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2 **A Retrospective Study of the Impact of Comorbidity,**

3 **Polypharmacy and Demographic Factors on Patient**

4 **Inclusion and Healthcare Delivery in Phase I Oncology**

5 **Trials**

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8 **ABSTRACT**

9 **Background:** Phase I trials include patients with metastatic cancer and complex health conditions.
10 Understanding baseline comorbidity and demographic features is critical to improving trial design.

11 **Methods:** We used electronic patient records to study the association of comorbidity, polypharmacy, and
12 demographic factors on trial recruitment, time on trial, and health service utilisation.

13 **Results:** A cohort of 1671 patients was considered for allocation to a phase I study, of whom 518 patients
14 were recruited to a phase I study and 1153 patients were not. A multivariable analysis revealed
15 polypharmacy was associated with lower recruitment to phase I trials with an odds ratio of 0.95 (95% CI:
16 [0.92, 0.99], p = 0.01), and a greater number of emergency admissions with a risk ratio of 1.1 (95% CI:
17 [1.03, 1.17], p = 0.01). Interestingly, comorbidity was not associated with lower recruitment but was

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18 associated with a lower time on trial with a hazard ratio of 0.75 (95% CI: [0.62, 0.90], $p \leq 0.001$).
19 Demographic factors, including ethnicity, distance of residence from the hospital, and index of multiple
20 deprivation, did not significantly influence these parameters.

21 **Conclusion:** Polypharmacy and comorbidity should be considered both in the design of phase I oncology
22 trials and in planning for healthcare utilisation during these trials.

23 **Background**

24 Comorbidity refers to the presence of two or more chronic conditions within an individual and poses
25 significant challenges for healthcare systems (1). In the UK, patients with comorbidity account for most
26 primary care consultations, prescriptions, and hospitalisations (2,3). The higher risk of comorbidity in
27 cancer patients results in the risk of polypharmacy and its detrimental impact on their quality of life (4).
28 Hence, examining polypharmacy along with comorbidity in cancer patients is crucial. Researchers focused
29 on the impact of comorbidity and polypharmacy on the management of patients with a range of cancers and
30 found that either comorbidity, polypharmacy, or both reduced the chance or delayed the institution of
31 systemic anticancer therapy and, in some cases, was correlated to shorter survival (5–7).

32 Clinical trials are crucial in cancer care. Primarily, to ensure a robust assessment of safety, efficacy,
33 and utility, participants in cancer clinical trials should be representative of the target population. However,
34 comorbidity is prevalent in the population of cancer patients, and it is therefore crucial that cancer patients
35 with comorbidity, who are a complex group with specific health service needs, are considered in trials. Due
36 to the fact that most clinical trials are designed with a single disease in mind, and there is a risk of concealing
37 the potential benefits of experimental treatment, performing such clinical trials has been limited (8–11).
38 Investigating comorbidity in cancer trial recruitment has rarely been studied. Unger et al. (9) investigated
39 whether clinical trial decision-making and participation were linked to comorbidity in patients with cancer.
40 The study conducted a web-based survey of patients with cancer and assessed multiple recruitment-related
41 outcomes, including discussion of participation, offer of participation, and participation. They found that
42 all the outcomes were negatively impacted by comorbidity.

43 Phase I trials are conducted primarily to recommend a safe dose/schedule of novel anticancer drugs.
44 These trials are conducted in patients with metastatic cancer who have previously received standard-of-care
45 treatments for their disease and often have significant cancer-related morbidity. Previous studies have
46 explored the impact of sociodemographic factors on recruitment to phase I cancer trials (12,13). However,
47 they have not examined the role of comorbidity and polypharmacy in this context. Additionally, the effect
48 of these clinical factors on health service utilisation during trials remains largely unaddressed. We aimed
49 to study if there is evidence that polypharmacy, comorbidity, and sociodemographic features (age, sex,
50 ethnicity, distance to the hospital, and index of multiple deprivation (IMD)) are associated with phase I

51 cancer trial recruitment. Further, we investigated if these factors interact with the experimental treatment
52 to affect other healthcare service use, namely, disease progression through an increase in the discontinuation
53 rate or the number of emergency scans or admissions and length of stay post-admission.

54 **Methods**

55 **Study population and data**

56 This retrospective study used electronic patient record (EPR) data from cancer patients referred to the
57 Drug Development Unit (DDU), a joint department at the Royal Marsden NHS Foundation Trust and The
58 Institute of Cancer Research from their local hospitals. All patients seen in the referred and seen in the new
59 patient clinic and subsequently discussed for consideration of recruitment to a phase I trial in the patient
60 allocation meeting (PAM) within 28 days of being seen between 01/10/2018 and 31/12/2021 were
61 considered for analysis. Patients were deemed to have started a phase I study if they had received at least
62 one drug dose. Data on individual patients were collected on the date they were first seen in the new patient
63 clinic and if they were recruited to the phase I trial till the last date they were seen on the trial. If the patient
64 was not allocated or was allocated and found ineligible, data was collected till the last recorded clinic visit
65 in the DDU.

66 The base dataset was collected from patients on the DDU patient list. It included data from trial
67 enrolment, trial start date, trial end date, death, clinic visit date, age at the time of referral, sex, ethnicity,
68 IMD (14), distance to the Royal Marsden Hospital - Sutton, the number of medications that were not directly
69 used to treat cancer, i.e., excluding chemotherapy, hormonal therapy or immunotherapy, or investigational
70 drug in the clinical trial, the number of diseases, emergency admissions, and emergency scans.

71 We filtered the dataset based on the closeness of the last clinic visit to the PAM and trial start dates.
72 The threshold to determine the cohort for patients being considered for recruitment was 28 days from the
73 last clinic visit and PAM date. The threshold to determine the trial group was 120 days from the last clinic
74 visit and trial start date. It is worth noting that the threshold for the trial group was larger than that of the
75 recruitment cohort, as we were more concerned with the clinician's sensitivity to the patient's baseline
76 characteristics in the decision to recruit into the trial.

77 **Data analysis**

78 In our analysis, independent variables comprised sociodemographic features and health-related
79 variables. Sociodemographic features included age at the first clinic appointment in the DDU, sex, ethnicity,
80 IMD score, and distance to the Royal Marsden Hospital - Sutton in miles. Ethnicity was initially recorded
81 in line with the NHS ethnic categories, resulting in small sample sizes for each group. Hence, we recorded

82 this variable as white and non-white groups. Due to non-disclosure, ten missing observations for the
83 ethnicity variable were imputed using the multiple imputation by chained equations algorithm. The IMD
84 was used as a surrogate for income deprivation and had the following components (weighting in brackets):
85 income (22.5%), employment (22.5%), health deprivation and disability (13.5%), education and skills
86 training (13.5%), crime (9.3%), barriers to housing and services (9.3%), and living environment (9.3%).
87 Higher scores for IMD indicate greater deprivation and are assigned from the postcode at registration. Also,
88 distance to the hospital was calculated using patients' postcodes.

89 Health-related variables included polypharmacy and comorbidity. There were several options
90 concerning the variable type for polypharmacy and comorbidity. Comorbidity is often quantified using
91 indices such as the Charlson comorbidity index (15) and the Elixhauser comorbidity index (16), primarily
92 developed as prognostic tools. However, both indices apply weighting schemes based on long-term
93 mortality risk, which may not be directly applicable or valid in early-phase oncology trials, where short-
94 term safety and tolerability are the primary endpoints. We chose the number of medications as a surrogate
95 for polypharmacy, which was a simple and reliable variable. Similarly, we initially opted for the number of
96 diseases as a surrogate for comorbidity; however, that resulted in small sample sizes for each group. Hence,
97 comorbidity was treated as a dichotomous variable, indicating the presence or absence of at least one non-
98 cancer condition in individuals with cancer. It is worth noting that in the remainder of this report, we refer
99 to comorbidity as the dichotomous variable.

100 Both the number of medications and the number of diseases were extracted from free-text patients' case
101 notes. Disease data was typically in paragraphs, with superfluous data including family medical history and
102 health behaviours. Hence, string manipulation and stop word removal were used to reduce text. The
103 algorithmic extraction of diseases was unfeasible due to synonyms, acronyms, and possible typos. Hence,
104 this was done manually, and the extracted list was validated by clinicians. The extracted diseases were then
105 summed per patient and then grouped into dichotomous for the comorbidity variable. Medications were
106 explicitly listed rather than nested in free text, and punctuation separated terms. There were issues with
107 superfluous text, and the inclusion of complementary medication was deemed unimportant. String
108 manipulation was used to remove additional text, and fuzzy matching was deployed to extract the
109 medications per patient. Medication data was extracted from clinical notes within the patients' EPR. As
110 such, the dataset may not capture medications prescribed by general practitioners (GPs) or any over-the-
111 counter medications taken by patients. Additionally, it is worth noting that only medicines included in the
112 British National Formulary (17) were extracted.

113 The outcome variables included recruitment into a clinical trial, time on trial, the number of emergency
114 scans, the number of emergency admissions, and the number of days in the hospital associated with those
115 emergency admissions. The number of emergency admissions and scans collected from patient case notes,

116 and the EPR involved a small set of terms; hence, rules-based algorithms were employed. In patients' case
117 notes, the data was collected during DDU clinic visits at the patient's discretion. In the EPR, admissions
118 and scans that were not routine were flagged as emergency. Scans contributed to the number of scans
119 variable, including CT, MRI, PET, X-ray, and ultrasound.

120 Independent variables were either binary or continuous. Comorbidity, sex, and ethnicity were recorded
121 as binary variables; the number of medications, the number of diseases, age, distance to the Royal Marsden
122 Hospital - Sutton, and IMD score were recorded as continuous variables. The outcome variables were split
123 into binary, continuous, and time-to-event variables. Trial recruitment was coded as a binary variable; the
124 number of emergency admissions, emergency scans, and length of stays after admissions were considered
125 continuous variables, and time on trial was regarded as a time-to-event variable. An event was defined as
126 either having disease progression or death led to a withdrawal.

127 We aimed to produce statistical models that estimated estimands with minimal bias and consistency.
128 To do so, we needed a directed acyclic graph (DAG) to define the variables required to identify the
129 estimands. Following the guidance from Rodrigues et al. (18) and with the assistance of clinicians, the DAG
130 was defined (supplementary). The DAG included additional observed and unobserved variables to find the
131 adjustment set that fulfilled the backdoor criterion (19). As validated by dagitty.com (20), the adjustment
132 set involved all independent variables, with additional variables being unadjusted as they were deemed
133 colliders. The DAG was considered general for our outcomes, so the adjustment set was carried over into
134 each statistical model.

135 **Statistical analysis**

136 Regression models were used to explore the effect of independent variables on the outcome variables.
137 The analysis was carried out in both univariate and multivariable settings. It is worth noting that in the
138 univariate analysis, the number of diseases and comorbidity were investigated to conduct a comprehensive
139 analysis. However, one of them had to be chosen for the multivariable analysis. Hence, comorbidity was
140 considered for the multivariable analysis. Also, before conducting the primary analysis, we examined
141 whether the number of medications and diseases interacted.

142 For trial recruitment, as a binary variable, a logistic regression model was used, and odds ratios (ORs)
143 were reported. For the number of emergency admissions, emergency scans, and length of stays after
144 admissions, as continuous variables, Poisson and negative binomial were considered according to the
145 regression-based test for overdispersion (21), and risk ratios (RRs) were reported. Since we found evidence
146 of overdispersion in the number of scans and length of stays, these models were fitted with negative
147 binomial models. Also, the number of emergency admissions variable was fitted with a Poisson model. For

148 time on treatment, as a time-to-event variable, we tested and found evidence for proportional hazards.
 149 Hence, a Cox proportional hazards model was fitted, and hazard ratios (HRs) were reported.

150 **Results**

151 A total of 1671 patients were referred and seen in the new patient clinic of the drug development unit
 152 and discussed in the patient allocation meeting for consideration of the phase I trial within 28 days of this
 153 initial visit. The patient characteristics are detailed in Table 1. Also, characteristics of outcome variables
 154 studied in patients who went on to be recruited to the phase I trial are presented in Table 2.

155 Table 1 shows the characteristics of all the patients included in the analysis. It also provides information
 156 based on whether the patients started the phase I trial or did not. Also, distributions for the independent and
 157 outcome variables are provided in the supplementary material. Moreover, we did not find evidence to
 158 support the correlation between the number of medications and diseases, as indicated by Pearson’s and
 159 Spearman’s correlation coefficients.

160 Table 1. Characteristics of all patients in the analysis.

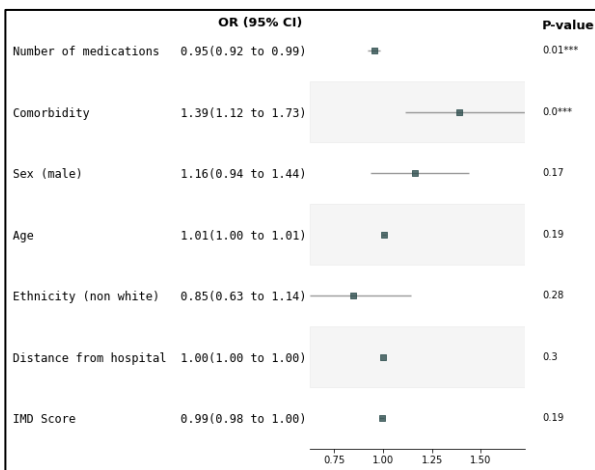
		On trial (N=518)	Not on trial (N=1153)	Overall (N=1671)
Number of medications	Mean (SD)	3.4 (3.1)	3.7 (3.2)	3.6 (3.2)
	Median [min, max]	3.0 [0.0, 17.0]	3.0 [0.0, 19.0]	3.0 [0.0, 19.0]
Number of diseases	Mean (SD)	1.0 (1.6)	0.8 (1.4)	0.9 (1.5)
	Median [min, max]	0.0 [0.0, 8.0]	0.0 [0.0, 7.0]	0.0 [0.0, 8.0]
Comorbidity	Yes	204 (39.4%)	370 (32.1%)	574 (34.4%)
	No	314 (60.6%)	783 (67.9%)	1097 (65.6%)
Sex	Male	267 (51.5%)	542 (47.0%)	809 (48.4%)
	Female	251 (48.5%)	611 (53.0%)	862 (51.6%)
Age	Mean (SD)	59.7 (12.7)	58.4 (13.3)	58.8 (13.1)
	Median [min, max]	61.0 [18.0, 83.0]	61.0 [18.0, 91.0]	61.0 [18.0, 91.0]
Ethnicity	White	441 (85.1%)	948 (82.2%)	1389 (83.1%)
	Non-white	77 (14.9%)	205 (17.8%)	282 (16.9%)
Distance from the hospital (miles)	Mean (SD)	68.0 (70.6)	71.6 (66.6)	70.5 (67.8)
	Median [min, max]	45.0 [0.0, 420.8]	49.8 [0.0, 406.5]	48.9 [0.0, 420.8]
Index for multiple deprivation score	Mean (SD)	13.8 (10.1)	14.9 (10.0)	14.5 (10.0)
	Median [min, max]	11.1 [0.9, 58.2]	12.3 [0.9, 60.9]	12.0 [0.9, 60.9]

161 Table 2. Characteristics of outcome variables in patients who went on to be recruited to the phase I trial.

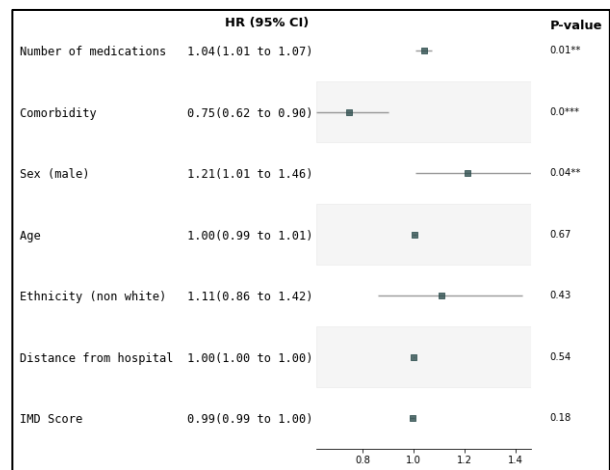
	Mean (SD)	Median [min, max]
Time on trial (days)	116.9 (192.2)	56.0 [0.5, 1645.0]
Number of emergency scans	2.8 (5.6)	1.0 [0.0, 50.0]

Number of emergency admissions	0.2 (0.4)	0.0 [0.0, 2.0]
Length of stays for emergency admissions (days)	0.9 (3.8)	0.0 [0.0, 59.0]

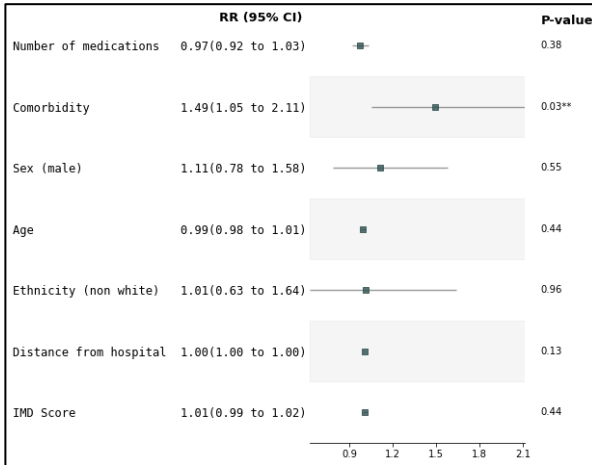
162 Fig. 1 shows the results of the multivariable analysis. It is worth noting that the results of univariate
163 analysis are presented in the supplementary. According to Fig. 1A, we identified two variables that were
164 associated with the trial enrolment after adjustment: the number of medications with an OR=0.954; 95%
165 CI: [0.921, 0.987] and comorbidity with an OR = 1.388; 95% CI: [1.115, 1.728]. The remaining variables
166 showed no association with trial recruitment. In the Cox proportional hazard model for time on trial (Fig.
167 1B) three variables had statistically significant coefficients: the number of medications with an HR = 1.039;
168 95% CI: [1.008, 1.071], comorbidity with an HR = 0.747; 95% CI: [0.618, 0.902], and sex (male) with an
169 HR = 1.212; 95% CI: [1.005, 1.461]. In the negative binomial model for the number of emergency scans
170 (Fig. 1C) the presence of comorbidity was associated with an increased risk of additional scans (RR =
171 1.491; 95% CI: [1.051, 2.115]). In the Poisson model for the number of emergency admissions (Fig. 1D),
172 the greater the number of medications a patient took was associated with an increased risk of emergency
173 admission after adjusting for other covariates (RR = 1.099; 95% CI: [1.028, 1.174]). Also, in the negative
174 binomial model for the length of stays (Fig. 1E), the risk of longer stays post admissions increased with the
175 growth of the number of medications (RR = 1.196; 95% CI: [1.06, 1.349]) but decreased in males (RR =
176 0.306; 95% CI: [0.143, 0.655]).



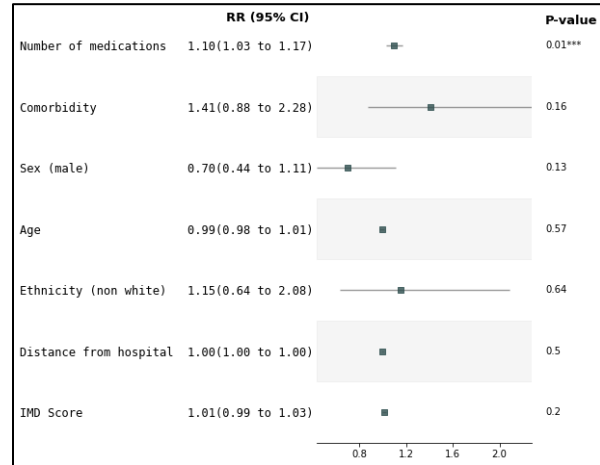
(A)



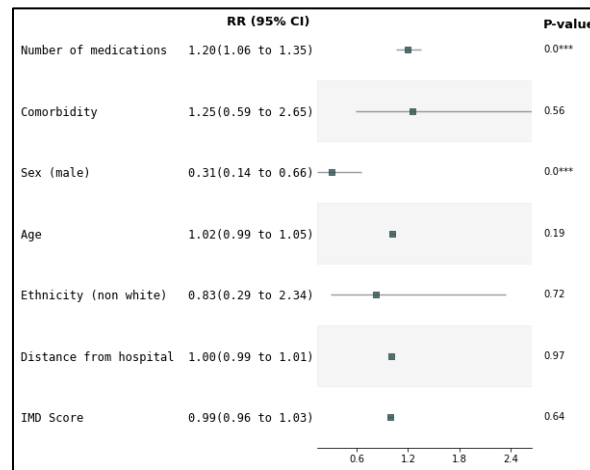
(B)



(C)



(D)



(E)

177 Fig. 1 Results of multivariable analysis: A) variables associated with trial enrolment, B) variables associated with time on trial,
 178 C) variables associated with number of emergency scans, D) variables associated with number of admissions, and E) variables
 179 associated with length of stay once admitted.

180 Discussion

181 To the best of our knowledge, for the first time, we provide the relationship of comorbidity,
 182 polypharmacy, and demographic features including ethnicity, distance from the hospital, and IMD score
 183 and the outcomes which include patients being recruited to an oncology phase I study and data related to
 184 health care utilisation including emergency admissions, emergency scans and time on the clinical trial. This
 185 new data will add to published data focusing on baseline organ function measured by blood tests, disease
 186 burden measured by imaging, and performance status and outcomes, including response to phase I agents
 187 and time on treatment in oncology phase I clinical trials (22–26) to help design and execute oncology phase
 188 I trials. Our findings will provide a comparison for future studies evaluating comorbidity, polypharmacy,
 189 and demographic factors in the setting of oncology phase I trials.

190 Our results support the subtle difference between polypharmacy and comorbidity, with our findings
191 indicating that each had distinct relationships with trial recruitment and health service utilisation. Our
192 findings suggest that the higher the number of medications a patient takes, the less likely they will be
193 recruited to phase I clinical trials of an anticancer drug. There could be multiple reasons, for instance, the
194 fact that patients with multiple medications are likely to be in poor health and not meet eligibility criteria
195 for phase I studies. Alternatively, being on various medications could rule patients out of phase I trials of
196 small molecules because of the risk of drug-drug interactions, which are part of the exclusion criteria.

197 Furthermore, a higher number of medications was associated with a greater risk of emergency
198 admission and a longer length of hospital stay after admission. These arguments align with the fact that
199 patients on multiple medications are in poorer health and survival rates (5). Interestingly, patients on a
200 larger number of drugs who entered the phase I trial stayed on trial longer. It is possible that the number of
201 medications in our study cohort included multiple medications to control symptoms of cancer, e.g., pain,
202 nausea, vomiting, diarrhoea, infection, and patients who have had many of these symptoms controlled due
203 to a large number of drugs stayed on trials for longer. This needs to be prospectively validated in larger
204 cohorts of patients and may not be relevant outside of cancer trials.

205 Despite the literature showing a negative effect of comorbidity on cancer trial participation (9), our
206 study surprisingly found that comorbidity was associated with increased odds of being recruited to the phase
207 I cancer trial. Our trial was based on data in a phase I unit, while the published data in this space was based
208 on a web-based survey of patients diagnosed with cancer. The discussion was related to any clinical trial
209 rather than specifically oncology phase I trials, and thus, it may be difficult to compare the two studies.
210 However, it is encouraging to observe that comorbidity was not associated with a lower likelihood of
211 enrolment into oncology phase I trials. This finding aligns with ongoing calls to reduce overly restrictive
212 eligibility criteria in clinical trials, which often exclude patients with comorbidity. Broadening inclusion
213 criteria could help ensure that trial populations more accurately reflect ‘real-world’ patients, rather than a
214 select group of ‘fit’ individuals, thereby improving the generalisability of trial results and maximising
215 benefits to patients in society when drugs are licensed (27,28). Moreover, this result may reflect a distinction
216 between referral and enrolment processes. While comorbidity may pose a barrier to referral in broader
217 cancer trials, it may not necessarily hinder enrolment once patients are referred to phase I oncology trials.
218 It is, however, possible that referring clinicians make assumptions of not referring patients to oncology
219 clinical trials if they have chronic infections like HIV/Hep C or chronic heart failure. However, in our study,
220 comorbidity was associated with reduced time on a trial and increased need for emergency scans. This
221 implies that cancer patients with comorbidity are less likely to benefit from trials requiring increased
222 healthcare resources.

223 On examination of patient characteristics, we found that males in our dataset had more time on trial
224 and a much lower risk of longer stays after admissions. Despite evidence in the literature suggesting that
225 social deprivation and ethnicity have been associated with poor recruitment to clinical trials and reduced
226 inclusivity (29–31), our study found no such associations for sociodemographic factors, including age,
227 ethnicity, and IMD score. Moreover, distance to the hospital, which is often presumed to be a barrier to
228 recruitment, did not affect patients' odds of recruitment to phase I cancer trial, remaining on trial, or utilising
229 healthcare resources, according to our multivariable analysis. It is important to clarify that the findings of
230 this study indicate no evidence of selection into trials based on the specified characteristics once patients
231 are referred. However, the study did not investigate referral patterns.

232 It is worth noting that our study population is skewed towards less deprived areas, as indicated by a
233 higher proportion of participants residing in areas with lower levels of deprivation based on IMD rankings,
234 compared to the national distribution. This may limit the generalisability of our findings to more deprived
235 populations, and discrepancies may emerge in larger datasets encompassing broader geographical areas.
236 From the registration data, the ethnicity of the population studied showed a population of 83% white, which
237 is slightly greater than the national average of 81% (32). However, because of the relatively small numbers
238 of patients from ethnic minorities, it is difficult to know if such patients have a lower recruitment to phase
239 I trials from this analysis. Further studies in areas with a more ethnically and socioeconomically diverse
240 population can be benchmarked against this study.

241 The outcomes of this study could be improved if we had access to drugs prescribed by GPs. While
242 electronic patient records of patients being considered for phase I studies are very detailed due to regulatory
243 reporting required for such studies, it will be key to have access to GP records in larger population-based
244 studies as hospital electronic patient data may not be as detailed as for patients on phase I clinical trials.
245 This study was conducted in a tertiary referral oncology hospital and a specialised phase I unit. While many
246 of the findings could be potentially generalisable to oncology-specific phase I practice, however, given the
247 differences in requirements of frequent follow up, infrastructure to monitor toxicity (workforce
248 specialisation and healthcare professional-to-patient ratio), our findings may not be generalisable to
249 randomised phase III oncology trials, which are typically focused on efficacy, and conducted in secondary
250 or tertiary care centres.

251 Phase I studies in oncology are conducted in patients with advanced cancer who have complex
252 health needs. Building on existing research into sociodemographic factors influencing recruitment
253 to phase I oncology trials, this study provides new insights into the role of comorbidity,
254 polypharmacy, and sociodemographic factors in both trial recruitment and subsequent healthcare
255 utilisation. These findings can inform the design of phase I oncology trials by guiding eligibility
256 criteria and helping to plan the healthcare resources needed to support trial participation in patients
257 with cancer.

258 **Additional Information**

259 **Authors' contributions**

260 CC and UB, co-investigators, conceived this study. BB and LB were involved in identifying patient
261 cohorts. SM and LS were involved in extracting digital data and curating it on the Biomedical Research
262 Informatics Digital Environment (BRIDgE). HN and MO analysed the data and developed the early drafts
263 of the manuscript. All authors reviewed the manuscript.

264 **Consent for publication**

265 Scientists from the Institute of Cancer Research had access to and analysed de-identified patient data.

266 **Ethics approval and consent to participate**

267 This service evaluation project uses fully anonymised data in accordance with the UK General Data
268 Protection Regulation (UK GDPR) and the Data Protection Act 2018. The anonymisation process ensures
269 that no individual can be identified, either directly or indirectly, from the data used.

270 The project is a service evaluation, as defined by the Health Research Authority (HRA), aimed at
271 assessing and improving current clinical practice and patient care at The Royal Marsden NHS Foundation
272 Trust. As it does not involve any deviation from standard care or the randomisation of patients, it does not
273 require review by a Research Ethics Committee (REC), in line with HRA guidance.

274 All data has been anonymised prior to analysis, and no identifiable personal data is accessed, stored, or
275 shared. The evaluation complies with NHS data protection requirements, including the principles outlined
276 in the Caldicott Guidelines. The use of anonymised data for this purpose supports our commitment to
277 maintaining patient confidentiality while continuously improving service quality.

278 This project has been registered with and approved by the appropriate internal governance procedures
279 at The Royal Marsden NHS Foundation Trust.

280 **Code and data availability**

281 The analysis was conducted using Python 3.6. The data supporting this study's findings was from the
282 drug development unit at the Royal Marsden Hospital NHS Foundation Trust. The study data was stored
283 within the secure collaborative workspace in the Royal Marsden's Trusted Research Environment,
284 BRIDgE. The code and data used in this study are not publicly available.

285 **Competing interests**

286 The authors declare no conflict of interest.

287 **Funding information**

288 This study was supported by the NIHR Biomedical Research Centre (BRC) at The Royal Marsden NHS
289 Foundation Trust and The Institute of Cancer Research, London. Infrastructure support for this research
290 was provided by the NIHR ICR/RMH BRC. The views expressed are those of the author(s) and not
291 necessarily those of the NIHR or the Department of Health and Social Care. The authors acknowledge
292 infrastructural support funding from the Experimental Cancer Medicine Centre and the Cancer Research
293 UK Convergence Science Centre funding that supports phase I trial activity at the Drug Development Unit.

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376 **Figure legends**

377 Fig. 1: Results of multivariable analysis

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