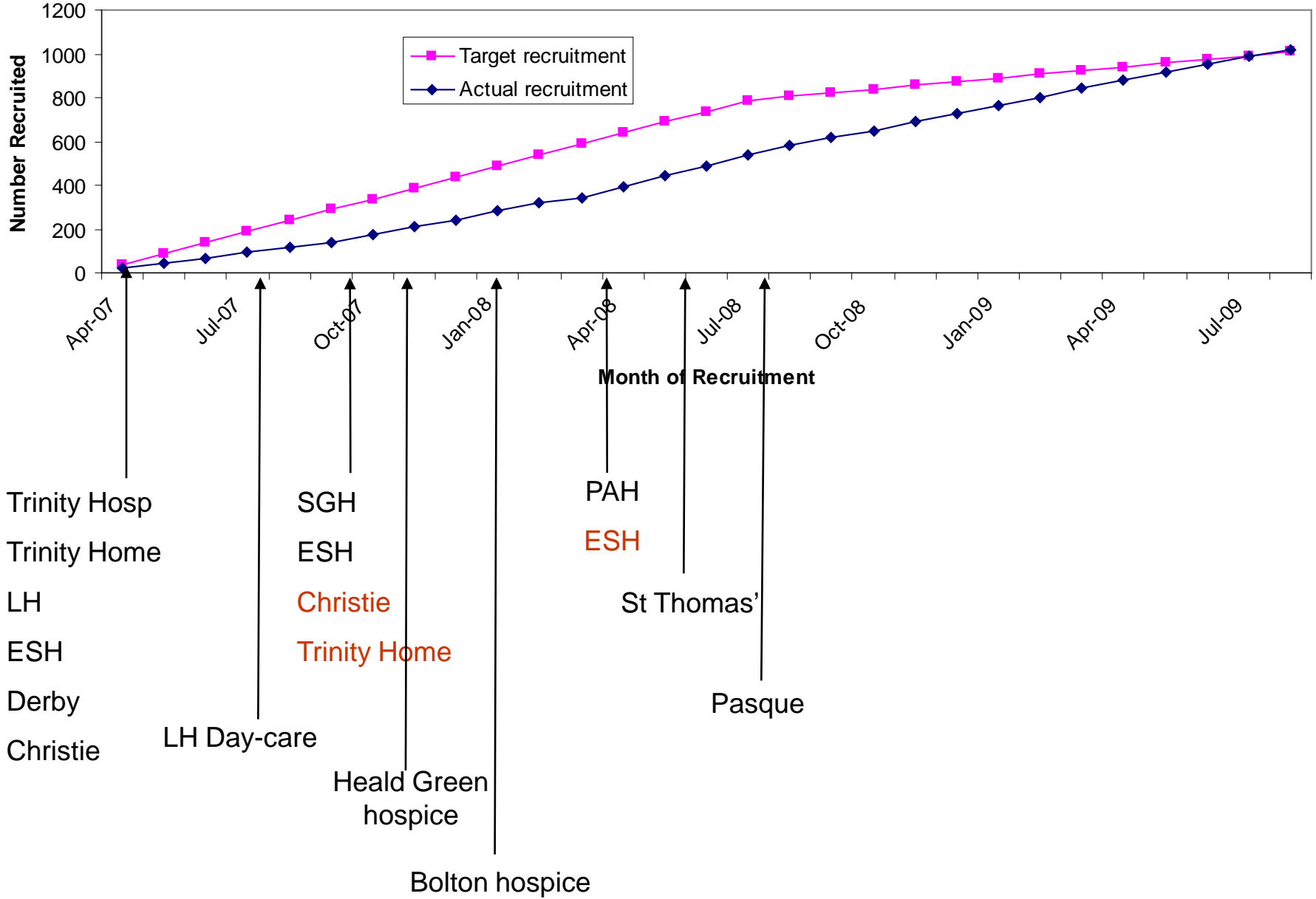
LH Day-care

SGH
 ESH
 Christie
 Trinity Home

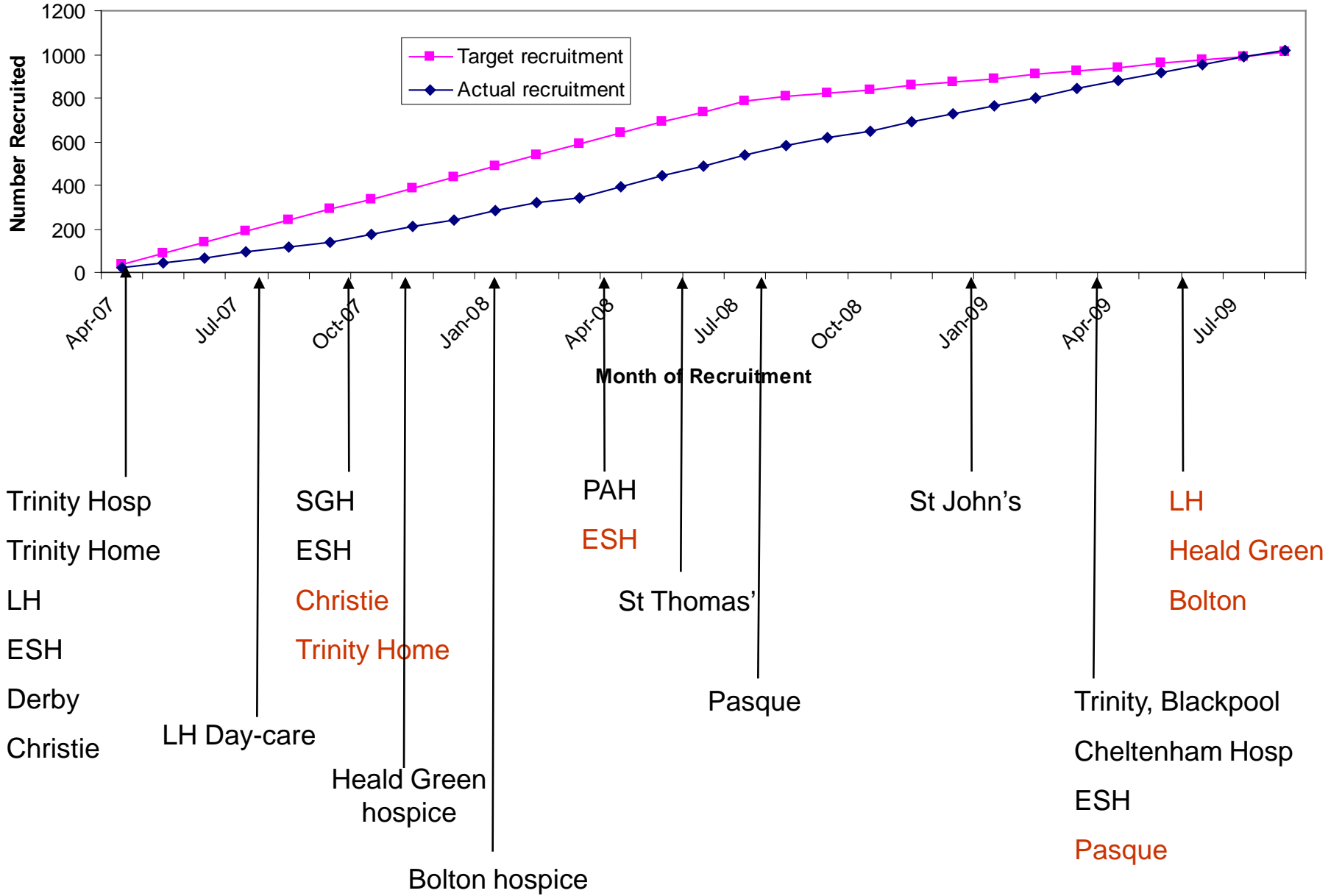
Heald Green
 hospice

Bolton hospice

Timeline for Total Recruitment August 2009



Timeline for Total Recruitment August 2009



12 140 screened

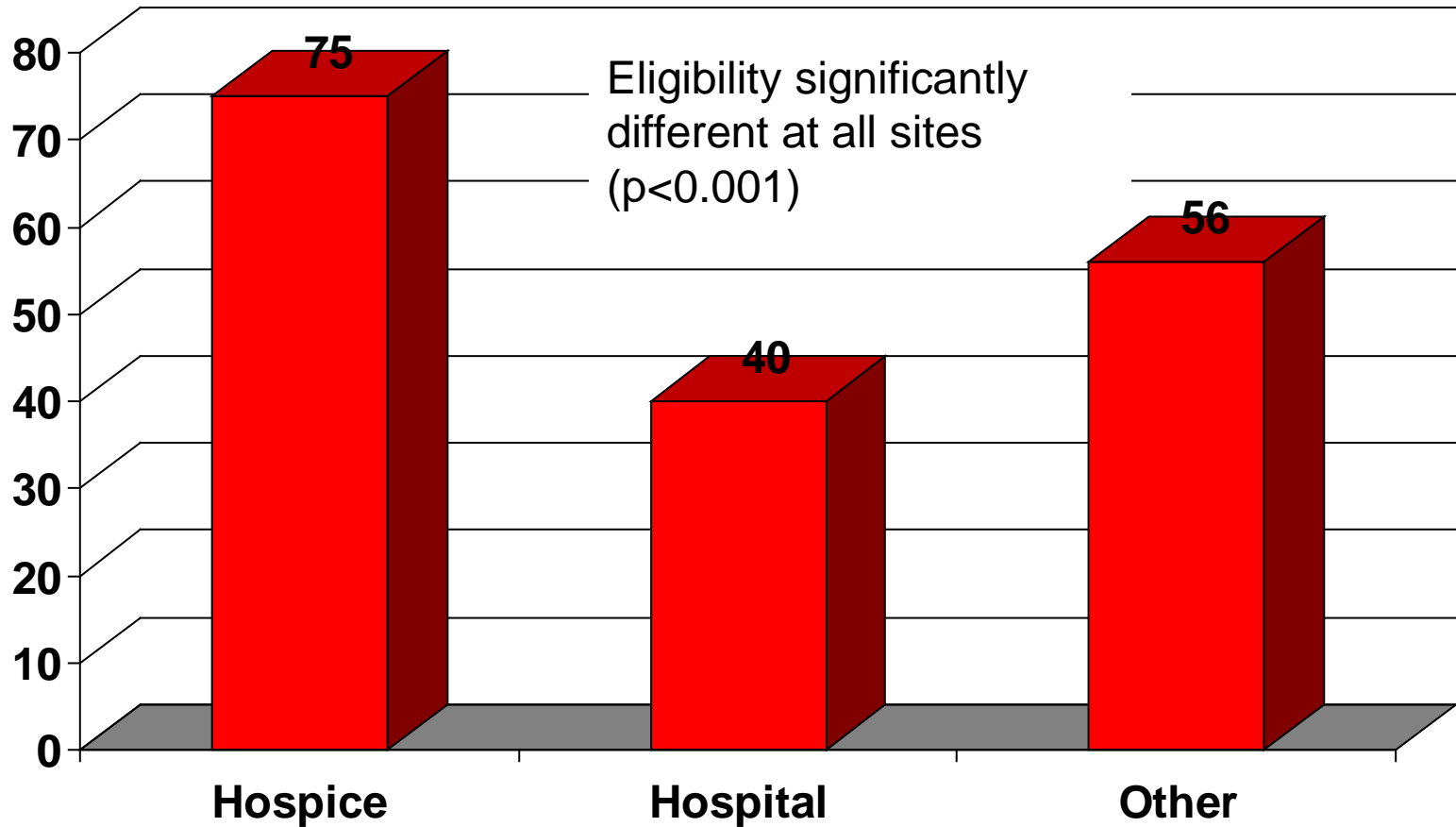
12 140 screened



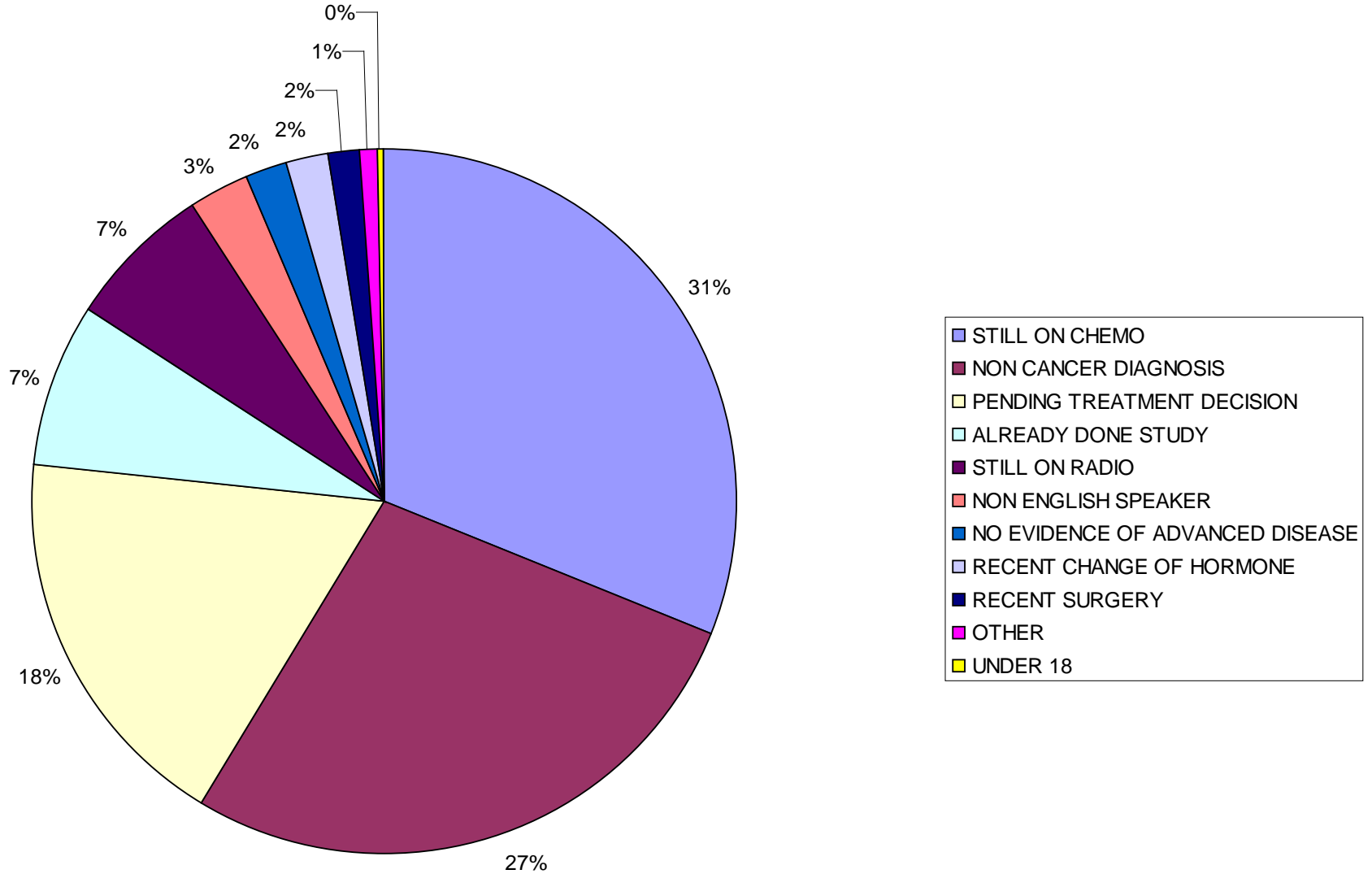
6 909 eligible

57% of screened

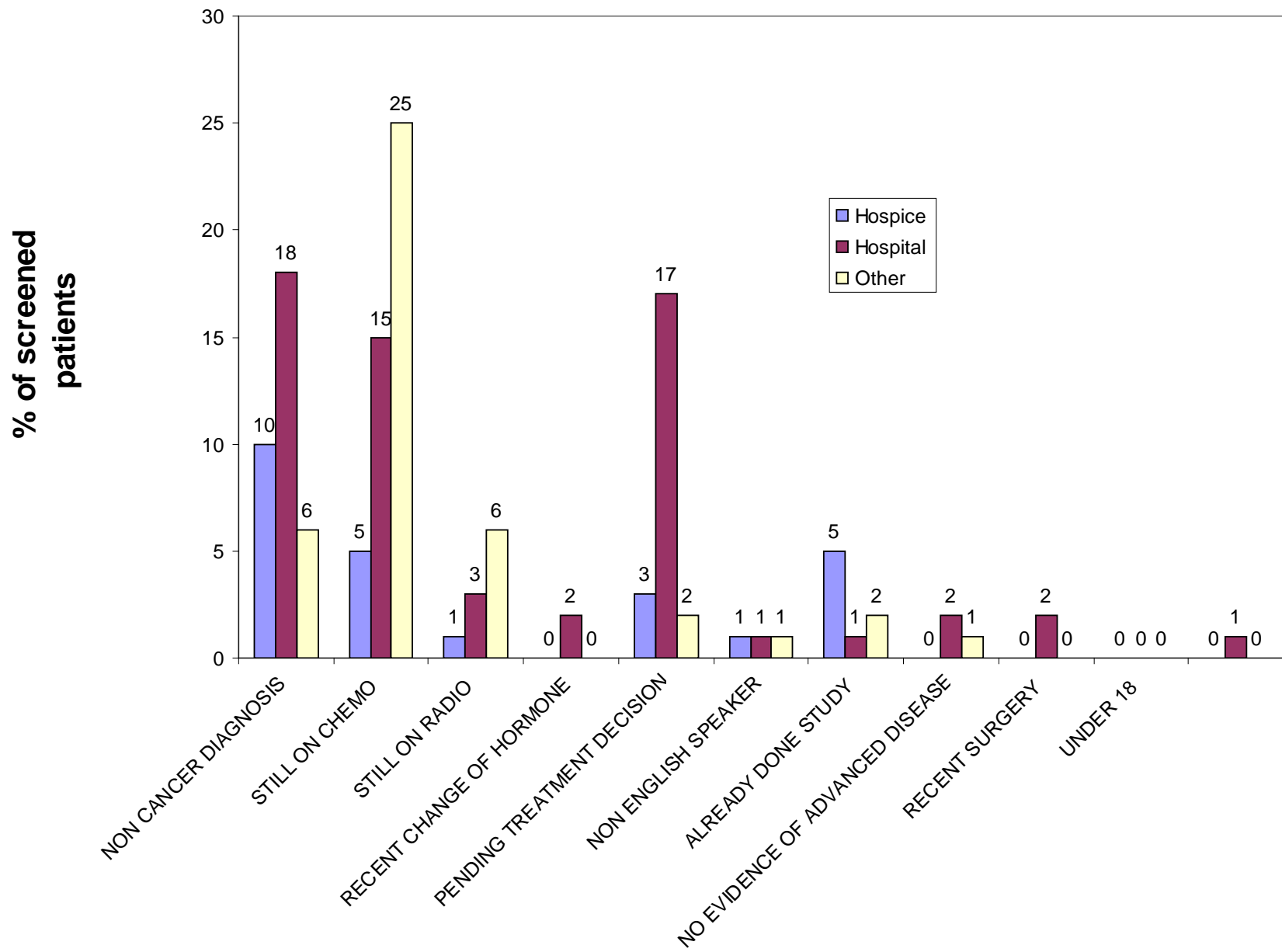
Eligibility (%) by recruitment site



Reasons why patients were ineligible



Reasons for ineligibility by site



Reasons for ineligibility by site

- In hospices
 - Patients most likely to have already been involved in study
- In hospitals
 - Patients more likely to have non-cancer diagnosis, to be awaiting a treatment decision or to be on chemotherapy
- In other settings
 - Patients most likely to still be receiving chemotherapy or radiotherapy

12 140 screened



6 909 eligible

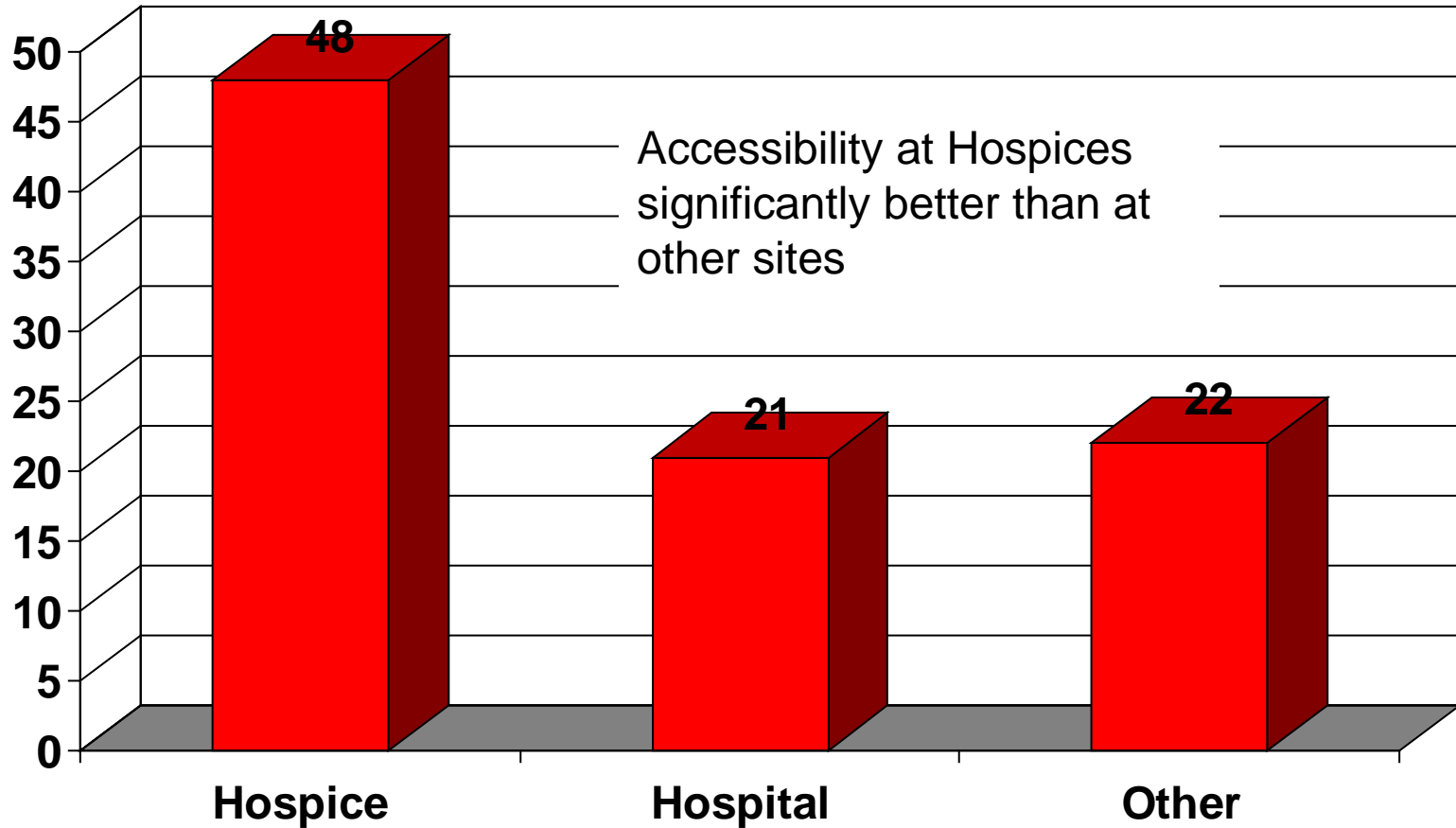


2378 approached

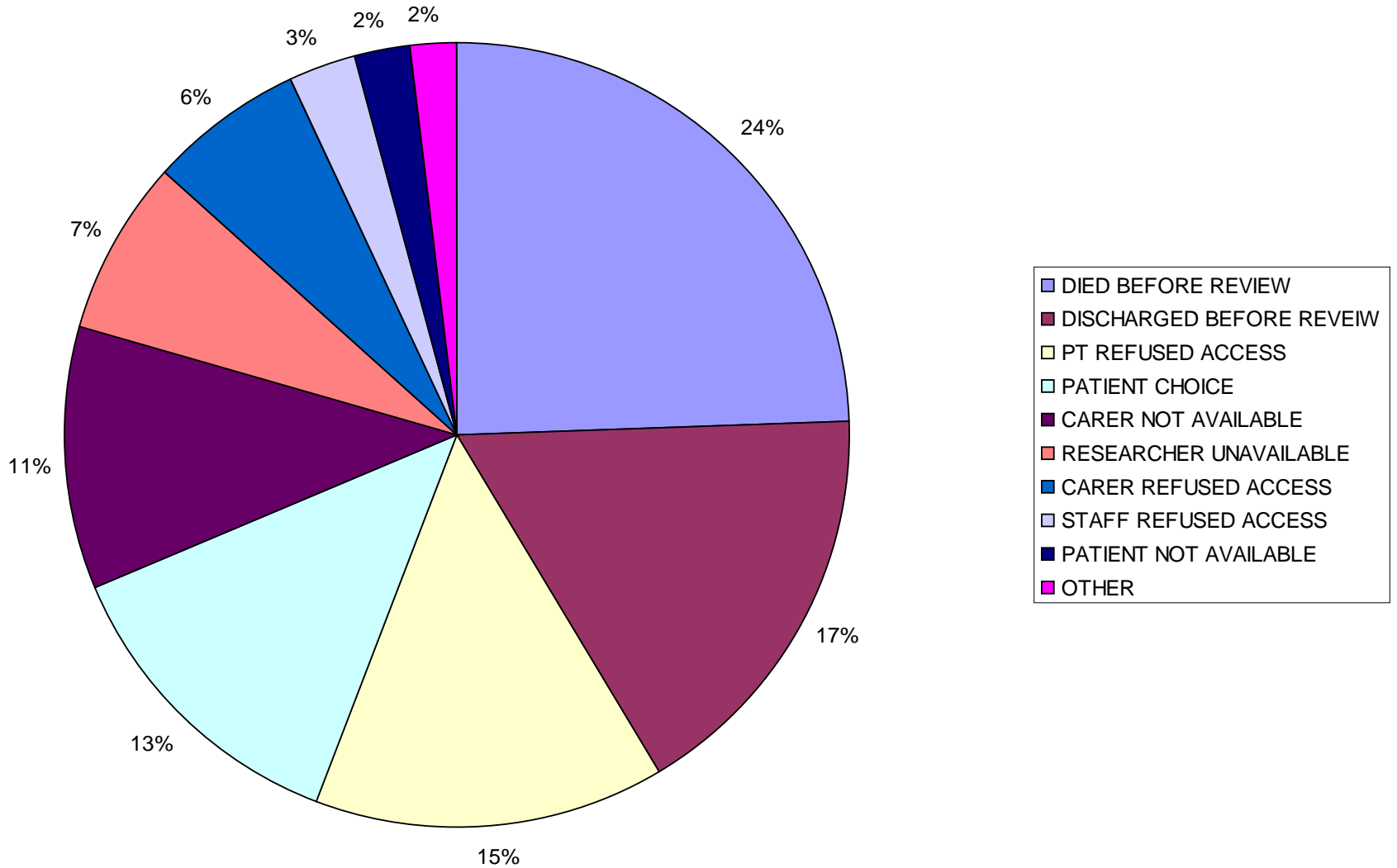
57% of screened

34% of eligible

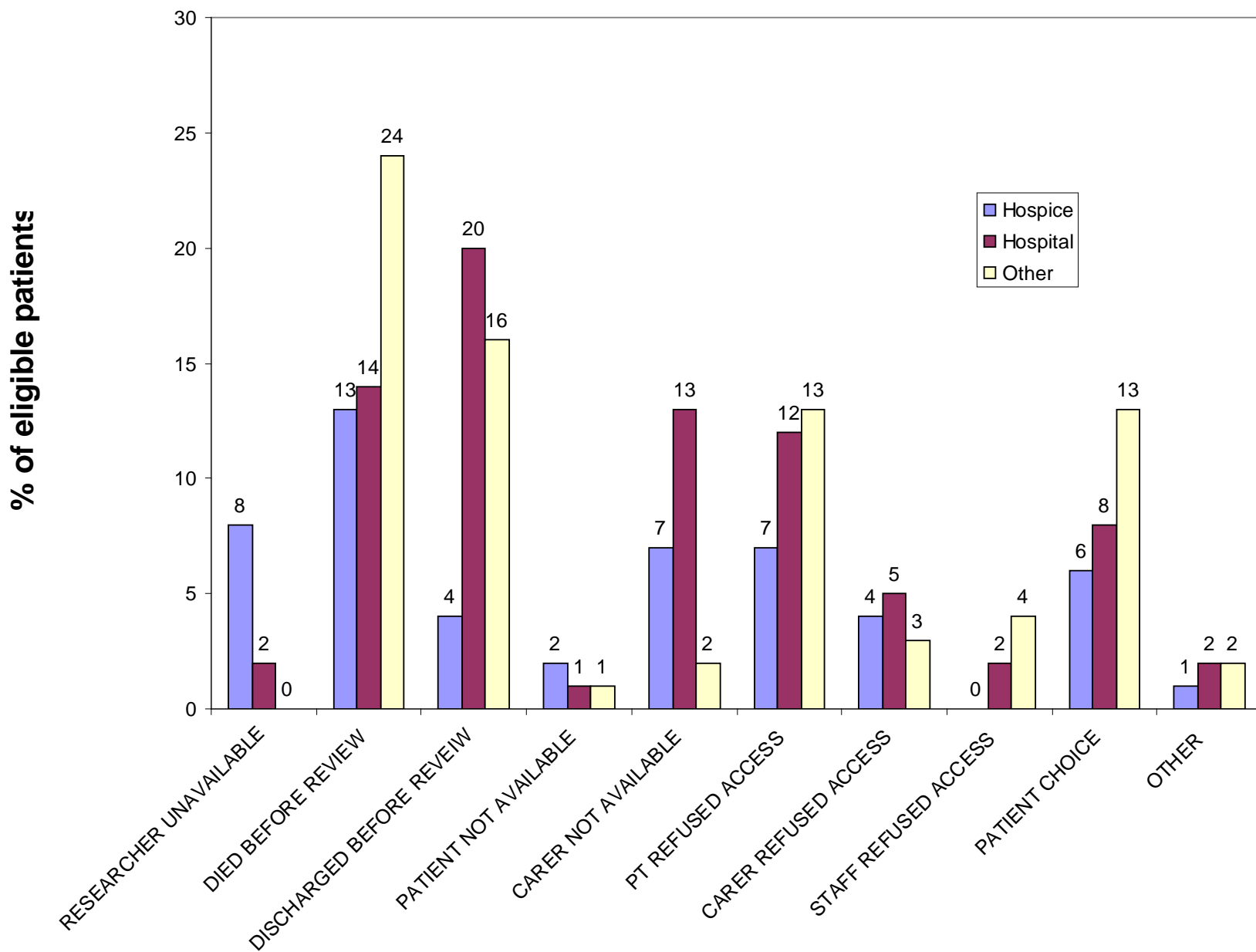
Accessed (%) by recruitment site



Reasons why patients were not accessed



Reasons why patients not accessed by site



Reasons why patients not accessed by site

- In hospices
 - Researcher more likely to be unavailable
- In hospitals
 - Patients more likely to be discharged before review
 - Carer less likely to be available
 - Patient and carer more likely to refuse access
- In other settings
 - Patients more likely to be discharged or die before review
 - Patients and staff more likely to refuse access

12 140 screened



6 909 eligible

57% of screened



2378 approached

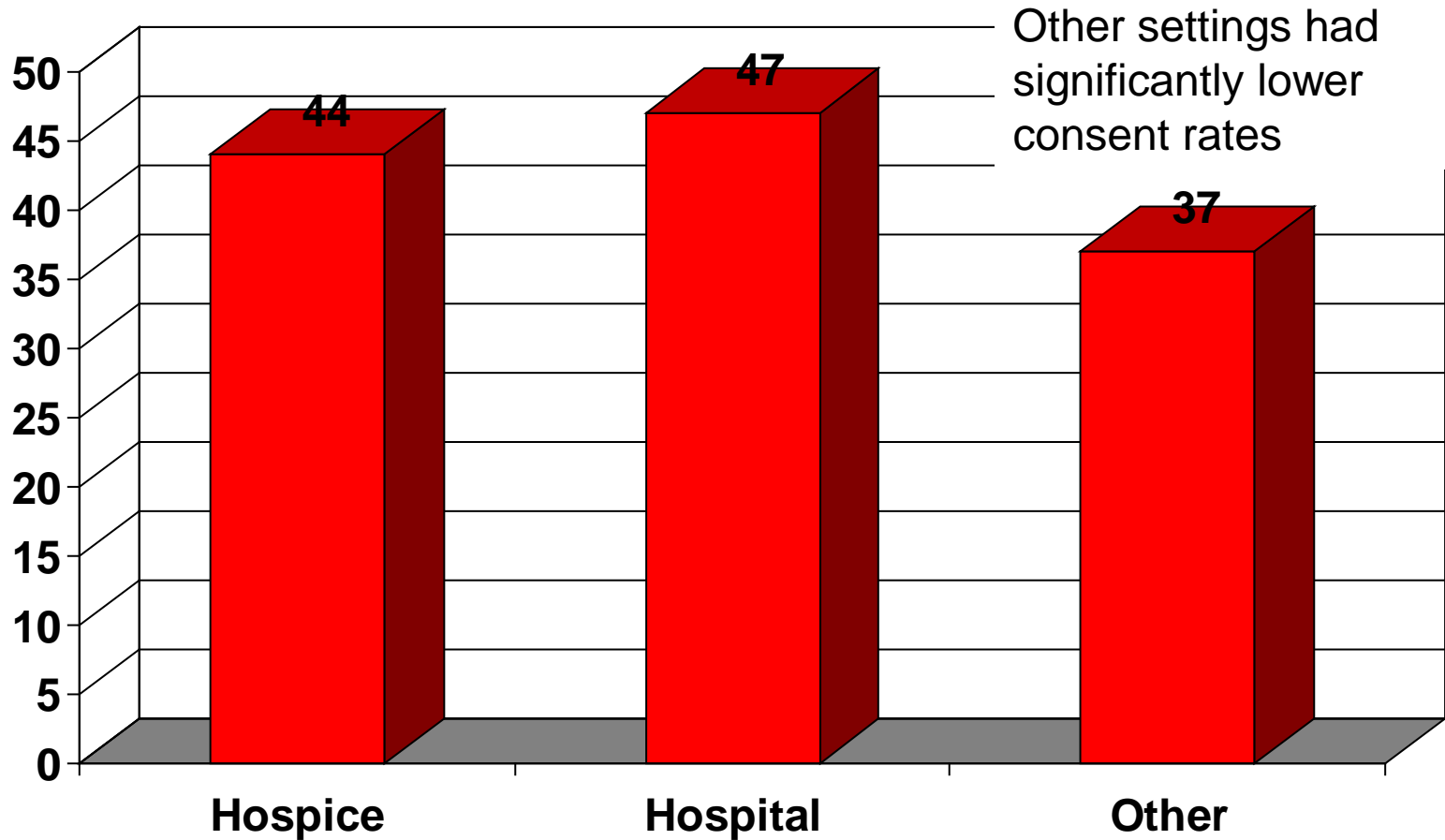
34% of eligible



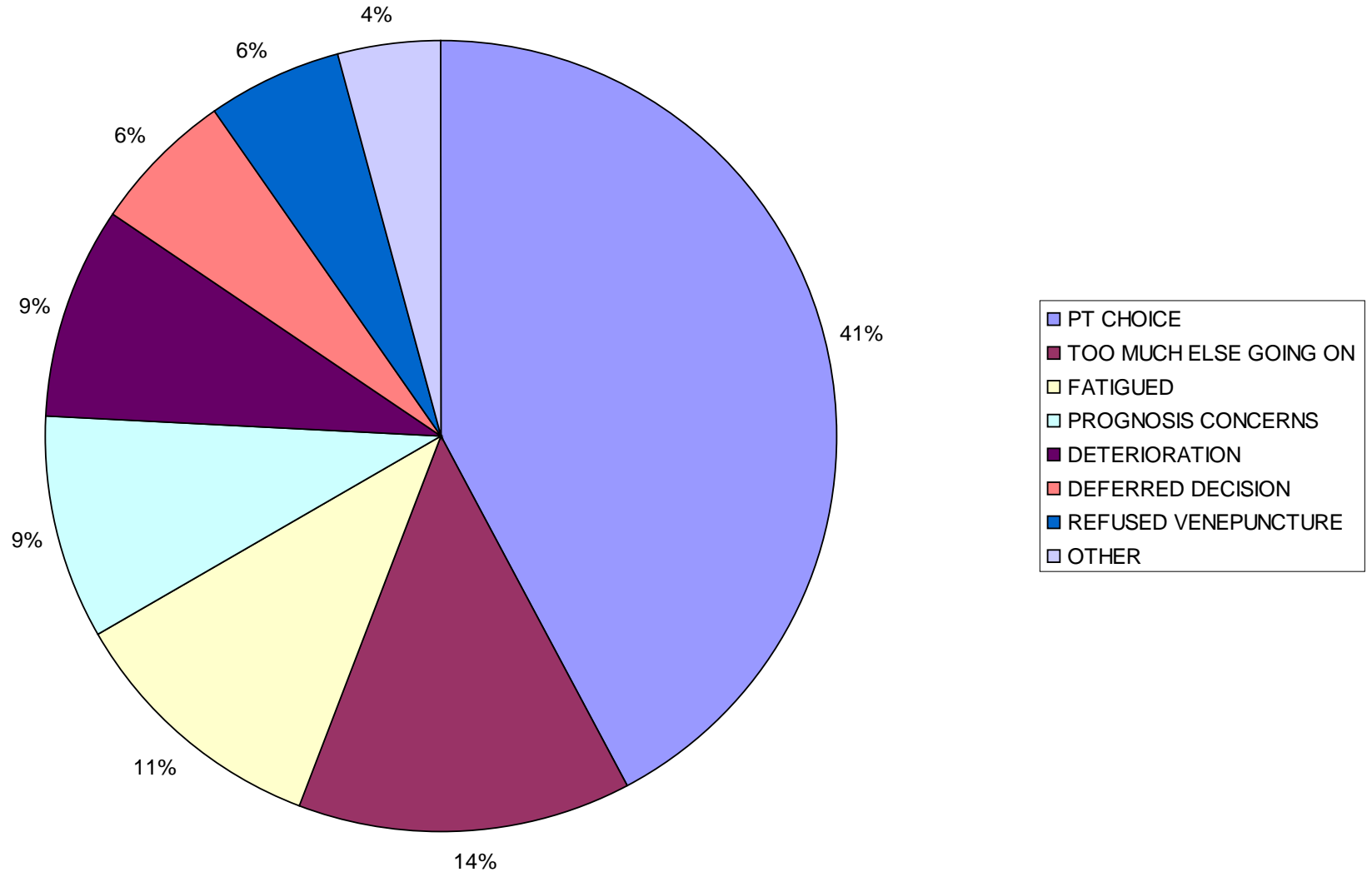
1021 consented

15% of eligible
43% of approached

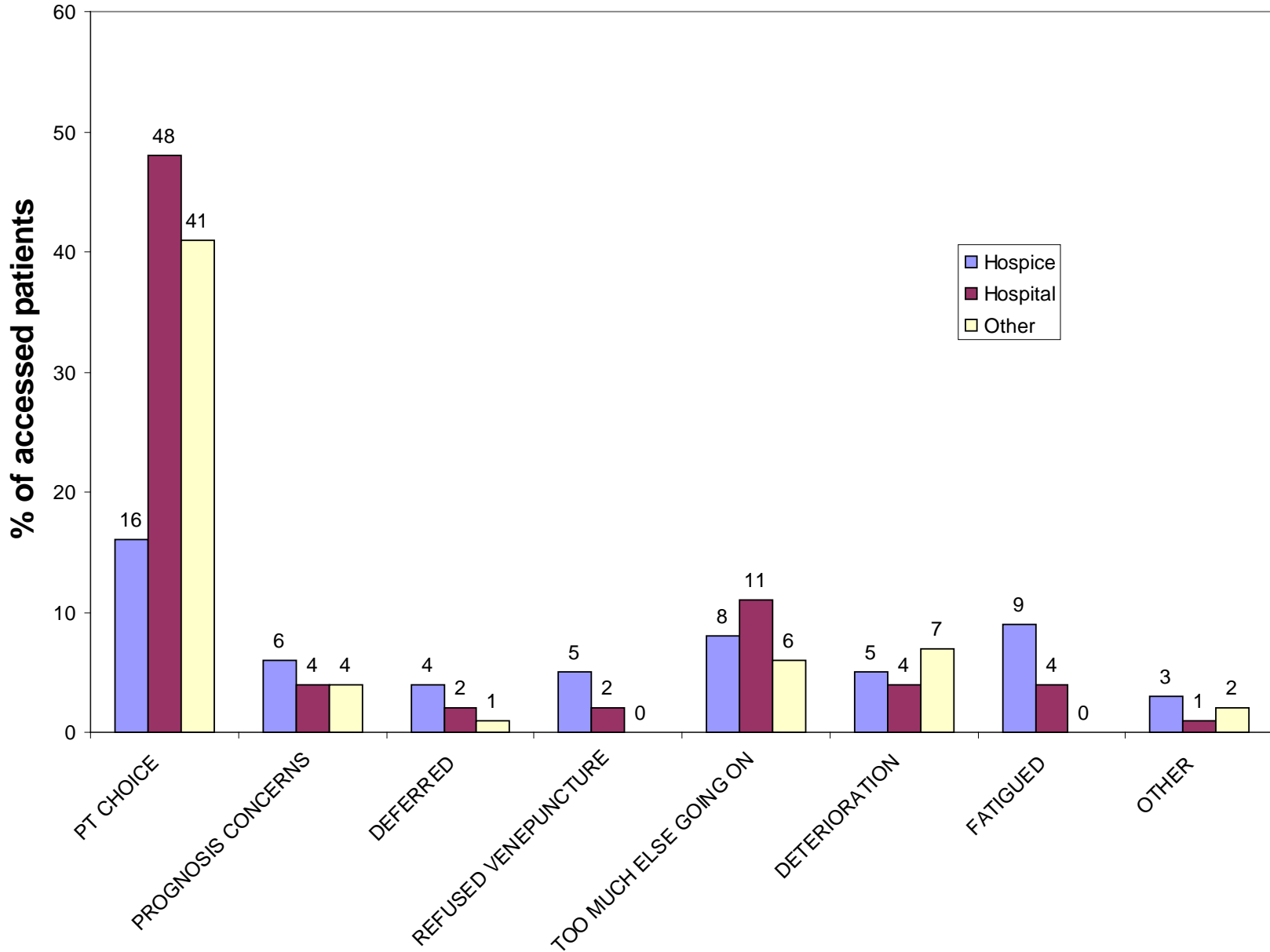
Reasons (%) for refusal of consent by site



Reasons why patients refused consent



Reasons pts did not consent by site



Reasons why patients did not consent by site

- In hospices
 - Patients more likely to be too fatigued, or to refuse venpuncture
 - Less likely to refuse because of “patient choice”
- In hospitals and other settings
 - more likely to refuse because of “patient choice”

12 140 screened

6 909 eligible

2378 approached

1021 consented

57% of screened

34% of eligible

15% of eligible
43% of approached

779 competent

242 incompetent

76% of consented

24% of consented

Lessons from the PiPS study

- Research takes time
- Dedicated research nurses are vital
- Ethics, Research Governance and data protection regulations add a huge administrative burden