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Are Survival and Mortality Rates Associated with Recruitment to Clinical Trials in Teenage and Young Adult Patients with Acute Lymphoblastic Leukaemia?

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TITLE:

Are Survival and Mortality Rates Associated with Recruitment to Clinical Trials in Teenage and Young Adult Patients with Acute Lymphoblastic Leukaemia?

RUNNING TITLE:

Impact of Trial Recruitment in TYA ALL

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ABSTRACT**Objective**

Participation rates in clinical trials are low in teenagers and young adults (TYA) with cancer.

Whilst the importance of clinical trials in informing best practice is well established, data regarding individual patient benefit are scarce. We have investigated the association between overall survival and trial recruitment in TYA patients with acute lymphoblastic leukaemia (ALL).

Design

Retrospective

Setting

National (England) TYA patients treated for ALL

Participants

511 patients aged 15-24 years diagnosed with ALL between 2004 to 2010 inclusive, of whom 239 (46.7%) participated in the UKALL2003 trial.

Outcome Measures

Patients were identified using National Clinical Trial (UKALL2003) and Cancer Registry (National Cancer Data Repository, English National Cancer Online Registration Environment) Databases. Relative survival rates were calculated for trial and non-trial patients and observed differences were modelled using a multiple regression approach. The numbers and percentages of deaths in those patients included in the survival analysis were determined for each three-month period, P values were calculated using the two-tailed z-test for difference between proportions and 95% confidence intervals for percentage deaths were derived using the Binomial distribution based on the Wilson Score method.

Results

Patients treated on the trial had a 17.9% better two-year survival (85.4% vs 67.5%, $p < 0.001$) and 8.9% better one-year survival (90.8% vs 81.9%, $p = 0.004$) than those not on the trial. 35 (14.6%) patients recruited to the trial died in the two years following diagnosis compared with 86 (32.6%) of those not recruited ($p < 0.001$).

Conclusions

TYA patients recruited to the clinical trial UKALL 2003 in England had a lower risk of mortality and a higher overall survival than contemporaneous non-trial patients. These data underline the potential for individual patient benefit in joining a clinical trial and the importance of international efforts to increase trial participation in the TYA age group.

STRENGTHS AND LIMITATIONS OF THIS STUDY

The study asks a fundamental question regarding the value to an individual of recruitment to a clinical trial

Large sample size including all TYA patients aged 15-24 years diagnosed with ALL in England between 2004-2010

This retrospective study is possible because a) the consent process for UKALL2003 included explicit consent for the trial data to be shared with regional and national cancer registries, and b) because the UK has full population coverage for cancer registration

Potential confounding variables include selection bias, centre effect and recruitment to other clinical trials

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INTRODUCTION

Although survival rates in teenage and young adult (TYA) patients with cancer have improved over the last two decades (O'Hara et al. 2015), these outcome gains have been modest and cancer remains the leading cause of non-accidental mortality in the TYA age group (Barr 2011; Meadows 2003).

The barriers to improving survival are likely to be multifactorial and include sub-optimal diagnostic pathways, complex tumour and host biology, access to age or site specific specialist care and poor compliance with treatment (Fern et al. 2014; Burke, Albritton, and Marina 2007). Importantly, recruitment rates to clinical trials in TYA cancer patients are the lowest of any age group (Bleyer et al. 1997; Burke, Albritton, and Marina 2007; Krailo et al. 1993; Fern et al. 2008). In those patients for whom clinical trials are available, factors influencing participation include whether the treating physician is from a paediatric or adult background (Tai et al. 2014; Parsons et al. 2011; Downs-Canner and Shaw 2009; Mitchell et al. 2004; Burke, Albritton, and Marina 2007), the type of treating centre (academic, tertiary or other)(Tai et al. 2014), and patient factors, notably the acceptability to and attitudes of TYA patients (Grigsby et al. 2014). In addition, there are often fewer clinical trials available to TYA patients than to younger or older cancer patients (Krailo et al. 1993; Shaw and Ritchey 2007; Fern et al. 2008), reflecting the unique distribution of tumours in this age group and the traditional separation between adult and paediatric clinical research programmes (Burke, Albritton, and Marina 2007).

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3 Whilst sequential clinical trials clearly inform evidence based best practice in cancer therapy
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5 and have improved outcomes in specific disease types (Stiller and Eatock 1999), the value of
6
7 participation for an individual patient is less clear. The benefits may include access to a
8
9 superior therapy not otherwise available, enhanced quality of care, access to a broader
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11 team of specialised professionals (Ferrari and Bleyer 2007) and stricter adherence to trial
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13 mandated treatment. However, to date, no study has demonstrated a survival advantage
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15 specifically associated with trial participation in TYA patients (Kumar et al. 2005; Peppercorn
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17 et al. 2004).

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24 Here, we report survival outcomes of TYA patients with acute lymphoblastic leukaemia (ALL)
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26 in England who were treated within or outside of the national clinical trial, UKALL2003.
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30 31 **METHODS**

32 33 34 35 36 **UKALL2003**

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38 UKALL2003 was the UK clinical trial of minimal residual disease (MRD)-directed
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40 chemotherapy for Philadelphia chromosome negative ALL in children and young people
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42 aged 1 to 24 years, which opened in 2003 and closed in 2011. The maximum age for trial
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44 entry was the 18th birthday when the trial began, but was increased to the 20th birthday in
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46 2006 and the 25th birthday in 2007. Details of the protocol and outcomes of the trial have
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48 been published previously (Vora et al. 2014; Vora et al. 2013; Hough et al. 2016).
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Study Population

The study population for this analysis was defined as any patient diagnosed with ALL in 2004-2010 (the 7 complete years during which UKALL2003 was recruiting), aged 15-24 years and resident in England at the time of diagnosis. Details were obtained on the 337 TYA patients who took part in the UKALL2003 Trial including name, date of birth and hospital of treatment, but not address or country of residence. Details of missing NHS numbers on UKALL2003 were obtained using the NHS Strategic Tracing Service (NSTS), which contains details of all individuals registered with a GP in England or Wales. The National Cancer Data Repository (NCDR) was the database used to undertake cancer analyses at the time this study commenced. It included details of all patients diagnosed with cancer who were resident in England. A frozen copy of NCDR was compiled from the eight regional registries then in existence, when cancer data for a given calendar year were considered to be near complete – a process which took considerable time. The version used in this study was that produced when 2010 data were considered complete. The patients in UKALL2003 were matched against those on the NCDR database who were diagnosed in 2004-2010 aged 15-24 with any cancer. Patients recorded on NCDR as having ALL and who were not on the UKALL database were included in our study as the non-trial arm.

The move to a single cancer registry for England, which was completed while this study was underway, resulted in the production of the English National Cancer Online Registration Environment (ENCORE). This is a live database, which is updated regularly. It is used by registry staff to determine if a given patient has already been registered. It contains details of all residents of England who have been diagnosed with cancer, including patients reported to the National Cancer Registration and Analysis Service (NCRAS) but with

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2
3 insufficient details to be counted as a case of cancer; these are called provisional
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5 registrations and are upgraded to full registrations when further details are obtained.
6
7 ENCORE also contains details of cancer patients managed at a hospital in England but
8
9 resident elsewhere. Patients on the UKALL database not found on NCDR were manually
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11 checked on ENCORE, in order to determine the reasons why these patients were not on
12
13 NCDR and to identify any patients reported to NCRAS after the NCDR was compiled. Those
14
15 whose records were found on ENCORE and who fulfilled the study definition were added to
16
17 patients on both UKALL and NCDR to make up the trial arm in our study.
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24 Details of patients on the UKALL database but not found on ENCORE were checked against
25
26 the NSTS to determine whether living in England or Wales. The UKALL database was
27
28 interrogated for the country of the treating hospital for those patients not found on NSTS.
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33 **Analyses**

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35 We determined the number and percentage of patients who participated in UKALL2003 by
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37 year of diagnosis and age group. Survival rates were calculated for patients in the trial and
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39 not in the trial, excluding patients on whom the only available data were from death
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41 certificates – death certificate only (DCO) registrations. Death details were obtained from
42
43 NCDR up to the end of 2012, with follow-up starting from the date of diagnosis recorded on
44
45 NCDR; the equivalent data were obtained from ENCORE for those patients not found on
46
47 NCDR. One-year, two-year and two-year conditional on one-year relative survival rates
48
49 were calculated for 15-24, 15-19 and 20-24 year olds for trial and non-trial patients.
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55 Relative survival was estimated from life tables stratified by age, sex and time using the
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3 Stata strs programme (Dickman et al. 2013). Expected survival was estimated using the
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5 Ederer II method.
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10 Differences in relative survival were modelled using a multiple regression approach based
11
12 on generalised linear models, assuming a Poisson distribution for the observed number of
13
14 deaths (Dickman et al. 2004). Differences were considered statistically significant if two-
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16 sided P values were <0.05 . All statistical analyses were conducted using Stata version 13.
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21 The numbers of deaths in those patients included in the survival analysis were determined
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23 for each three-month period during the two years of follow-up and percentages calculated
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25 based on the number of patients alive at the beginning of each three-month period. P
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27 values were calculated using the two-tailed z-test for difference between proportions. 95%
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29 confidence intervals for percentage deaths were derived using the Binomial distribution
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31 based on the Wilson Score method (Observatories 2008).
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38 **Completion of TYAC form**

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40 During 2009 and 2010, enhanced cancer registration forms were in use throughout the
41
42 English TYA Principal Treatment Centres (PTCs). The forms were developed by the
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44 professional organisation Teenagers and Young Adults with Cancer (TYAC)
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46 (<http://www.tyac.org.uk>) and were collected and matched with registry data by the lead UK
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48 regional registry for TYA cancer at the time, the North West Cancer Intelligence Service
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50 (now part of Public Health England). Receipt of a TYAC form by the registry was used as a
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52 proxy that the patient's management had been provided by or at least discussed with the
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54 regional TYA PTC. We calculated the percentage of patients in the trial for whom a TYAC
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3 form was completed to explore the relationship between access to TYA specialist services
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5 and participation in the trial.
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10 RESULTS

11 Study population

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17 The process by which the study population was selected is shown in Figure 1. Details on 227
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19 of the 337 patients on the UKALL database were found on NCDR; twenty of whom had a
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21 diagnosis other than ALL on NCDR. The most common diagnoses were leukaemia (5), acute
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23 leukaemia (4), acute myeloid leukaemia (4) and Non-Hodgkin lymphoma (4). 272 patients
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25 with a diagnosis of ALL on NCDR were not on the UKALL database and these constituted the
26
27 non-trial arm of this study.
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34 Of the 110 patients on UKALL2003 not found on NCDR, 43 were identified on ENCORE. 31
35
36 did not fulfil the study definition for the following reasons:

- 37 (a) 26 were diagnosed in 2011
- 38 (b) One diagnosed in 2003
- 39 (c) One aged 14 at time of diagnosis
- 40 (d) One treated in England but not a resident
- 41 (e) Two were provisional registrations that were not confirmed
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51 The twelve patients who fulfilled the study definition had been reported to the NCRAS after
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53 the NCDR was compiled. These patients were added to the 227 found on both the
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55 UKALL2003 and NCDR databases to make up the trial arm of this study.
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5 Of the 67 patients on the UKALL2003 database not found on ENCORE, 60 were not resident
6 in England confirmed by having a non-English address on NSTS and/or the treating hospital
7 recorded on UKALL2003 as being outside England. The remaining seven patients, who did
8 fulfil the study definition, were excluded for a number of reasons, including not being
9 reported to the registry by the treating hospital or insufficient details provided to allow a
10 full registration, and inaccurate personal details on the UKALL2003 database resulting in
11 patients not being found on ENCORE.
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24 **Participation in UKALL2003**

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26 A total of 511 patients aged 15-24 years were included in the analyses, of whom 239
27 (47.5%) had participated in UKALL2003 (Table 1a). The overall number of 20-24 year old
28 patients recruited (36 patients) was lower than 18-19 year olds (54 patients) and 15-17 year
29 olds (149 patients). In total, 203 (84.9%) of 239 trial patients were aged 15-19 years. Trial
30 participation improved over time, from 59.3% in 2004-2007 to 76.7% in 2008-2010 ($p =$
31 0.007) in the 15-17 year old group (the only group eligible for the trial for the entire study
32 period)(Table 1b). It is likely that the sequential changes in age eligibility criteria for
33 UKALL2003 were partly responsible for low recruitment numbers in the older age groups.
34 However, for the period 2008-2010, during which all 15-24 year olds were eligible for the
35 study, participation remained higher in younger patients: 76.3% of 15-19 year olds
36 compared with 45.1% of 20-24 year olds ($p < 0.001$).
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Survival

503 patients were included in the survival analysis: 239 in the trial arm and 264 in the non-trial arm. Patients aged 15-24 years recruited to the UKALL2003 trial had 17.9% better two-year survival (85.4% vs 67.5%, $p < 0.001$), 8.9% better one-year survival (90.8% vs 81.9%, $p = 0.004$) and 11.6% better two-year survival conditional on one-year survival (94.1% vs 82.5%, $p = 0.001$) compared to non-trial patients (Table 2, Figure 2). To determine whether the effects of trial recruitment on survival were measurable across the age cohort we analysed 15-19 year olds and 20-24 year olds separately. The differences in survival at all time points remained significant in the 15-19 year old age group (Table 2). Two-year and conditional two-year survival showed a non-significant trend to better in trial patients than non-trial patients in the 20-24 year old cohort.

To determine whether the deaths were evenly spaced after diagnosis we next analysed the number of deaths in trial and non-trial patients by quarter-year from diagnosis. Table 3 shows the number and percentage of deaths by trial status for each quarter-year and year of follow-up. A total of 35 (14.6%) trial patients died in the two years following diagnosis compared with 86 (32.6%) of non-trial patients ($p < 0.001$). The difference in the proportion of deaths between trial and non-trial patients was 9% (18.2% - 9.2%; $p = 0.004$) fewer deaths in trial patients during the first year and 11.6% (17.6% - 6.0%; $p < 0.001$) during the second. However, the largest number of deaths overall and the largest difference between trial and non-trial patients for any quarter was in the first three months after diagnosis: 6 (2.5%) trial patients died compared with 21 (8.0%) non-trial patients ($p = 0.007$).

Exploratory analysis of trial recruitment by place of care

The data available in national registry records were not sufficient to allow us to determine the reasons for non-recruitment of non-trial patients or how non-trial patients were treated. However, we were able to compare trial recruitment rates between patients for whom an enhanced TYAC cancer registration form had been submitted and those with no TYAC form. The trial recruitment rates were significantly different between the two groups: 73.5% of patients with a submitted TYAC form were recruited compared to 51.9% of those for whom a form was not submitted ($p=0.001$, Table 4). The difference was highest among patients aged 20-24 years (61.5% trial recruitment among patients with associated TYAC forms versus 36.4% without). Patients for whom a TYAC form was submitted had a two-year survival of 80.8% compared with 82.8% for those without a form ($p = 0.771$).

DISCUSSION

By combining trial and national cancer registry data we have demonstrated a significant survival advantage to participation in the most recently completed, large prospective clinical trial for TYA patients with ALL, which is measurable at a population level. This is the first study to have demonstrated such a survival advantage in any cancer type in the TYA age group. The difference in survival was highly significant and equated to a survival benefit at two years of approximately 130% in trial patients compared to non-trial patients. The risk of mortality at 2 years in those treated outside of the trial was twice that of those on UKALL2003 (32.6% compared to 14.6%, $p<0.001$) and was most striking during the first 3 months after diagnosis (8.0% compared to 2.5%, $p=0.007$).

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3 This retrospective analysis of the impact of clinical trial recruitment on survival was possible
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5 because the consent process for UKALL2003 included explicit consent for the trial data to be
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7 shared with regional and national cancer registries, and because the UK has full population
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9 coverage for cancer registration. This study, however, did show a number of limitations of
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11 the cancer registration system for England during the period 2004-2010 including a)
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13 Accuracy of diagnosis: twenty patients on UKALL2003 with a diagnosis other than ALL on
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15 NCDR and b) Timeliness: twelve patients on ENCORE but not on NCDR. In addition, the main
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17 source of diagnostic data for cancer registries during the study period was histopathology
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19 laboratories, leading to difficulties in obtaining high quality data on patients with ALL. Data
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21 were collected by regional registries and then compiled into a national database, which took
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23 considerable time. Public Health England (PHE) has made many improvements since taking
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25 over the NCRAS a few years ago including a) Moving to a single, completely integrated
26
27 national registry, b) Setting up systems that report in real time from a wide variety of
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29 sources, such as MDTs, leading to more timely and accurate data and c) Reviewing access to
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31 specialist haematological diagnostic datasets to improve the data quality of haematological
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33 cancers and d) Producing an analysis database that is constantly kept up to date.
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43 We also recognise a number of potential confounding variables in this study. Potential
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45 confounders which could increase the observed difference between those on trial compared
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47 to those treated off trial include centre effect and selection bias, and those reducing the
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49 difference include recruitment to other ALL clinical trials.
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55 Any potential benefit to participation of young people in clinical trials may be derived from
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57 the treating centre rather than trial participation itself (centre effect). Centres offering
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3 clinical trials are often larger, academic institutions, seeing a higher number of patients with
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5 a specific disease, a larger clinical research infrastructure and a more resourced workforce,
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7 all of which may contribute to a more favourable outcome (Ferrari and Bleyer 2007). Over
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9 the last 10 years there has been a gradual reconfiguration of services providing care for
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11 young people aged 16-24 years with cancer in the UK; this includes the development of
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13 Principal Treatment Centres, designated of other hospitals offering TYA services closer to
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15 the patients' homes and an overview of the holistic care of all patients provided by the TYA
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17 multidisciplinary team (MDT). Between 2004 to 2010, these pathways were not fully
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19 established, but the submission of TYAC enhanced cancer registration forms have been used
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21 as a surrogate indicator that an individual patient received treatment according to regionally
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23 agreed and commissioned TYA pathways under the supervision of the TYA PTC. It is
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25 therefore interesting to note that a significantly higher proportion of patients recruited onto
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27 UKALL2003 had been registered centrally via the TYAC notification system than non-trial
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29 patients (73.5% with a TYAC form compared to 51.9% without, $p=0.001$). This was
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31 particularly marked in the older age group. However, the finding that two-year survival was
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33 not higher in those patients with a submitted TYAC form does not support the argument
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35 that the better survival for those in the trial was mainly due to having been managed at
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37 larger centres.
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48 Whilst selection bias, in which the highest risk patients (eg those with a very high white
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50 count, renal or hepatic impairment or large mediastinal mass at presentation) could not
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52 participate in the trial, may be a confounder it is unlikely to have had a significant impact on
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54 our results as a) UKALL2003 was a population-based trial for which all children and young
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56 people with ALL were eligible, irrespective of severity or risk group at presentation and b) it
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3 also permitted recruitment within 7 days of commencement of chemotherapy. Patients
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5 with Philadelphia chromosome positive (Ph+ve) ALL were ineligible for UKALL2003 , but
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7 Ph+ve patients were included in the non-trial arm, as NCDR did not include details of Ph
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9 chromosome status . The presence of the Philadelphia chromosome in ALL confers a poorer
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11 prognosis (Pui and Evans 2006) and could therefore increase the survival difference
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13 observed in this study. However we feel that this is unlikely to have been a significant
14
15 confounding variable since the prevalence of Ph+ve ALL in UKALL2003 overall was only 1.8%
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17 and the observed difference between groups was smaller in the older patients despite the
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19 frequency of the Philadelphia chromosome increasing with increasing age.
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26 During the study period, TYA patients with Ph+ve disease were eligible for the ESPHALL or
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28 UKALLXII (until 2006) trials, depending on age, and older patients with Ph-ve disease were
29
30 eligible for recruitment onto UKALLXII (lower age limit 18th birthday from 2004, 20th birthday
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32 from 2006 and 25th birthday from 2007). Whilst we do not know the proportions of non-
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34 UKALL2003 patients recruited to these trials, if trial participation in itself confers a survival
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36 advantage, recruitment of patients to these other clinical trials would be expected to reduce
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38 observed differences between our two study groups, reduce any residual confounding from
39
40 the exclusion of Ph+ve patients from UKALL2003 and may have also contributed to the
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42 smaller difference in survival between trial and non-trial patients in the 20-24 year old
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44 group.
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52 Recruitment to clinical trials in TYA cancer patients is poor due to a range of factors
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54 including lack of an available trial, heterogenous referral pathways, differences in treating
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56 centres as well as lack of desire to participate by this age group (Hendricks-Ferguson et al.
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3 2013; Tai et al. 2014; Fern et al. 2014; Grigsby et al. 2014). Overall, approximately 50% of
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5 TYA patients in England with ALL participated in UKALL2003. Although this figure is lower
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7 than the proportion of younger children who participated in the trial, it compares
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9 favourably to other cancer trials reported in this age group; in the UK between 2005 to
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11 2010, only 850 of 2860 patients aged 15–19 years (30%), and 562 of 4011 patients aged 20–
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13 24 years (14%) were recruited to a clinical trial (Fern et al. 2014). Encouragingly,
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15 recruitment to UKALL2003 improved over time. In part, this was expected in the 18-24 year
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17 old group, given the sequential increase in age eligibility criteria over time. However, even
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19 in the 15-17 year old patients who were eligible for participation throughout the study
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21 period, participation increased from 59.3% in 2004-2007 to 76.7% in 2008-2010 ($p = 0.007$).
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23 Despite this, there were still a substantial number of young people who did not participate,
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25 particularly amongst 20-24 year olds, where participation was only 45.1%. Fern et al
26
27 propose that there are five factors (five “A’s”) important in improving TYA cancer trial
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29 recruitment; available, accessible, aware, appropriate, and acceptable. The relatively high
30
31 level of recruitment of TYA ALL patients to UKALL2003 and its improvement over time
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33 probably reflects an increasing awareness and acceptability amongst paediatric and adult
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35 haematologists that UKALL2003 offered an effective (i.e. appropriate) treatment strategy,
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37 with increasing availability and accessibility as the age range was increased and a greater
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39 number of adult centres opened the trial.
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50 In conclusion, we report a specific survival advantage to participation in the UKALL2003 trial
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52 for TYA patients with ALL. This is the first study to have demonstrated a survival advantage
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54 of trial participation in TYA patients with any cancer and suggests a benefit to an individual
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56 patient in taking part. These data highlight the importance of national and international
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3 efforts to a) improve recruitment of TYA cancer patients to clinical trials, b) configure TYA
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5 cancer services to provide young people with access to appropriate trials and the
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7 opportunity to participate and c) the need to continue to collect accurate treatment and
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9 outcome data at a population level to allow evaluation of treatment in patients who have
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11 not accessed clinical trials. In England these duties are the responsibilities respectively of
12
13 the National Cancer Research Institute, NHS England and Public Health England, working
14
15 together towards the goal of best patient outcomes. The data we present suggest that
16
17 significant improvements in the delivery of appropriate cancer treatment are still much
18
19 needed for this vulnerable young population.
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26 **ACKNOWLEDGEMENTS AND AUTHOR CONTRIBUTIONS**

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31 Patients, families and clinicians participating in UKALL2003

32
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34 Regional and institutional data managers

35
36 The study was designed by RH, AM, SS, MK, RF, CS and MMC. RH, CR and AV designed,
37
38 recruited to and analysed data for the UKALL2003 study. The statistical analysis of this
39
40 study was performed by SS, MK, AM and MMC. All authors contributed to the
41
42 interpretation of data and preparation of the manuscript and approve this final version.
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COMPETING INTERESTS STATEMENT

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

DATA SHARING STATEMENT

There are no additional unpublished data from this study

For peer review only

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FIGURE AND TABLE TITLES

Figure 1: Study population derived from matching UKALL2003 against the National Cancer

Data Repository (NCDR) and ENCORE

Figure 2: Two-year relative survival by age group and trial status

Table 1: Participation in UKALL2003 by age group and year of diagnosis

Table 1a: All Patients

Table 1b: Trial Participation over time in 15-17 year olds

Table 2: One- and two-year survival by age group and trial status

Table 3: Number and percentage of patients aged 15-24 who died in the two years

following diagnosis, by 3 month period, year and trial status

Table 4: Number and percentage of patients in trial by whether a TYAC form was received

by age group in 2009-10

Table 1: Participation in UKALL2003 by age group and year of diagnosis

Table 1a: All Patients

Year of diagnosis	15-17 years			18-19 years			20-24 years			15-24 years		
	Proportion	Percentage	95% CI	Proportion	Percentage	95% CI	Proportion	Percentage	95% CI	Proportion	Percentage	95% CI
2004	19/34	55.9	39.5-71.1	0/6	0.0	0.0-39.0	0/25	0.0	0-13.3	19/65	29.2	19.6-41.2
2005	26/45	57.8	43.3-71.0	0/20	0.0	0-16.1	0/23	0.0	0-14.3	26/88	29.5	21.0-39.8
2006	18/29	62.1	44.0-77.3	9/26	34.6	19.4-53.8	0/19	0.0	0-29.9	27/74	36.5	26.4-47.9
2007	20/32	62.5	45.3-77.1	8/14	57.1	32.6-78.6	4/32	12.5	5.0-28.1	32/78	41.0	30.8-52.1
2008	23/30	76.7	59.1-88.2	16/18	88.9	67.2-96.9	8/23	34.8	18.8-55.1	47/71	66.2	54.6-76.1
2009	24/31	77.4	60.2-88.6	13/20	65.0	43.3-81.9	10/26	38.5	22.4-57.5	47/77	61.0	49.9-71.2
2010	19/25	76.0	56.6-88.5	8/11	72.7	43.4-90.3	14/22	63.6	43.0-80.3	41/58	70.7	58.0-80.8
2004-07	83/140	59.3	51.0-67.1	17/66	25.8	16.7-37.4	4/99	4.0	1.6-9.9	104/305	34.1	29.0-39.6
2008-10	66/86	76.7	66.8-84.4	37/49	75.5	61.9-85.4	32/71	45.1	34.0-56.6	135/206	45.1	34.0-56.6
2004-10	149/226	65.9	59.5-71.8	54/115	47.0	38.1-56.0	36/170	21.2	15.7-27.9	239/511	46.8	42.5-51.1

Table 1b: Trial Participation over time in 15-17 year olds

Year of diagnosis	Proportion	Percentage	95% CI	p value
2004-07	83/140	59.3	51.0-67.1	0.007
2008-10	66/86	76.7	66.8-84.4	

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Table 2: One- and two-year survival by age group and trial status

Trial Status	Age group	Number of patients	Deaths	Survival (%)	95% CI	P value
1-year survival						
Trial	15-19	203	17	91.7	86.9-94.7	<0.001
Non-Trial		134	30	77.6	69.6-83.8	
Trial	20-24	36	5	86.2	69.8-94.0	0.969
Non-Trial		130	18	86.2	79.0-91.1	
Trial	15-24	239	22	90.8	86.4-93.9	0.004
Non-Trial		264	48	81.9	76.6-86.0	
2-year conditional on 1-year survival						
Trial	15-19	186	10	94.7	90.3-97.1	0.008
Non-Trial		104	16	84.7	76.2-90.4	
Trial	20-24	31	3	90.4	73.0-96.9	0.236
Non-Trial		112	22	80.4	71.8-86.7	
Trial	15-24	217	13	94.1	90.0-96.6	0.001
Non-Trial		216	38	82.5	76.7-87.0	
2-year survival						
Trial	15-19	203	27	86.8	81.3-90.7	<0.001
Non-Trial		134	46	65.7	57.0-73.1	
Trial	20-24	36	8	77.9	60.5-88.3	0.381
Non-Trial		130	40	69.3	60.6-76.5	
Trial	15-24	239	35	85.4	80.3-89.3	<0.001
Non-Trial		264	86	67.5	61.5-72.8	

Table 3: Number and percentage of patients aged 15-24 who died in the two years following diagnosis, by 3 month period, year and trial status

Year	Quarter	<i>In trial</i>				<i>Not in trial</i>				p values
		Number of patients at start of period	Number of deaths	% Died	95% CI	Number of patients at start of period	Number of deaths	% Died	95% CI	
	1st	239	6	2.5	1.2-5.4	264	21	8.0	5.3-11.9	0.007
	2nd	233	4	1.7	0.7-4.3	243	5	2.1	0.9-4.7	0.785
	3rd	229	5	2.2	0.9-5.0	238	11	4.6	2.6-8.1	0.148
	4th	224	7	3.1	1.5-6.3	227	11	4.8	2.7-8.5	0.351
1st	-	239	22	9.2	6.2-13.5	264	48	18.2	14.0-23.3	0.004
	5th	217	2	0.9	0.3-3.3	216	11	5.1	2.9-8.9	0.011
	6th	215	4	1.9	0.7-4.7	205	10	4.9	2.7-8.7	0.0851
	7th	211	3	1.4	0.5-4.1	195	8	4.1	2.1-7.9	0.0965
	8th	208	4	1.9	0.8-4.8	187	9	4.8	2.6-8.9	0.108
2nd	-	217	13	6.0	3.5-10.0	216	38	17.6	13.1-23.2	<0.001
1st and 2nd	-	239	35	14.6	10.7-19.7	264	86	32.6	27.2-38.4	<0.001

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Table 4: Number and percentage of patients in trial by whether a TYAC form was received by age group in 2009-10

Age	<i>Proportion of patients with a TYAC form who were in trial</i>			<i>Proportion of patients without a TYAC form who were in trial</i>			p value
	Proportion	Percentage	95% CI	Proportion	Percentage	95% CI	
15-19	45/57	78.9	66.7-87.5	19/30	63.3	45.5-78.1	0.117
20-24	16/26	61.5	42.5-77.6	8/22	36.4	19.7-57.0	0.082
15-24	61/83	73.5	63.1-81.8	27/52	51.9	38.7-64.9	0.011

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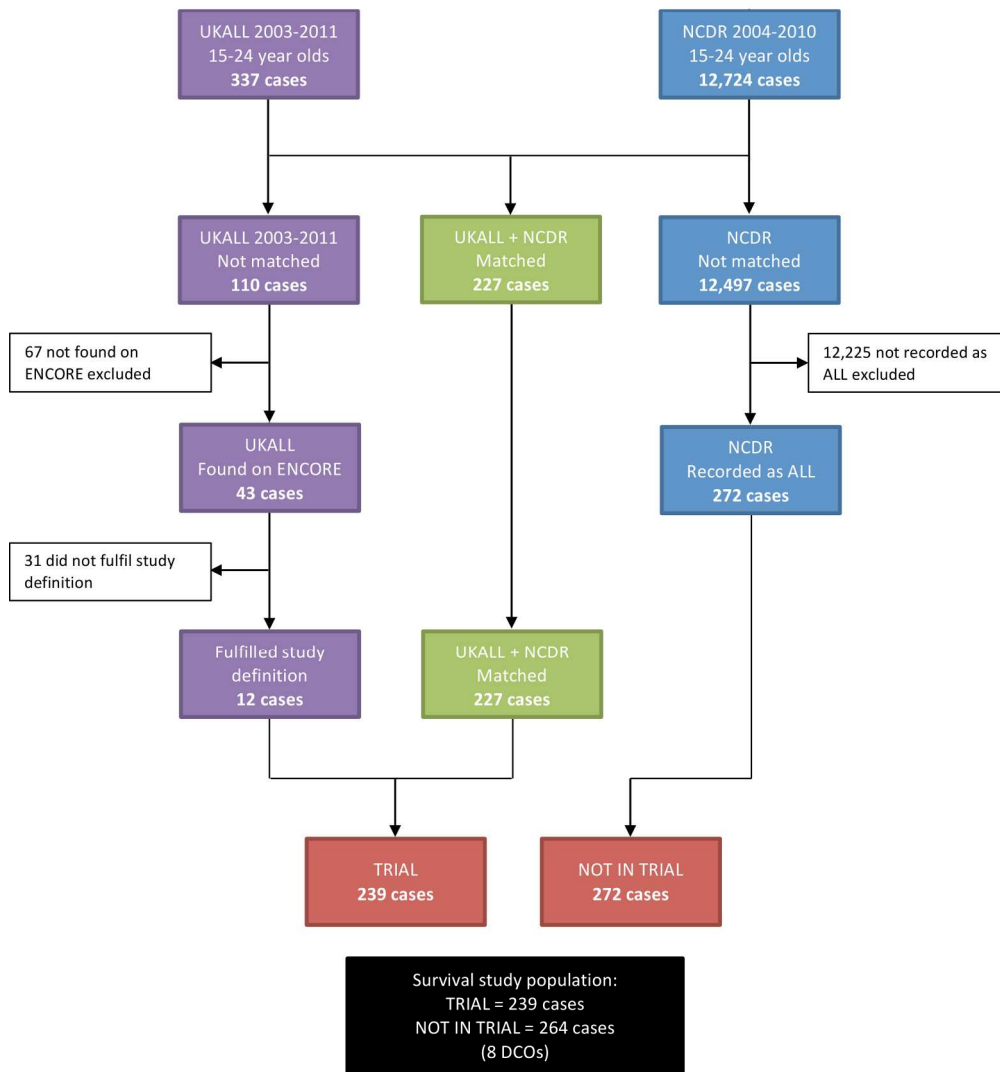


Figure 1: Study population derived from matching UKALL2003 against the National Cancer Data Repository (NCDR) and ENCORE

182x212mm (300 x 300 DPI)

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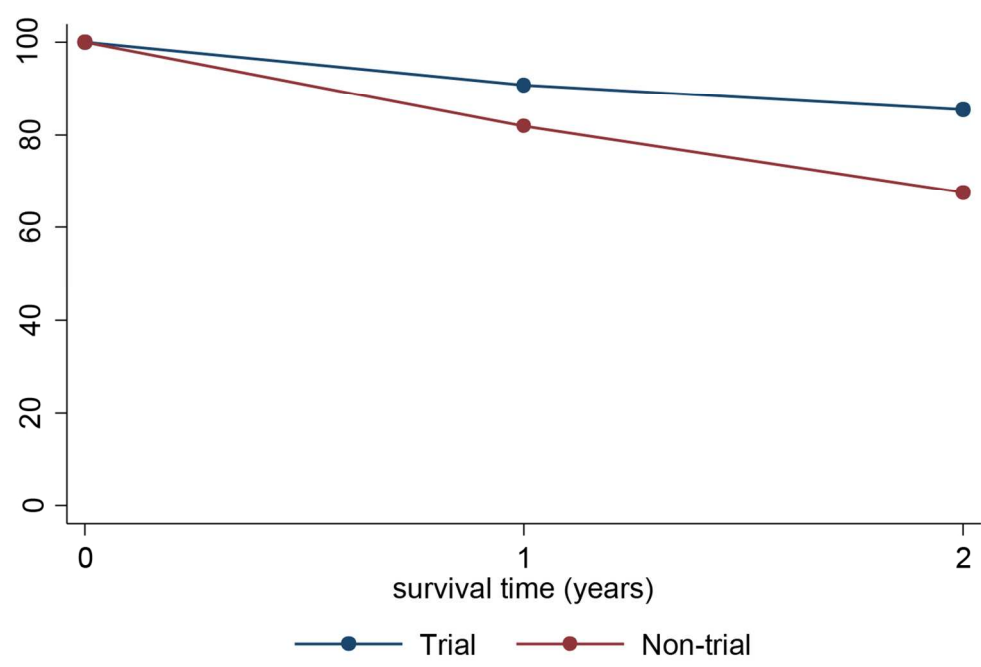


Figure 2: Two-year relative survival by age group and trial status
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BMJ Open

Are Survival and Mortality Rates Associated with Recruitment to Clinical Trials in Teenage and Young Adult Patients with Acute Lymphoblastic Leukaemia?

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Secondary Subject Heading:	Evidence based practice
Keywords:	Clinical trials < THERAPEUTICS, Survival, Teenage and young adult, Acute lymphoblastic leukaemia

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Manuscripts

TITLE:

Are Survival and Mortality Rates Associated with Recruitment to Clinical Trials in Teenage and Young Adult Patients with Acute Lymphoblastic Leukaemia?

RUNNING TITLE:

Impact of Trial Recruitment in TYA ALL

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ABSTRACT**Objective**

Participation rates in clinical trials are low in teenagers and young adults (TYA) with cancer.

Whilst the importance of clinical trials in informing best practice is well established, data regarding individual patient benefit are scarce. We have investigated the association between overall survival and trial recruitment in TYA patients with acute lymphoblastic leukaemia (ALL).

Design

Retrospective

Setting

National (England) TYA patients treated for ALL

Participants

511 patients aged 15-24 years diagnosed with ALL between 2004 to 2010 inclusive, of whom 239 (46.7%) participated in the UKALL2003 trial.

Outcome Measures

Patients were identified using National Clinical Trial (UKALL2003) and Cancer Registry (National Cancer Data Repository, English National Cancer Online Registration Environment) Databases. Relative survival rates were calculated for trial and non-trial patients and observed differences were modelled using a multiple regression approach. The numbers and percentages of deaths in those patients included in the survival analysis were determined for each three-month period, P values were calculated using the two-tailed z-test for difference between proportions and 95% confidence intervals for percentage deaths were derived using the Binomial distribution based on the Wilson Score method.

Results

Patients treated on the trial had a 17.9% better two-year survival (85.4% vs 67.5%, $p < 0.001$) and 8.9% better one-year survival (90.8% vs 81.9%, $p = 0.004$) than those not on the trial. 35 (14.6%) patients recruited to the trial died in the two years following diagnosis compared with 86 (32.6%) of those not recruited ($p < 0.001$).

Conclusions

TYA patients recruited to the clinical trial UKALL 2003 in England had a lower risk of mortality and a higher overall survival than contemporaneous non-trial patients. These data underline the potential for individual patient benefit in joining a clinical trial and the importance of international efforts to increase trial participation in the TYA age group.

STRENGTHS AND LIMITATIONS OF THIS STUDY

The study asks a fundamental question regarding the value to an individual of recruitment to a clinical trial

Large sample size including all TYA patients aged 15-24 years diagnosed with ALL in England between 2004-2010

This retrospective study is possible because a) the consent process for UKALL2003 included explicit consent for the trial data to be shared with regional and national cancer registries, and b) because the UK has full population coverage for cancer registration

Potential confounding variables include selection bias, centre effect and recruitment to other clinical trials

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INTRODUCTION

Although survival rates in teenage and young adult (TYA) patients with cancer have improved over the last two decades [1], these outcome gains have been modest and cancer remains the leading cause of non-accidental mortality in the TYA age group [2, 3].

The barriers to improving survival are likely to be multifactorial and include sub-optimal diagnostic pathways, complex tumour and host biology, access to age or site specific specialist care and poor compliance with treatment [4, 5]. Importantly, recruitment rates to clinical trials in TYA cancer patients are the lowest of any age group [5-8]. In those patients for whom clinical trials are available, factors influencing participation include whether the treating physician is from a paediatric or adult background [5, 9-12], the type of treating centre (academic, tertiary or other)[9], and patient factors, notably the acceptability to and attitudes of TYA patients [13]. In addition, there are often fewer clinical trials available to TYA patients than to younger or older cancer patients [7, 8, 14], reflecting the unique distribution of tumours in this age group and the traditional separation between adult and paediatric clinical research programmes [5].

Whilst sequential clinical trials clearly inform evidence based best practice in cancer therapy and have improved outcomes in specific disease types [15], the value of participation for an individual patient is less clear. The benefits may include access to a superior therapy not otherwise available, enhanced quality of care, access to a broader team of specialised professionals [16] and stricter adherence to trial mandated treatment. However, to date,

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3 no study has demonstrated a survival advantage specifically associated with trial
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5 participation in TYA patients [17, 18].
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10 Here, we report survival outcomes of TYA patients with acute lymphoblastic leukaemia (ALL)
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12 in England who were treated within or outside of the national clinical trial, UKALL2003.
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15 16 17 **METHODS** 18 19

20 21 **UKALL2003** 22

23 UKALL2003 was the UK clinical trial of minimal residual disease (MRD)-directed
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25 chemotherapy for Philadelphia chromosome negative ALL in children and young people
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27 aged 1 to 24 years, which opened in 2003 and closed in 2011. The maximum age for trial
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29 entry was the 18th birthday when the trial began, but was increased to the 20th birthday in
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31 2006 and the 25th birthday in 2007. Details of the protocol and outcomes of the trial have
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33 been published previously [19-21]. The consent form for UKALL2003 included explicit
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35 consent for data sharing with national cancer registries. Patients with Philadelphia
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37 chromosome positive ALL were eligible for post induction recruitment to the ESPHALL trial if
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39 aged less than 18 years (until 2009) or UKALL XII if aged 18 years or older (until 2006). The
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41 lower age limit for recruitment of patients with Philadelphia negative ALL to UKALL XII was
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43 sequentially increased according to the change in the upper age limit for UKALL2003 to
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45 avoid overlapping age eligibility for the two trials. These changes to age eligibility for
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47 UKALL2003 and UKALL XII were communicated in newsletters circulated by the clinical trials
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49 unit and presented at both paediatric and adult annual national leukaemia trials update
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3 meetings. The National Institute for Health Research also hosts a trial database, which
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5 summarised all of these trials and was searchable by any clinician.
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9 10 **Study Population**

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12 The study population for this analysis was defined as any patient diagnosed with ALL in
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14 2004-2010 (the 7 complete years during which UKALL2003 was recruiting), aged 15-24 years
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16 and resident in England at the time of diagnosis. The diagnosis reported to the registry and
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18 trial was made in the laboratories of treating centre, without central verification. Details
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20 were obtained on the 337 TYA patients who took part in the UKALL2003 Trial including
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22 name, date of birth and hospital of treatment, but not address or country of residence.
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24 Details of missing NHS numbers on UKALL2003 were obtained using the NHS Strategic
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26 Tracing Service (NSTS), which contains details of all individuals registered with a GP in
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28 England or Wales. The National Cancer Data Repository (NCDR) was the database used to
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30 undertake cancer analyses at the time this study commenced. It included details of all
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32 patients diagnosed with cancer who were resident in England. A frozen copy of NCDR was
33
34 compiled from the eight regional registries then in existence, when cancer data for a given
35
36 calendar year were considered to be near complete – a process which took considerable
37
38 time. The version used in this study was that produced when 2010 data were considered
39
40 complete. The patients in UKALL2003 were matched against those on the NCDR database
41
42 who were diagnosed in 2004-2010 aged 15-24 with any cancer. Patients recorded on NCDR
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44 as having ALL and who were not on the UKALL database were included in our study as the
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46 non-trial arm.
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3 The move to a single cancer registry for England, which was completed while this study was
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5 underway, resulted in the production of the English National Cancer Online Registration
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7 Environment (ENCORE). This is a live database, which is updated regularly. It is used by
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9 registry staff to determine if a given patient has already been registered. It contains details
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11 of all residents of England who have been diagnosed with cancer, including patients
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13 reported to the National Cancer Registration and Analysis Service (NCRAS) but with
14
15 insufficient details to be counted as a case of cancer; these are called provisional
16
17 registrations and are upgraded to full registrations when further details are obtained.
18
19 ENCORE also contains details of cancer patients managed at a hospital in England but
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21 resident elsewhere. Patients on the UKALL database not found on NCDR were manually
22
23 checked on ENCORE, in order to determine the reasons why these patients were not on
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25 NCDR and to identify any patients reported to NCRAS after the NCDR was compiled. Those
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27 whose records were found on ENCORE and who fulfilled the study definition were added to
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29 patients on both UKALL and NCDR to make up the trial arm in our study.
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Details of patients on the UKALL database but not found on ENCORE were checked against the NSTS to determine whether living in England or Wales. The UKALL database was interrogated for the country of the treating hospital for those patients not found on NSTS.

Consent

Registry data was routinely submitted to the national cancer registry under legal permissions that were initially included under Section 60 of the Health and Social Care Act 2001 and more recently Section 251 of the NHS Act 2006. This permission is renewed

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3 annually. Identifiable trial data were shared with explicit patient consent obtained during
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5 trial registration.
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10 11 12 **Analyses**

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14 We determined the number and percentage of patients who participated in UKALL2003 by
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16 year of diagnosis and age group. Survival rates were calculated for patients in the trial and
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18 not in the trial, excluding patients on whom the only available data were from death
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20 certificates – death certificate only (DCO) registrations. Death details were obtained from
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22 NCDR up to the end of 2012, with follow-up starting from the date of diagnosis recorded on
23
24 NCDR; the equivalent data were obtained from ENCORE for those patients not found on
25
26 NCDR. One-year, two-year and two-year conditional on one-year relative survival rates
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28 were calculated for 15-24, 15-19 and 20-24 year olds for trial and non-trial patients.
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30 Relative survival was estimated from life tables stratified by age, sex and time using the
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32 Stata strsr programme [22]. Expected survival was estimated using the Ederer II method.
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40 Differences in relative survival were modelled using a multiple regression approach based
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42 on generalised linear models, assuming a Poisson distribution for the observed number of
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44 deaths [23]. Differences were considered statistically significant if two-sided P values were
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46 <0.05. All statistical analyses were conducted using Stata version 13.
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52 The numbers of deaths in those patients included in the survival analysis were determined
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54 for each three-month period during the two years of follow-up and percentages calculated
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56 based on the number of patients alive at the beginning of each three-month period. P
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3 values were calculated using the two-tailed z-test for difference between proportions. 95%
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5 confidence intervals for percentage deaths were derived using the Binomial distribution
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7 based on the Wilson Score method [24].
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10 11 12 **Completion of TYAC form** 13

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15 During 2009 and 2010, enhanced cancer registration forms were in use throughout the
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17 English TYA Principal Treatment Centres (PTCs). The forms were developed by the
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19 professional organisation Teenagers and Young Adults with Cancer (TYAC)
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21 (<http://www.tyac.org.uk>) and were collected and matched with registry data by the lead UK
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23 regional registry for TYA cancer at the time, the North West Cancer Intelligence Service
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25 (now part of Public Health England). Receipt of a TYAC form by the registry was used as a
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27 proxy that the patient's management had been provided by or at least discussed with the
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29 regional TYA PTC. We calculated the percentage of patients in the trial for whom a TYAC
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31 form was completed to explore the relationship between access to TYA specialist services
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33 and participation in the trial.
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RESULTS

Study population

The process by which the study population was selected is shown in Figure 1. Details on 227 of the 337 patients on the UKALL database were found on NCDR; twenty of whom had a diagnosis other than ALL on NCDR. The most common diagnoses were leukaemia (5), acute leukaemia (4), acute myeloid leukaemia (4) and Non-Hodgkin lymphoma (4). 272 patients with a diagnosis of ALL on NCDR were not on the UKALL database and these constituted the non-trial arm of this study.

Of the 110 patients on UKALL2003 not found on NCDR, 43 were identified on ENCORE. 31 did not fulfil the study definition for the following reasons:

- (a) 26 were diagnosed in 2011
- (b) One diagnosed in 2003
- (c) One aged 14 at time of diagnosis
- (d) One treated in England but not a resident
- (e) Two were provisional registrations that were not confirmed

The twelve patients who fulfilled the study definition had been reported to the NCRAS after the NCDR was compiled. These patients were added to the 227 found on both the UKALL2003 and NCDR databases to make up the trial arm of this study.

Of the 67 patients on the UKALL2003 database not found on ENCORE, 60 were not resident in England confirmed by having a non-English address on NSTS and/or the treating hospital

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3 recorded on UKALL2003 as being outside England. The remaining seven patients, who did
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5 fulfil the study definition, were excluded for a number of reasons, including not being
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7 reported to the registry by the treating hospital or insufficient details provided to allow a
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9 full registration, and inaccurate personal details on the UKALL2003 database resulting in
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11 patients not being found on ENCORE.
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14 15 16 17 **Participation in UKALL2003**

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19 A total of 511 patients aged 15-24 years were included in the analyses, of whom 239
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21 (47.5%) had participated in UKALL2003 (Table 1a). The overall number of 20-24 year old
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23 patients recruited (36 patients) was lower than 18-19 year olds (54 patients) and 15-17 year
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25 olds (149 patients). In total, 203 (84.9%) of 239 trial patients were aged 15-19 years. Trial
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27 participation improved over time, from 59.3% in 2004-2007 to 76.7% in 2008-2010 ($p =$
28
29 0.007) in the 15-17 year old group (the only group eligible for the trial for the entire study
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31 period)(Table 1b). It is likely that the sequential changes in age eligibility criteria for
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33 UKALL2003 were partly responsible for low recruitment numbers in the older age groups.
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35 However, for the period 2008-2010, during which all 15-24 year olds were eligible for the
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37 study, participation remained higher in younger patients: 76.3% of 15-19 year olds
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39 compared with 45.1% of 20-24 year olds ($p < 0.001$).
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48 **Recruitment to Other Clinical Trials**

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50 Since the trial consent forms for ESPHALL and UKALLXII did not include explicit consent for
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52 data sharing with the national registries, it was not possible to access detailed information
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54 from these trial databases. However, the overall number of UK patients recruited to these
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56 trials within the study period included 3 patients aged 15-17 years recruited to ESPHALL and
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3 100 patients aged 15-24 years recruited to UKALL XII. Although ESPHALL recruited only
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5 those with Philadelphia chromosome positive disease, UKALL XII recruited both Philadelphia
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7 chromosome positive and negative ALL patients. Given the sequential increase in the lower
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9 age limit for UKALL XII for Philadelphia chromosome negative ALL was sequentially
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11 increased over time, the highest proportion of patients recruited to UKALL XII would be
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13 those with Philadelphia chromosome negative disease in the older age group..
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22 **Survival**

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24 503 patients were included in the survival analysis: 239 in the trial arm and 264 in the non-
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26 trial arm. Patients aged 15-24 years recruited to the UKALL2003 trial had 17.9% better two-
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28 year survival (85.4% vs 67.5%, $p < 0.001$), 8.9% better one-year survival (90.8% vs 81.9%, $p =$
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30 0.004) and 11.6% better two-year survival conditional on one-year survival (94.1% vs 82.5%,
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32 $p = 0.001$) compared to non-trial patients (Table 2, Figure 2). To determine whether the
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34 effects of trial recruitment on survival were measurable across the age cohort we analysed
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36 15-19 year olds and 20-24 year olds separately. The differences in survival at all time points
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38 remained significant in the 15-19 year old age group (Table 2). Two-year and conditional
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40 two-year survival showed a non-significant trend to better in trial patients than non-trial
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42 patients in the 20-24 year old cohort. The results for 2008-10 (after closure of UKALLXII) are
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44 similar to those for the whole study period: 20-24 year olds in the trial had a two-year
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46 survival 10.2% better than those not in the trial, but this did not reach statistical significance p
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48 = 0.393.
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3 To determine whether the deaths were evenly spaced after diagnosis we next analysed the
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5 number of deaths in trial and non-trial patients by quarter-year from diagnosis. Table 3
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7 shows the number and percentage of deaths by trial status for each quarter-year and year
8
9 of follow-up. A total of 35 (14.6%) trial patients died in the two years following diagnosis
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11 compared with 86 (32.6%) of non-trial patients ($p < 0.001$). The difference in the proportion
12
13 of deaths between trial and non-trial patients was 9% (18.2% - 9.2%; $p = 0.004$) fewer
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15 deaths in trial patients during the first year and 11.6% (17.6% - 6.0%; $p < 0.001$) during the
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17 second. However, the largest number of deaths overall and the largest difference between
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19 trial and non-trial patients for any quarter was in the first three months after diagnosis: 6
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21 (2.5%) trial patients died compared with 21 (8.0%) non-trial patients ($p = 0.007$).
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29 **Exploratory analysis of trial recruitment by place of care**

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31 The data available in national registry records were not sufficient to allow us to determine
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33 the reasons for non-recruitment of non-trial patients, how non-trial patients were treated
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35 or the training background of treating physicians (paediatric, TYA or adult). However, we
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37 were able to compare trial recruitment rates between patients for whom an enhanced TYAC
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39 cancer registration form had been submitted and those with no TYAC form. The trial
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41 recruitment rates were significantly different between the two groups: 73.5% of patients
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43 with a submitted TYAC form were recruited compared to 51.9% of those for whom a form
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45 was not submitted ($p = 0.001$, Table 4). The difference was highest among patients aged 20-
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47 24 years (61.5% trial recruitment among patients with associated TYAC forms versus 36.4%
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49 without). Patients for whom a TYAC form was submitted had a two-year survival of 80.8%
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51 compared with 82.8% for those without a form ($p = 0.771$).
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DISCUSSION

By combining trial and national cancer registry data we have demonstrated a significant survival advantage to participation in the most recently completed, large prospective clinical trial for TYA patients with ALL, which is measurable at a population level. This is the first study to have demonstrated such a survival advantage in any cancer type in the TYA age group. The difference in survival was highly significant, with a 17.9% superior survival at two years in trial patients compared to non-trial patients. The risk of mortality at 2 years in those treated outside of the trial was twice that of those on UKALL2003 (32.6% compared to 14.6%, $p < 0.001$) and was most striking during the first 3 months after diagnosis (8.0% compared to 2.5%, $p = 0.007$).

This retrospective analysis of the impact of clinical trial recruitment on survival was possible because the consent process for UKALL2003 included explicit consent for the trial data to be shared with regional and national cancer registries, and because the UK has full population coverage for cancer registration. This study, however, did show a number of limitations of the cancer registration system for England during the period 2004-2010 including a) Accuracy of diagnosis: twenty patients on UKALL2003 with a diagnosis other than ALL on NCDR and b) Timeliness: twelve patients on ENCORE but not on NCDR. In addition, the main source of diagnostic data for cancer registries during the study period was histopathology laboratories, leading to difficulties in obtaining high quality data on patients with ALL. In addition, there were no data available for the well-established prognostic variables in ALL, thus precluding comparison of the frequency of different risk groups between those treated on or off trial. Data were collected by regional registries and then compiled into a national

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3 database, which took considerable time. Public Health England (PHE) has made many
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5 improvements since taking over the NCRAS a few years ago including a) Moving to a single,
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7 completely integrated national registry, b) Setting up systems that report in real time from a
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9 wide variety of sources, such as MDTs, leading to more timely and accurate data and c)
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11 Reviewing access to specialist haematological diagnostic datasets to improve the data
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13 quality of haematological cancers and d) Producing an analysis database that is constantly
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15 kept up to date.
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21 We also recognise a number of potential confounding variables in this study. Potential
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23 confounders which could increase the observed difference between those on trial compared
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25 to those treated off trial include centre effect, selection bias and use of a superior protocol,
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27 and those reducing the difference include recruitment to other ALL clinical trials.
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33 Any potential benefit to participation of young people in clinical trials may be derived from
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35 the treating centre rather than trial participation itself (centre effect). Centres offering
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37 clinical trials are often larger, academic institutions, seeing a higher number of patients with
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39 a specific disease, a larger clinical research infrastructure and a more resourced workforce,
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41 all of which may contribute to a more favourable outcome [16]. Over the last 10 years there
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43 has been a gradual reconfiguration of services providing care for young people aged 16-24
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45 years with cancer in the UK; this includes the development of Principal Treatment Centres,
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47 designated of other hospitals offering TYA services closer to the patients' homes and an
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49 overview of the holistic care of all patients provided by the TYA multidisciplinary team
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51 (MDT). Between 2004 to 2010, these pathways were not fully established, but the
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53 submission of TYAC enhanced cancer registration forms have been used as a surrogate
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3 indicator that an individual patient received treatment according to regionally agreed and
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5 commissioned TYA pathways under the supervision of the TYA PTC. It is therefore
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7 interesting to note that a significantly higher proportion of patients recruited onto
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9 UKALL2003 had been registered centrally via the TYAC notification system than non-trial
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11 patients (73.5% with a TYAC form compared to 51.9% without, $p=0.001$). This was
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13 particularly marked in the older age group. However, the finding that two-year survival was
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15 not higher in those patients with a submitted TYAC form does not support the argument
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17 that the better survival for those in the trial was mainly due to having been managed at
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19 larger centres.
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27 Whilst selection bias, in which the highest risk patients (eg those with a very high white
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29 count, renal or hepatic impairment or large mediastinal mass at presentation) could not
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31 participate in the trial, may be a confounder it is unlikely to have had a significant impact on
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33 our results as a) UKALL2003 was a population-based trial for which all children and young
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35 people with ALL were eligible, irrespective of severity or risk group at presentation and b) it
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37 also permitted recruitment within 7 days of commencement of chemotherapy. Patients
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39 with Philadelphia chromosome positive (Ph+ve) ALL were ineligible for UKALL2003 , but
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41 Ph+ve patients were included in the non-trial arm, as NCDR did not include details of Ph
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43 chromosome status . The presence of the Philadelphia chromosome in ALL confers a poorer
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45 prognosis [25] and could therefore increase the survival difference observed in this study.
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48 However we feel that this is unlikely to have been a significant confounding variable since
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50 the prevalence of Ph+ve ALL in UKALL2003 overall was only 1.8% and the observed
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52 difference between groups was non-significant in the older patients despite the frequency
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54 of the Philadelphia chromosome increasing with increasing age.
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5 During the study period, TYA patients with Ph+ve disease were eligible for the ESPHALL or
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7 UKALLXII (until 2006) trials, depending on age, and older patients with Ph-ve disease were
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9 eligible for recruitment onto UKALLXII (lower age limit 18th birthday from 2004, 20th birthday
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11 from 2006 and 25th birthday from 2007). Whilst we do not know the proportions of non-
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13 UKALL2003 patients recruited to these trials, if trial participation in itself confers a survival
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15 advantage, recruitment of patients to these other clinical trials would be expected to reduce
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17 observed differences between our two study groups, reduce any residual confounding from
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19 the exclusion of Ph+ve patients from UKALL2003 and may have also contributed to the non-
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21 significant difference in survival between trial and non-trial patients in the 20-24 year old
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23 group. This is further supported by the observation that only 3 UK patients aged 15-17
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25 years were recruited to ESPHALL (Ph+ve ALL only), but 100 patients aged 16-24 years were
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27 recruited to UKALLXII (Ph+ve and -ve ALL). The relative contribution of treatment protocol
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29 on outcome differences was impossible to assess in this study, since the registry dataset did
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31 not include which specific regimen was used.
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41 Recruitment to clinical trials in TYA cancer patients is poor due to a range of factors
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43 including lack of an available trial, heterogenous referral pathways, differences in treating
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45 centres as well as lack of desire to participate by this age group [4, 9, 13, 26]. Overall,
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47 approximately 50% of TYA patients in England with ALL participated in UKALL2003.
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50 Although this figure is lower than the proportion of younger children who participated in
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52 the trial, it compares favourably to other cancer trials reported in this age group; in the UK
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54 between 2005 to 2010, only 850 of 2860 patients aged 15–19 years (30%), and 562 of 4011
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56 patients aged 20–24 years (14%) were recruited to a clinical trial [4]. Encouragingly,
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3 recruitment to UKALL2003 improved over time. In part, this was expected in the 18-24 year
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5 old group, given the sequential increase in age eligibility criteria over time. However, even
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7 in the 15-17 year old patients who were eligible for participation throughout the study
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9 period, participation increased from 59.3% in 2004-2007 to 76.7% in 2008-2010 ($p = 0.007$).
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11 Despite this, there were still a substantial number of young people who did not participate,
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13 particularly amongst 20-24 year olds, where participation was only 45.1%. Fern et al
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15 propose that there are five factors (five "A's") important in improving TYA cancer trial
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17 recruitment; available, accessible, aware, appropriate, and acceptable. The relatively high
18
19 level of recruitment of TYA ALL patients to UKALL2003 and its improvement over time
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21 probably reflects an increasing awareness (as a result of newsletters and the trial
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23 coordinators presenting at a series of national meetings) and acceptability amongst
24
25 paediatric and adult haematologists that UKALL2003 offered an effective (i.e. appropriate)
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27 treatment strategy, with increasing availability and accessibility as the age range was
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29 increased and a greater number of adult centres opened the trial.
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In conclusion, we report a specific survival advantage to participation in the UKALL2003 trial
for TYA patients with ALL. This is the first study to have demonstrated a survival advantage
of trial participation in TYA patients with any cancer and suggests a benefit to an individual
patient in taking part. These data highlight the importance of national and international
efforts to a) improve recruitment of TYA cancer patients to clinical trials, b) configure TYA
cancer services to provide young people with access to appropriate trials and the
opportunity to participate and c) the need to continue to collect accurate treatment and
outcome data at a population level to allow evaluation of treatment in patients who have
not accessed clinical trials. In England these duties are the responsibilities respectively of

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the National Cancer Research Institute, NHS England and Public Health England, working together towards the goal of best patient outcomes. The data we present suggest that significant improvements in the delivery of appropriate cancer treatment are still much needed for this vulnerable young population.

For peer review only

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Regional and institutional data managers

The study was designed by RH, AM, SS, MK, RF, CS and MMC. RH, CR and AV designed, recruited to and analysed data for the UKALL2003 study. The statistical analysis of this study was performed by SS, MK, AM and MMC. All authors contributed to the interpretation of data and preparation of the manuscript and approve this final version.

COMPETING INTERESTS STATEMENT

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

DATA SHARING STATEMENT

There are no additional unpublished data from this study

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FIGURE AND TABLE TITLES

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by age group in 2009-10

Table 1: Participation in UKALL2003 by age group and year of diagnosis

Table 1a: All Patients

Year of diagnosis	15-17 years			18-19 years			20-24 years			15-24 years		
	Proportion	Percentage	95% CI	Proportion	Percentage	95% CI	Proportion	Percentage	95% CI	Proportion	Percentage	95% CI
2004	19/34	55.9	39.5-71.1	0/6	0.0	0.0-39.0	0/25	0.0	0-13.3	19/65	29.2	19.6-41.2
2005	26/45	57.8	43.3-71.0	0/20	0.0	0-16.1	0/23	0.0	0-14.3	26/88	29.5	21.0-39.8
2006	18/29	62.1	44.0-77.3	9/26	34.6	19.4-53.8	0/19	0.0	0-29.9	27/74	36.5	26.4-47.9
2007	20/32	62.5	45.3-77.1	8/14	57.1	32.6-78.6	4/32	12.5	5.0-28.1	32/78	41.0	30.8-52.1
2008	23/30	76.7	59.1-88.2	16/18	88.9	67.2-96.9	8/23	34.8	18.8-55.1	47/71	66.2	54.6-76.1
2009	24/31	77.4	60.2-88.6	13/20	65.0	43.3-81.9	10/26	38.5	22.4-57.5	47/77	61.0	49.9-71.2
2010	19/25	76.0	56.6-88.5	8/11	72.7	43.4-90.3	14/22	63.6	43.0-80.3	41/58	70.7	58.0-80.8
2004-07	83/140	59.3	51.0-67.1	17/66	25.8	16.7-37.4	4/99	4.0	1.6-9.9	104/305	34.1	29.0-39.6
2008-10	66/86	76.7	66.8-84.4	37/49	75.5	61.9-85.4	32/71	45.1	34.0-56.6	135/206	45.1	34.0-56.6
2004-10	149/226	65.9	59.5-71.8	54/115	47.0	38.1-56.0	36/170	21.2	15.7-27.9	239/511	46.8	42.5-51.1

Table 1b: Trial Participation over time in 15-17 year olds

Year of diagnosis	Proportion	Percentage	95% CI	p value
2004-07	83/140	59.3	51.0-67.1	0.007
2008-10	66/86	76.7	66.8-84.4	

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Table 2: One- and two-year survival by age group and trial status

Trial Status	Age group	Number of patients	Deaths	Survival (%)	95% CI	P value
1-year survival						
Trial	15-19	203	17	91.7	86.9-94.7	<0.001
Non-Trial		134	30	77.6	69.6-83.8	
Trial	20-24	36	5	86.2	69.8-94.0	0.969
Non-Trial		130	18	86.2	79.0-91.1	
Trial	15-24	239	22	90.8	86.4-93.9	0.004
Non-Trial		264	48	81.9	76.6-86.0	
2-year conditional on 1-year survival						
Trial	15-19	186	10	94.7	90.3-97.1	0.008
Non-Trial		104	16	84.7	76.2-90.4	
Trial	20-24	31	3	90.4	73.0-96.9	0.236
Non-Trial		112	22	80.4	71.8-86.7	
Trial	15-24	217	13	94.1	90.0-96.6	0.001
Non-Trial		216	38	82.5	76.7-87.0	
2-year survival						
Trial	15-19	203	27	86.8	81.3-90.7	<0.001
Non-Trial		134	46	65.7	57.0-73.1	
Trial	20-24	36	8	77.9	60.5-88.3	0.381
Non-Trial		130	40	69.3	60.6-76.5	
Trial	15-24	239	35	85.4	80.3-89.3	<0.001
Non-Trial		264	86	67.5	61.5-72.8	

Table 3: Number and percentage of patients aged 15-24 who died in the two years following diagnosis, by 3 month period, year and trial status

Year	Quarter	<i>In trial</i>				<i>Not in trial</i>				p values
		Number of patients at start of period	Number of deaths	% Died	95% CI	Number of patients at start of period	Number of deaths	% Died	95% CI	
	1st	239	6	2.5	1.2-5.4	264	21	8.0	5.3-11.9	0.007
	2nd	233	4	1.7	0.7-4.3	243	5	2.1	0.9-4.7	0.785
	3rd	229	5	2.2	0.9-5.0	238	11	4.6	2.6-8.1	0.148
	4th	224	7	3.1	1.5-6.3	227	11	4.8	2.7-8.5	0.351
1st	-	239	22	9.2	6.2-13.5	264	48	18.2	14.0-23.3	0.004
	5th	217	2	0.9	0.3-3.3	216	11	5.1	2.9-8.9	0.011
	6th	215	4	1.9	0.7-4.7	205	10	4.9	2.7-8.7	0.0851
	7th	211	3	1.4	0.5-4.1	195	8	4.1	2.1-7.9	0.0965
	8th	208	4	1.9	0.8-4.8	187	9	4.8	2.6-8.9	0.108
2nd	-	217	13	6.0	3.5-10.0	216	38	17.6	13.1-23.2	<0.001
1st and 2nd	-	239	35	14.6	10.7-19.7	264	86	32.6	27.2-38.4	<0.001

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Table 4: Number and percentage of patients in trial by whether a TYAC form was received by age group in 2009-10

Age	<i>Proportion of patients with a TYAC form who were in trial</i>			<i>Proportion of patients without a TYAC form who were in trial</i>			p value
	Proportion	Percentage	95% CI	Proportion	Percentage	95% CI	
15-19	45/57	78.9	66.7-87.5	19/30	63.3	45.5-78.1	0.117
20-24	16/26	61.5	42.5-77.6	8/22	36.4	19.7-57.0	0.082
15-24	61/83	73.5	63.1-81.8	27/52	51.9	38.7-64.9	0.011

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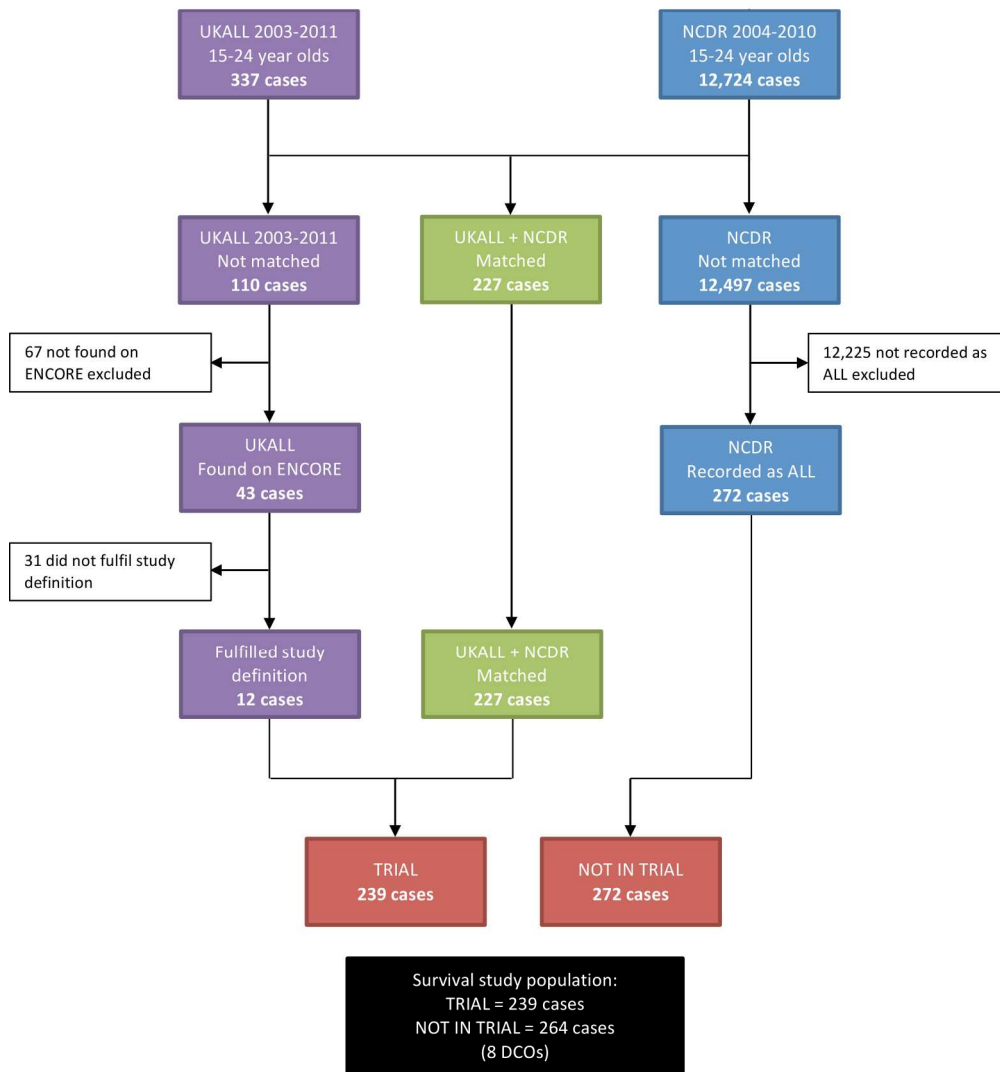


Figure 1: Study population derived from matching UKALL2003 against the National Cancer Data Repository (NCDR) and ENCORE

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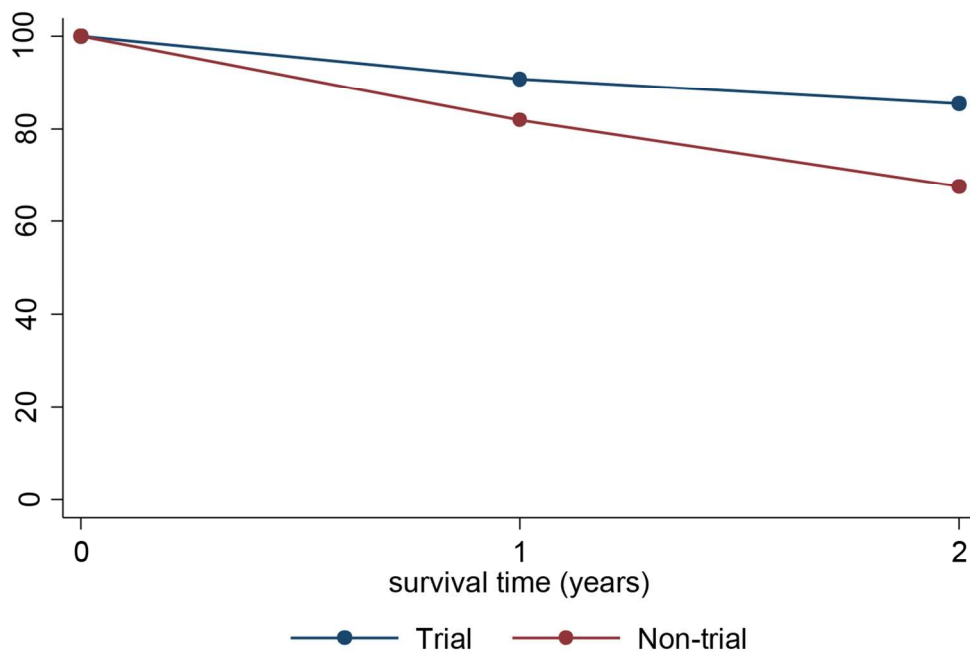


Figure 2: Two-year relative survival by age group and trial status

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BMJ Open

Are Survival and Mortality Rates Associated with Recruitment to Clinical Trials in Teenage and Young Adult Patients with Acute Lymphoblastic Leukaemia? A Retrospective Observational Analysis in England

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TITLE:

Are Survival and Mortality Rates Associated with Recruitment to Clinical Trials in Teenage and Young Adult Patients with Acute Lymphoblastic Leukaemia? A Retrospective Observational Analysis in England

RUNNING TITLE:

Impact of Trial Recruitment in TYA ALL

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ABSTRACT**Objective**

Participation rates in clinical trials are low in teenagers and young adults (TYA) with cancer.

Whilst the importance of clinical trials in informing best practice is well established, data regarding individual patient benefit are scarce. We have investigated the association between overall survival and trial recruitment in TYA patients with acute lymphoblastic leukaemia (ALL).

Design

Retrospective

Setting

National (England) TYA patients treated for ALL

Participants

511 patients aged 15-24 years diagnosed with ALL between 2004 to 2010 inclusive, of whom 239 (46.7%) participated in the UKALL2003 trial.

Outcome Measures

Patients were identified using National Clinical Trial (UKALL2003) and Cancer Registry (National Cancer Data Repository, English National Cancer Online Registration Environment) Databases. Relative survival rates were calculated for trial and non-trial patients and observed differences were modelled using a multiple regression approach. The numbers and percentages of deaths in those patients included in the survival analysis were determined for each three-month period, P values were calculated using the two-tailed z-test for difference between proportions and 95% confidence intervals for percentage deaths were derived using the Binomial distribution based on the Wilson Score method.

Results

Patients treated on the trial had a 17.9% better two-year survival (85.4% vs 67.5%, $p < 0.001$) and 8.9% better one-year survival (90.8% vs 81.9%, $p = 0.004$) than those not on the trial. 35 (14.6%) patients recruited to the trial died in the two years following diagnosis compared with 86 (32.6%) of those not recruited ($p < 0.001$).

Conclusions

TYA patients recruited to the clinical trial UKALL 2003 in England had a lower risk of mortality and a higher overall survival than contemporaneous non-trial patients. These data underline the potential for individual patient benefit in joining a clinical trial and the importance of international efforts to increase trial participation in the TYA age group.

STRENGTHS AND LIMITATIONS OF THIS STUDY

The study asks a fundamental question regarding the value to an individual of recruitment to a clinical trial

Large sample size including all TYA patients aged 15-24 years diagnosed with ALL in England between 2004-2010

This retrospective study is possible because a) the consent process for UKALL2003 included explicit consent for the trial data to be shared with regional and national cancer registries, and b) because the UK has full population coverage for cancer registration

Clinically significant outcomes of survival and mortality in those recruited to the clinical trial, UKALL2003, are compared to contemporaneous patients treated off trial

Given the retrospective design of this study, there is an inherent risk of potential confounding variables influencing the observations, which are fully explored in the

1
2
3 discussion; these include selection bias, centre effect, protocol used and recruitment to
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5 other clinical trials
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14 **FUNDING**

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16
17 This research received no specific grant from any funding agency in the public, commercial
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19 or not-for-profit sectors.
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INTRODUCTION

Although survival rates in teenage and young adult (TYA) patients with cancer have improved over the last two decades ¹, these outcome gains have been modest and cancer remains the leading cause of non-accidental mortality in the TYA age group ^{2,3}.

The barriers to improving survival are likely to be multifactorial and include sub-optimal diagnostic pathways, complex tumour and host biology, access to age or site specific specialist care and poor compliance with treatment ^{4,5}. Importantly, recruitment rates to clinical trials in TYA cancer patients are the lowest of any age group ⁵⁻⁸. In those patients for whom clinical trials are available, factors influencing participation include whether the treating physician is from a paediatric or adult background ^{5,9-12}, the type of treating centre (academic, tertiary or other)⁹, and patient factors, notably the acceptability to and attitudes of TYA patients ¹³. In addition, there are often fewer clinical trials available to TYA patients than to younger or older cancer patients ^{7,8,14}, reflecting the unique distribution of tumours in this age group and the traditional separation between adult and paediatric clinical research programmes ⁵.

Whilst sequential clinical trials clearly inform evidence based best practice in cancer therapy and have improved outcomes in specific disease types ¹⁵, the value of participation for an individual patient is less clear. The benefits may include access to a superior therapy not otherwise available, enhanced quality of care, access to a broader team of specialised professionals ¹⁶ and stricter adherence to trial mandated treatment. However, to date, no

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3 study has demonstrated a survival advantage specifically associated with trial participation
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5 in TYA patients^{17 18}.
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10 The objective of this study was to report survival outcomes of TYA patients with acute
11 lymphoblastic leukaemia (ALL) in England who were treated within or outside of the
12 national clinical trial, UKALL2003.
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20 **METHODS**

21 **UKALL2003**

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23
24 UKALL2003 was the UK clinical trial of minimal residual disease (MRD)-directed
25 chemotherapy for Philadelphia chromosome negative ALL in children and young people
26 aged 1 to 24 years, which opened in 2003 and closed in 2011. The maximum age for trial
27 entry was the 18th birthday when the trial began, but was increased to the 20th birthday in
28 2006 and the 25th birthday in 2007. Details of the protocol and outcomes of the trial have
29 been published previously¹⁹⁻²¹. The consent form for UKALL2003 included explicit consent
30 for data sharing with national cancer registries. Patients with Philadelphia chromosome
31 positive ALL were eligible for post induction recruitment to the ESPHALL trial if aged less
32 than 18 years (until 2009) or UKALL XII if aged 18 years or older (until 2006). The lower age
33 limit for recruitment of patients with Philadelphia negative ALL to UKALL XII was
34 sequentially increased according to the change in the upper age limit for UKALL2003 to
35 avoid overlapping age eligibility for the two trials. These changes to age eligibility for
36 UKALL2003 and UKALL XII were communicated in newsletters circulated by the clinical trials
37 unit and presented at both paediatric and adult annual national leukaemia trials update
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3 meetings. The National Institute for Health Research also hosts a trial database, which
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5 summarised all of these trials and was searchable by any clinician. The STROBE guidelines
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7 for the reporting of observational studies was followed.
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10 11 12 **Study Population**

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14 The study population for this analysis was defined as any patient diagnosed with ALL in
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16 2004-2010 (the 7 complete years during which UKALL2003 was recruiting), aged 15-24 years
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18 and resident in England at the time of diagnosis. The diagnosis reported to the registry and
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20 trial was made in the laboratories of treating centre, without central verification. Details
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22 were obtained on the 337 TYA patients who took part in the UKALL2003 Trial including
23
24 name, date of birth and hospital of treatment, but not address or country of residence.
25
26 Details of missing NHS numbers on UKALL2003 were obtained using the NHS Strategic
27
28 Tracing Service (NSTS), which contains details of all individuals registered with a GP in
29
30 England or Wales. The National Cancer Data Repository (NCDR) was the database used to
31
32 undertake cancer analyses at the time this study commenced. It included details of all
33
34 patients diagnosed with cancer who were resident in England. A frozen copy of NCDR was
35
36 compiled from the eight regional registries then in existence, when cancer data for a given
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38 calendar year were considered to be near complete – a process which took considerable
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40 time. The version used in this study was that produced when 2010 data were considered
41
42 complete. The patients in UKALL2003 were matched against those on the NCDR database
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44 who were diagnosed in 2004-2010 aged 15-24 with any cancer. Patients recorded on NCDR
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46 as having ALL and who were not on the UKALL database were included in our study as the
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48 non-trial arm.
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3 The move to a single cancer registry for England, which was completed while this study was
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5 underway, resulted in the production of the English National Cancer Online Registration
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7 Environment (ENCORE). This is a live database, which is updated regularly. It is used by
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9 registry staff to determine if a given patient has already been registered. It contains details
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11 of all residents of England who have been diagnosed with cancer, including patients
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13 reported to the National Cancer Registration and Analysis Service (NCRAS) but with
14
15 insufficient details to be counted as a case of cancer; these are called provisional
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17 registrations and are upgraded to full registrations when further details are obtained.
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19 ENCORE also contains details of cancer patients managed at a hospital in England but
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21 resident elsewhere. Patients on the UKALL database not found on NCDR were manually
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23 checked on ENCORE, in order to determine the reasons why these patients were not on
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25 NCDR and to identify any patients reported to NCRAS after the NCDR was compiled. Those
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27 whose records were found on ENCORE and who fulfilled the study definition were added to
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29 patients on both UKALL and NCDR to make up the trial arm in our study.
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Details of patients on the UKALL database but not found on ENCORE were checked against the NSTS to determine whether living in England or Wales. The UKALL database was interrogated for the country of the treating hospital for those patients not found on NSTS.

Consent

Registry data was routinely submitted to the national cancer registry under legal permissions that were initially included under Section 60 of the Health and Social Care Act 2001 and more recently Section 251 of the NHS Act 2006. This permission is renewed

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3 annually. Identifiable trial data were shared with explicit patient consent obtained during
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5 trial registration.
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10 11 12 **Analyses**

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14 We determined the number and percentage of patients who participated in UKALL2003 by
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16 year of diagnosis and age group. Survival rates were calculated for patients in the trial and
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18 not in the trial, excluding patients on whom the only available data were from death
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20 certificates – death certificate only (DCO) registrations. Death details were obtained from
21
22 NCDR up to the end of 2012, with follow-up starting from the date of diagnosis recorded on
23
24 NCDR; the equivalent data were obtained from ENCORE for those patients not found on
25
26 NCDR. One-year, two-year and two-year conditional on one-year relative survival rates
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28 were calculated for 15-24, 15-19 and 20-24 year olds for trial and non-trial patients.
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30 Relative survival was estimated from life tables stratified by age, sex and time using the
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32 Stata strsr programme²². Expected survival was estimated using the Ederer II method.
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40 Differences in relative survival were modelled using a multiple regression approach based
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42 on generalised linear models, assuming a Poisson distribution for the observed number of
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44 deaths²³. Differences were considered statistically significant if two-sided P values were
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46 <0.05. All statistical analyses were conducted using Stata version 13.
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52 The numbers of deaths in those patients included in the survival analysis were determined
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54 for each three-month period during the two years of follow-up and percentages calculated
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56 based on the number of patients alive at the beginning of each three-month period. P
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3 values were calculated using the two-tailed z-test for difference between proportions. 95%
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5 confidence intervals for percentage deaths were derived using the Binomial distribution
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7 based on the Wilson Score method²⁴.
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10 11 12 **Completion of TYAC form**

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14 During 2009 and 2010, enhanced cancer registration forms were in use throughout the
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16 English TYA Principal Treatment Centres (PTCs). The forms were developed by the
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18 professional organisation Teenagers and Young Adults with Cancer (TYAC)
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20 (<http://www.tyac.org.uk>) and were collected and matched with registry data by the lead UK
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22 regional registry for TYA cancer at the time, the North West Cancer Intelligence Service
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24 (now part of Public Health England). Receipt of a TYAC form by the registry was used as a
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26 proxy that the patient's management had been provided by or at least discussed with the
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28 regional TYA PTC. We calculated the percentage of patients in the trial for whom a TYAC
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30 form was completed to explore the relationship between access to TYA specialist services
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32 and participation in the trial.
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RESULTS

Study population

The process by which the study population was selected is shown in Figure 1. Details on 227 of the 337 patients on the UKALL database were found on NCDR; twenty of whom had a diagnosis other than ALL on NCDR. The most common diagnoses were leukaemia (5), acute leukaemia (4), acute myeloid leukaemia (4) and Non-Hodgkin lymphoma (4). 272 patients with a diagnosis of ALL on NCDR were not on the UKALL database and these constituted the non-trial arm of this study.

Of the 110 patients on UKALL2003 not found on NCDR, 43 were identified on ENCORE. 31 did not fulfil the study definition for the following reasons:

- (a) 26 were diagnosed in 2011
- (b) One diagnosed in 2003
- (c) One aged 14 at time of diagnosis
- (d) One treated in England but not a resident
- (e) Two were provisional registrations that were not confirmed

The twelve patients who fulfilled the study definition had been reported to the NCRAS after the NCDR was compiled. These patients were added to the 227 found on both the UKALL2003 and NCDR databases to make up the trial arm of this study.

Of the 67 patients on the UKALL2003 database not found on ENCORE, 60 were not resident in England confirmed by having a non-English address on NSTS and/or the treating hospital

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3 recorded on UKALL2003 as being outside England. The remaining seven patients, who did
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5 fulfil the study definition, were excluded for a number of reasons, including not being
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7 reported to the registry by the treating hospital or insufficient details provided to allow a
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9 full registration, and inaccurate personal details on the UKALL2003 database resulting in
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11 patients not being found on ENCORE.
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14 15 16 17 **Participation in UKALL2003**

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19 A total of 511 patients aged 15-24 years were included in the analyses, of whom 239
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21 (47.5%) had participated in UKALL2003 (Table 1a). The overall number of 20-24 year old
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23 patients recruited (36 patients) was lower than 18-19 year olds (54 patients) and 15-17 year
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25 olds (149 patients). In total, 203 (84.9%) of 239 trial patients were aged 15-19 years. Trial
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27 participation improved over time, from 59.3% in 2004-2007 to 76.7% in 2008-2010 ($p =$
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29 0.007) in the 15-17 year old group (the only group eligible for the trial for the entire study
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31 period)(Table 1b). It is likely that the sequential changes in age eligibility criteria for
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33 UKALL2003 were partly responsible for low recruitment numbers in the older age groups.
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35 However, for the period 2008-2010, during which all 15-24 year olds were eligible for the
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37 study, participation remained higher in younger patients: 76.3% of 15-19 year olds
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39 compared with 45.1% of 20-24 year olds ($p < 0.001$).
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48 **Recruitment to Other Clinical Trials**

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50 Since the trial consent forms for ESPHALL and UKALLXII did not include explicit consent for
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52 data sharing with the national registries, it was not possible to access detailed information
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54 from these trial databases. However, the overall number of UK patients recruited to these
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56 trials within the study period included 3 patients aged 15-17 years recruited to ESPHALL and
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3 100 patients aged 15-24 years recruited to UKALL XII. Although ESPHALL recruited only
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5 those with Philadelphia chromosome positive disease, UKALL XII recruited both Philadelphia
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7 chromosome positive and negative ALL patients. Given the sequential increase in the lower
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9 age limit for UKALL XII for Philadelphia chromosome negative ALL was sequentially
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11 increased over time, the highest proportion of patients recruited to UKALL XII would be
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13 those with Philadelphia chromosome negative disease in the older age group.
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22 **Survival**

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24 503 patients were included in the survival analysis: 239 in the trial arm and 264 in the non-
25
26 trial arm. Patients aged 15-24 years recruited to the UKALL2003 trial had 17.9% better two-
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28 year survival (85.4% vs 67.5%, $p < 0.001$), 8.9% better one-year survival (90.8% vs 81.9%, $p =$
29
30 0.004) and 11.6% better two-year survival conditional on one-year survival (94.1% vs 82.5%,
31
32 $p = 0.001$) compared to non-trial patients (Table 2, Figure 2). To determine whether the
33
34 effects of trial recruitment on survival were measurable across the age cohort we analysed
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36 15-19 year olds and 20-24 year olds separately. The differences in survival at all time points
37
38 remained significant in the 15-19 year old age group (Table 2). Two-year and conditional
39
40 two-year survival showed a non-significant trend to better in trial patients than non-trial
41
42 patients in the 20-24 year old cohort. The results for 2008-10 (after closure of UKALLXII) are
43
44 similar to those for the whole study period: 20-24 year olds in the trial had a two-year
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46 survival 10.2% better than those not in the trial, but this did not reach statistical significance p
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48 = 0.393.
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3 To determine whether the deaths were evenly spaced after diagnosis we next analysed the
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5 number of deaths in trial and non-trial patients by quarter-year from diagnosis. Table 3
6
7 shows the number and percentage of deaths by trial status for each quarter-year and year
8
9 of follow-up. A total of 35 (14.6%) trial patients died in the two years following diagnosis
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11 compared with 86 (32.6%) of non-trial patients ($p < 0.001$). The difference in the proportion
12
13 of deaths between trial and non-trial patients was 9% (18.2% - 9.2%; $p = 0.004$) fewer
14
15 deaths in trial patients during the first year and 11.6% (17.6% - 6.0%; $p < 0.001$) during the
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17 second. However, the largest number of deaths overall and the largest difference between
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19 trial and non-trial patients for any quarter was in the first three months after diagnosis: 6
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21 (2.5%) trial patients died compared with 21 (8.0%) non-trial patients ($p = 0.007$).
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29 **Exploratory analysis of trial recruitment by place of care**

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31 The data available in national registry records were not sufficient to allow us to determine
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33 the reasons for non-recruitment of non-trial patients, how non-trial patients were treated
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35 or the training background of treating physicians (paediatric, TYA or adult). However, we
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37 were able to compare trial recruitment rates between patients for whom an enhanced TYAC
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39 cancer registration form had been submitted and those with no TYAC form. The trial
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41 recruitment rates were significantly different between the two groups: 73.5% of patients
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43 with a submitted TYAC form were recruited compared to 51.9% of those for whom a form
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45 was not submitted ($p = 0.001$, Table 4). The difference was highest among patients aged 20-
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47 24 years (61.5% trial recruitment among patients with associated TYAC forms versus 36.4%
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49 without). Patients for whom a TYAC form was submitted had a two-year survival of 80.8%
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51 compared with 82.8% for those without a form ($p = 0.771$).
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DISCUSSION

By combining trial and national cancer registry data we have demonstrated a significant survival advantage to participation in the most recently completed, large prospective clinical trial for TYA patients with ALL, which is measurable at a population level. This is the first study to have demonstrated such a survival advantage in any cancer type in the TYA age group. The difference in survival was highly significant, with a 17.9% superior survival at two years in trial patients compared to non-trial patients. The risk of mortality at 2 years in those treated outside of the trial was twice that of those on UKALL2003 (32.6% compared to 14.6%, $p < 0.001$) and was most striking during the first 3 months after diagnosis (8.0% compared to 2.5%, $p = 0.007$).

This retrospective analysis of the impact of clinical trial recruitment on survival was possible because the consent process for UKALL2003 included explicit consent for the trial data to be shared with regional and national cancer registries, and because the UK has full population coverage for cancer registration. This study, however, did show a number of limitations of the cancer registration system for England during the period 2004-2010 including a) Accuracy of diagnosis: twenty patients on UKALL2003 with a diagnosis other than ALL on NCDR and b) Timeliness: twelve patients on ENCORE but not on NCDR. In addition, the main source of diagnostic data for cancer registries during the study period was histopathology laboratories, leading to difficulties in obtaining high quality data on patients with ALL. In addition, there were no data available for the well-established prognostic variables in ALL, thus precluding comparison of the frequency of different risk groups between those treated on or off trial. Data were collected by regional registries and then compiled into a national

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3 database, which took considerable time. Public Health England (PHE) has made many
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5 improvements since taking over the NCRAS a few years ago including a) Moving to a single,
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7 completely integrated national registry, b) Setting up systems that report in real time from a
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9 wide variety of sources, such as MDTs, leading to more timely and accurate data and c)
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11 Reviewing access to specialist haematological diagnostic datasets to improve the data
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13 quality of haematological cancers and d) Producing an analysis database that is constantly
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15 kept up to date.
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21 We also recognise a number of potential confounding variables in this study. Potential
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23 confounders which could increase the observed difference between those on trial compared
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25 to those treated off trial include centre effect, selection bias and use of a superior protocol,
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27 and those reducing the difference include recruitment to other ALL clinical trials.
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33 Any potential benefit to participation of young people in clinical trials may be derived from
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35 the treating centre rather than trial participation itself (centre effect). Centres offering
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37 clinical trials are often larger, academic institutions, seeing a higher number of patients with
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39 a specific disease, a larger clinical research infrastructure and a more resourced workforce,
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41 all of which may contribute to a more favourable outcome¹⁶. Over the last 10 years there
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43 has been a gradual reconfiguration of services providing care for young people aged 16-24
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45 years with cancer in the UK; this includes the development of Principal Treatment Centres,
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47 designated of other hospitals offering TYA services closer to the patients' homes and an
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49 overview of the holistic care of all patients provided by the TYA multidisciplinary team
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51 (MDT). Between 2004 to 2010, these pathways were not fully established, but the
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53 submission of TYAC enhanced cancer registration forms have been used as a surrogate
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3 indicator that an individual patient received treatment according to regionally agreed and
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5 commissioned TYA pathways under the supervision of the TYA PTC. It is therefore
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7 interesting to note that a significantly higher proportion of patients recruited onto
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9 UKALL2003 had been registered centrally via the TYAC notification system than non-trial
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11 patients (73.5% with a TYAC form compared to 51.9% without, $p=0.001$). This was
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13 particularly marked in the older age group. However, the finding that two-year survival was
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15 not higher in those patients with a submitted TYAC form does not support the argument
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17 that the better survival for those in the trial was mainly due to having been managed at
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19 larger centres.
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27 Whilst selection bias, in which the highest risk patients (eg those with a very high white
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29 count, renal or hepatic impairment or large mediastinal mass at presentation) could not
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31 participate in the trial, may be a confounder it is unlikely to have had a significant impact on
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33 our results as a) UKALL2003 was a population-based trial for which all children and young
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35 people with ALL were eligible, irrespective of severity or risk group at presentation and b) it
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37 also permitted recruitment within 7 days of commencement of chemotherapy. Patients
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39 with Philadelphia chromosome positive (Ph+ve) ALL were ineligible for UKALL2003 , but
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41 Ph+ve patients were included in the non-trial arm, as NCDR did not include details of Ph
42
43 chromosome status . The presence of the Philadelphia chromosome in ALL confers a poorer
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45 prognosis²⁵ and could therefore increase the survival difference observed in this study.
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48 However we feel that this is unlikely to have been a significant confounding variable since
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50 the prevalence of Ph+ve ALL in UKALL2003 overall was only 1.8% and the observed
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52 difference between groups was non-significant in the older patients despite the frequency
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54 of the Philadelphia chromosome increasing with increasing age.
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5 During the study period, TYA patients with Ph+ve disease were eligible for the ESPHALL or
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7 UKALLXII (until 2006) trials, depending on age, and older patients with Ph-ve disease were
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9 eligible for recruitment onto UKALLXII (lower age limit 18th birthday from 2004, 20th birthday
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11 from 2006 and 25th birthday from 2007). Whilst we do not know the proportions of non-
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13 UKALL2003 patients recruited to these trials, if trial participation in itself confers a survival
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15 advantage, recruitment of patients to these other clinical trials would be expected to reduce
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17 observed differences between our two study groups, reduce any residual confounding from
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19 the exclusion of Ph+ve patients from UKALL2003 and may have also contributed to the non-
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21 significant difference in survival between trial and non-trial patients in the 20-24 year old
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23 group. This is further supported by the observation that only 3 UK patients aged 15-17
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25 years were recruited to ESPHALL (Ph+ve ALL only), but 100 patients aged 16-24 years were
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27 recruited to UKALLXII (Ph+ve and -ve ALL). The relative contribution of treatment protocol
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29 on outcome differences was impossible to assess in this study, since the registry dataset did
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31 not include which specific regimen was used.
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41 Recruitment to clinical trials in TYA cancer patients is poor due to a range of factors
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43 including lack of an available trial, heterogenous referral pathways, differences in treating
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45 centres as well as lack of desire to participate by this age group^{4 9 13 26}. Overall,
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47 approximately 50% of TYA patients in England with ALL participated in UKALL2003.
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50 Although this figure is lower than the proportion of younger children who participated in
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52 the trial, it compares favourably to other cancer trials reported in this age group; in the UK
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54 between 2005 to 2010, only 850 of 2860 patients aged 15–19 years (30%), and 562 of 4011
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56 patients aged 20–24 years (14%) were recruited to a clinical trial⁴. Encouragingly,
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3 recruitment to UKALL2003 improved over time. In part, this was expected in the 18-24 year
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5 old group, given the sequential increase in age eligibility criteria over time. However, even
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7 in the 15-17 year old patients who were eligible for participation throughout the study
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9 period, participation increased from 59.3% in 2004-2007 to 76.7% in 2008-2010 ($p = 0.007$).
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11 Despite this, there were still a substantial number of young people who did not participate,
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13 particularly amongst 20-24 year olds, where participation was only 45.1%. Fern et al
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15 propose that there are five factors (five "A's") important in improving TYA cancer trial
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17 recruitment; available, accessible, aware, appropriate, and acceptable. The relatively high
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19 level of recruitment of TYA ALL patients to UKALL2003 and its improvement over time
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21 probably reflects an increasing awareness (as a result of newsletters and the trial
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23 coordinators presenting at a series of national meetings) and *acceptability* amongst
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25 paediatric and adult haematologists that UKALL2003 offered an effective (i.e. *appropriate*)
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27 treatment strategy, with increasing *availability* and *accessibility* as the age range was
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29 increased and a greater number of adult centres opened the trial.
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38 In conclusion, we report a specific survival advantage to participation in the UKALL2003 trial
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40 for TYA patients with ALL. This is the first study to have demonstrated a survival advantage
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42 of trial participation in TYA patients with any cancer and suggests a benefit to an individual
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44 patient in taking part. These data highlight the importance of national and international
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46 efforts to a) improve recruitment of TYA cancer patients to clinical trials, b) configure TYA
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48 cancer services to provide young people with access to appropriate trials and the
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50 opportunity to participate and c) the need to continue to collect accurate treatment and
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52 outcome data at a population level to allow evaluation of treatment in patients who have
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54 not accessed clinical trials. In England these duties are the responsibilities respectively of
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the National Cancer Research Institute, NHS England and Public Health England, working together towards the goal of best patient outcomes. The data we present suggest that significant improvements in the delivery of appropriate cancer treatment are still much needed for this vulnerable young population.

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Regional and institutional data managers

The study was designed by RH, AM, SS, MK, RF, CS and MMC. RH, CR and AV designed, recruited to and analysed data for the UKALL2003 study. The statistical analysis of this study was performed by SS, MK, AM and MMC. All authors contributed to the interpretation of data and preparation of the manuscript and approve this final version.

COMPETING INTERESTS STATEMENT

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

DATA SHARING STATEMENT

There are no additional unpublished data from this study

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FIGURE AND TABLE TITLES

Figure 1: Study population derived from matching UKALL2003 against the National Cancer

Data Repository (NCDR) and ENCORE

Figure 2: Two-year relative survival by age group and trial status

Table 1: Participation in UKALL2003 by age group and year of diagnosis

Table 1a: All Patients

Table 1b: Trial Participation over time in 15-17 year olds

Table 2: One- and two-year survival by age group and trial status

Table 3: Number and percentage of patients aged 15-24 who died in the two years

following diagnosis, by 3 month period, year and trial status

Table 4: Number and percentage of patients in trial by whether a TYAC form was received

by age group in 2009-10

Table 1: Participation in UKALL2003 by age group and year of diagnosis

Table 1a: All Patients

Year of diagnosis	15-17 years			18-19 years			20-24 years			15-24 years		
	Proportion	Percentage	95% CI	Proportion	Percentage	95% CI	Proportion	Percentage	95% CI	Proportion	Percentage	95% CI
2004	19/34	55.9	39.5-71.1	0/6	0.0	0.0-39.0	0/25	0.0	0-13.3	19/65	29.2	19.6-41.2
2005	26/45	57.8	43.3-71.0	0/20	0.0	0-16.1	0/23	0.0	0-14.3	26/88	29.5	21.0-39.8
2006	18/29	62.1	44.0-77.3	9/26	34.6	19.4-53.8	0/19	0.0	0-29.9	27/74	36.5	26.4-47.9
2007	20/32	62.5	45.3-77.1	8/14	57.1	32.6-78.6	4/32	12.5	5.0-28.1	32/78	41.0	30.8-52.1
2008	23/30	76.7	59.1-88.2	16/18	88.9	67.2-96.9	8/23	34.8	18.8-55.1	47/71	66.2	54.6-76.1
2009	24/31	77.4	60.2-88.6	13/20	65.0	43.3-81.9	10/26	38.5	22.4-57.5	47/77	61.0	49.9-71.2
2010	19/25	76.0	56.6-88.5	8/11	72.7	43.4-90.3	14/22	63.6	43.0-80.3	41/58	70.7	58.0-80.8
2004-07	83/140	59.3	51.0-67.1	17/66	25.8	16.7-37.4	4/99	4.0	1.6-9.9	104/305	34.1	29.0-39.6
2008-10	66/86	76.7	66.8-84.4	37/49	75.5	61.9-85.4	32/71	45.1	34.0-56.6	135/206	45.1	34.0-56.6
2004-10	149/226	65.9	59.5-71.8	54/115	47.0	38.1-56.0	36/170	21.2	15.7-27.9	239/511	46.8	42.5-51.1

Table 1b: Trial Participation over time in 15-17 year olds

Year of diagnosis	Proportion	Percentage	95% CI	p value
2004-07	83/140	59.3	51.0-67.1	0.007
2008-10	66/86	76.7	66.8-84.4	

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Table 2: One- and two-year survival by age group and trial status

Trial Status	Age group	Number of patients	Deaths	Survival (%)	95% CI	P value
1-year survival						
Trial	15-19	203	17	91.7	86.9-94.7	<0.001
Non-Trial		134	30	77.6	69.6-83.8	
Trial	20-24	36	5	86.2	69.8-94.0	0.969
Non-Trial		130	18	86.2	79.0-91.1	
Trial	15-24	239	22	90.8	86.4-93.9	0.004
Non-Trial		264	48	81.9	76.6-86.0	
2-year conditional on 1-year survival						
Trial	15-19	186	10	94.7	90.3-97.1	0.008
Non-Trial		104	16	84.7	76.2-90.4	
Trial	20-24	31	3	90.4	73.0-96.9	0.236
Non-Trial		112	22	80.4	71.8-86.7	
Trial	15-24	217	13	94.1	90.0-96.6	0.001
Non-Trial		216	38	82.5	76.7-87.0	
2-year survival						
Trial	15-19	203	27	86.8	81.3-90.7	<0.001
Non-Trial		134	46	65.7	57.0-73.1	
Trial	20-24	36	8	77.9	60.5-88.3	0.381
Non-Trial		130	40	69.3	60.6-76.5	
Trial	15-24	239	35	85.4	80.3-89.3	<0.001
Non-Trial		264	86	67.5	61.5-72.8	

Table 3: Number and percentage of patients aged 15-24 who died in the two years following diagnosis, by 3 month period, year and trial status

Year	Quarter	<i>In trial</i>				<i>Not in trial</i>				p values
		Number of patients at start of period	Number of deaths	% Died	95% CI	Number of patients at start of period	Number of deaths	% Died	95% CI	
	1st	239	6	2.5	1.2-5.4	264	21	8.0	5.3-11.9	0.007
	2nd	233	4	1.7	0.7-4.3	243	5	2.1	0.9-4.7	0.785
	3rd	229	5	2.2	0.9-5.0	238	11	4.6	2.6-8.1	0.148
	4th	224	7	3.1	1.5-6.3	227	11	4.8	2.7-8.5	0.351
1st	-	239	22	9.2	6.2-13.5	264	48	18.2	14.0-23.3	0.004
	5th	217	2	0.9	0.3-3.3	216	11	5.1	2.9-8.9	0.011
	6th	215	4	1.9	0.7-4.7	205	10	4.9	2.7-8.7	0.0851
	7th	211	3	1.4	0.5-4.1	195	8	4.1	2.1-7.9	0.0965
	8th	208	4	1.9	0.8-4.8	187	9	4.8	2.6-8.9	0.108
2nd	-	217	13	6.0	3.5-10.0	216	38	17.6	13.1-23.2	<0.001
1st and 2nd	-	239	35	14.6	10.7-19.7	264	86	32.6	27.2-38.4	<0.001

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Table 4: Number and percentage of patients in trial by whether a TYAC form was received by age group in 2009-10

Age	<i>Proportion of patients with a TYAC form who were in trial</i>			<i>Proportion of patients without a TYAC form who were in trial</i>			p value
	Proportion	Percentage	95% CI	Proportion	Percentage	95% CI	
15-19	45/57	78.9	66.7-87.5	19/30	63.3	45.5-78.1	0.117
20-24	16/26	61.5	42.5-77.6	8/22	36.4	19.7-57.0	0.082
15-24	61/83	73.5	63.1-81.8	27/52	51.9	38.7-64.9	0.011

For peer review only

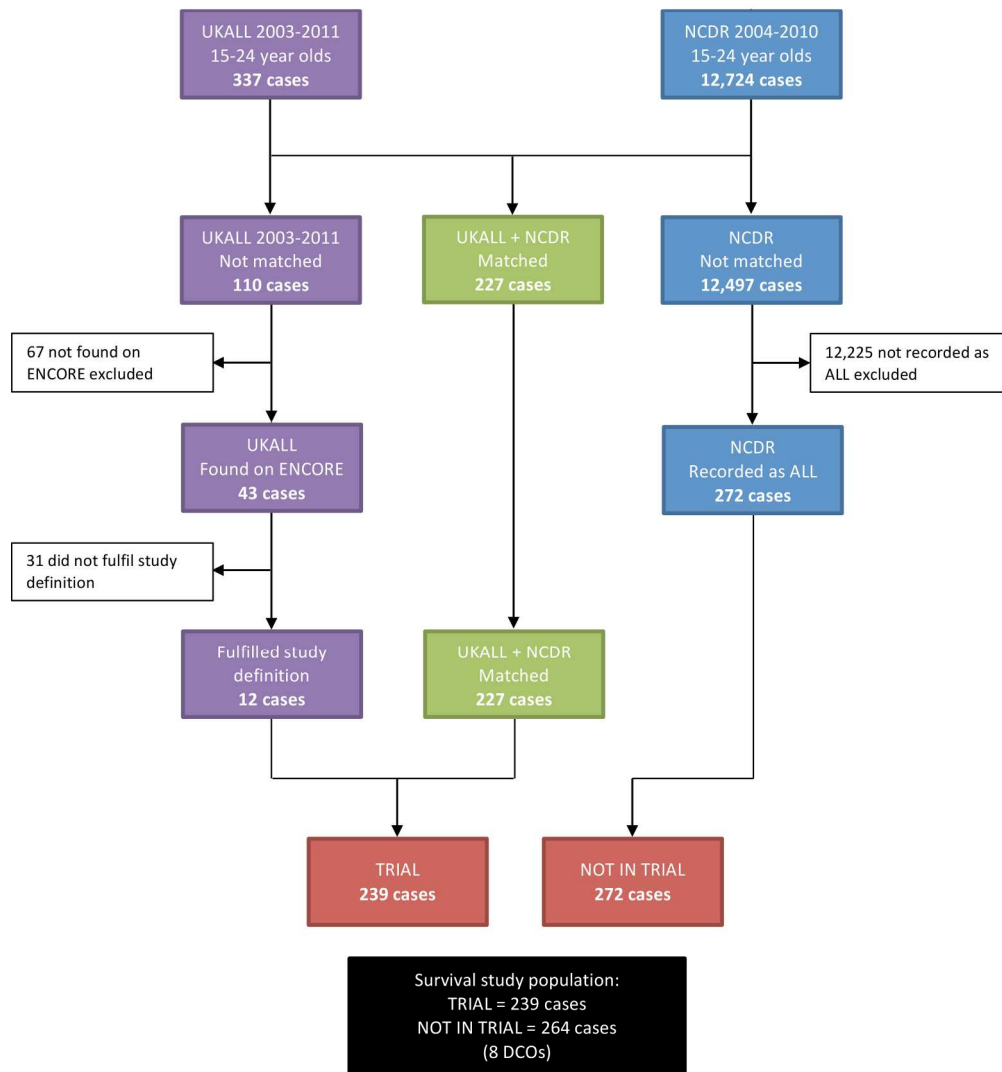


Figure 1: Study population derived from matching UKALL2003 against the National Cancer Data Repository (NCDR) and ENCORE

182x212mm (300 x 300 DPI)

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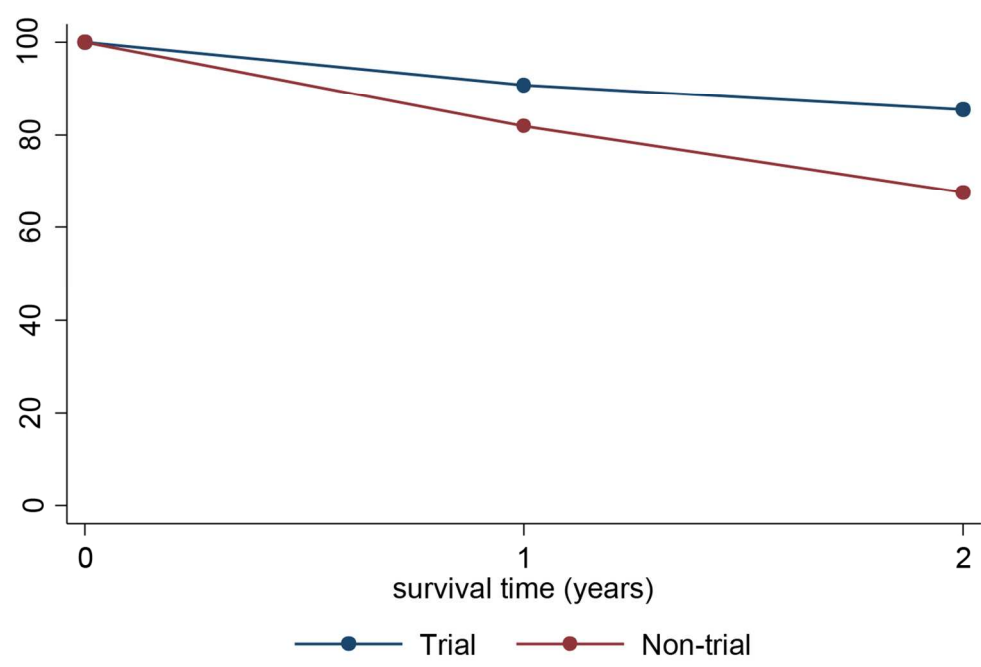


Figure 2: Two-year relative survival by age group and trial status
122x82mm (300 x 300 DPI)

view only

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract <i>Page 1, line 2-4</i> (b) Provide in the abstract an informative and balanced summary of what was done and what was found <i>Pages 3-4</i>
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported <i>Pages 6-7</i>
Objectives	3	State specific objectives, including any prespecified hypotheses <i>Page 7, line 4-7</i>
Methods		
Study design	4	Present key elements of study design early in the paper <i>Pages 8-11</i>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection <i>Pages 8-11</i>
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants <i>Page 8, lines 6-23</i> (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable <i>Pages 10-11</i> <i>Pages 17, line 9 -19, line 14</i>
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group <i>Pages 8-9</i> <i>Page 11, lines 5-14</i>
Bias	9	Describe any efforts to address potential sources of bias <i>Pages 17, line 9 -19, line 14</i>
Study size	10	Explain how the study size was arrived at <i>Page 8, lines 6-23</i>
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

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Pages 8-9

Page 11, lines 5-14

Statistical methods

12

(a) Describe all statistical methods, including those used to control for confounding

Page 10, line 3 - Page 11, line 3

(b) Describe any methods used to examine subgroups and interactions

Page 10, line 3 - Page 11

Page 11, line 3 lines 4-14

(c) Explain how missing data were addressed

Page 8, line 5 - Page 9, line 18

(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed

Case-control study—If applicable, explain how matching of cases and controls was addressed

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy

NA

(e) Describe any sensitivity analyses

NA

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 12, line 4 - Page 13, line 18 Figure 1
		(b) Give reasons for non-participation at each stage Page 12, line 4 - Page 13, line 18
		(c) Consider use of a flow diagram Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 12, line 7 – Page 13, line 6
		(b) Indicate number of participants with missing data for each variable of interest Page 12, line 4 – Page 13, line 4
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) Table 1
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures Tables 1,2,3 and 4 Pages 13-15
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Tables 2,3 and 4 Pages 14-15
		(b) Report category boundaries when continuous variables were categorized Tables 2,3 and 4 Pages 14-15
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Page 15, line 13-23
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 60, line 3-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Pages 17, line 9 -19, line 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Pages 16-21

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2 Generalisability 21 Discuss the generalisability (external validity) of the study results

3 [Page 20, line 16 – Page 21, line 4](#)

4 **Other information**

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6 Funding 22 Give the source of funding and the role of the funders for the present study and, if applicable,
7 for the original study on which the present article is based

8 NA

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11 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and
12 unexposed groups in cohort and cross-sectional studies.

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14 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
15 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
16 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
17 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
18 available at www.strobe-statement.org.