PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Hough, Rachael (proxy) (contact); Sandhu, Sabrina; Khan, Maria; Moran, Anthony; Feltbower, Richard; Stiller, Charles; Stevens, Mike; Rowntree, Clare; Vora, Ajay; McCabe, Martin

VERSION 1 - REVIEW

REVIEWER	Motohiro Kato MD, PhD National Center for Child Health and Development, Japan
REVIEW RETURNED	02-May-2017

GENERAL COMMENTS	Hough R et al. reported comparison of TYA-ALL on UKALL2003 trial or not. As authors mentioned, this survey could provide clinically important information although the study is retrospective and there are some potential selection biases. The following issues to be addressed; #1. Authors focused on outcomes of TYA patients. I understand poor enrollment is important and problematic especially in this age, but to emphasize importance of this issue, it would be nice if authors could provide similar data for ALL under 15 years of age. #2. In page 17, authors insisted that "the prevalence of Ph+ve ALL in UKALL2003 overall was only 1.8% and the observed difference between groups was smaller in the older patients". However, the difference of survival in the 20-24 age group did not reach statistical significance mainly due to smaller sample size compared to the 15-19 age group. #3. Could authors provide information of treating physician (pediatric or adult background) for non-trial cases?

REVIEWER	Josep-Maria Ribera ICO-Hospital germans Trias i Pujol, Badalona, Spain
REVIEW RETURNED	04-May-2017

GENERAL COMMENTS	The paper by Hough et al addresses a very important aspect in the outcome of TYA: the inclusion into clinical trials. This is an interesting and very difficult-to-perform study. The methodology of selection of patients is accurate and the groups of comparison have been well selected. The statistical methodology seems appropriate

	(although I have limitations in understanding the selection of the statistical methods), the results are sound and the discussion is well performed, with special emphasis in the limitations and potential biases of the study. Specific comments to authors: 1. Although I assume that the clinical and biologic characteristics of ALL in TYA not in trial are difficult to obtain, a minimum data apart of age could be retrieved (eg, gender, T vs. B ALL and even the WBC count at diagnosis). It would be desirable if these data could be retrieved to provide more insights on the comparability of the two groups. 2. The discussion of the potential bias by the Ph chromosome status is very well addressed in the Discussion section. However, data on the number of TYA patients included in the specific trials for Ph ALL activated during the study period could be provided in order to know the proportion of Ph-ve and Ph+ve TYA patients included in clinical trials 3. Was this study evaluated by and IRB?. If yes, this information should be included in the Patients and Methods section 4. The ways by which an implementation of the trials is notified to all the English centers should be included in the Patients and Methods section. Depending of that, the failure of broad communication of activation of national clinical trials could be included as another potential reason for the lack of recruitment of some patients. 5. Although I assume that is very difficult to know details about the treatment administered to the TYA patients not in trial, it is possible that some of them could receive the same treatment as that of the UKAL2003 trial, but were not included in the trial. This possibility should be mentioned in the discussion

REVIEWER	Helene Hallböök Dept of Medical Sciences, Haematology, Uppsala University, Uppsala, Sweden
REVIEW RETURNED	16-May-2017

GENERAL COMMENTS	This an interesting and well written manuscript discussing the impact of clinical trials on treatment outcome, in this case regarding young adults with ALL. Major comments: The survival rates after leukemia treatment is probably multifactorial which is discussed in the manuscript, however the effectiveness of the treatment protocol itself (UKALL 2003) versus contemporary ALL protocols used for non trial patients could be a very important factor for outcome. Even if the non trial treatments used is not known this could be considered as an important confounding factor and could be discussed. Discussion (p18, line 26-47). The confounding factor of participating in other clinical trials as in UKALLXII is discussed. As the

	recruitment to this trial stopped in 2007 for the <25y patients, and the majority of 20-24y patients in the present trial was diagnosed from 2008, a subgroup analysis 2008-2010 could be of value (even if the numbers are small). As presented now, it's difficult to draw firm conclusions for the 20-24y age group. Minor: RESULTS: Study population (p12, line 22). The discrepancy between UKALL and NCDR databases regarding diagnosis is a bit unclear regarding confirmed diagnosis. Could it be clarified that the UKALL database diagnosis was confirmed/reviewed? DISCUSSION: (p15, line 44) "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." This way of describing the survival benefit might be unintuitive for the reader to understand.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Motohiro Kato MD, PhD
Institution and Country: National Center for Child Health and Development, Japan Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below Hough R et al. reported comparison of TYA-ALL on UKALL2003 trial or not. As authors mentioned, this survey could provide clinically important information although the study is retrospective and there are some potential selection biases. The following issues to be addressed;

#1. Authors focused on outcomes of TYA patients. I understand poor enrollment is important and problematic especially in this age, but to emphasize importance of this issue, it would be nice if authors could provide similar data for ALL under 15 years of age.
We agree that investigating recruitment rates in younger patients would be very interesting. The focus of our study was specifically chosen to be in TYA patients because recruitment is poorer in this age group and outcomes are inferior. The overall survival in children with ALL is around 90% and trial recruitment exceeds 75% in the UK (see reference below). Thus the clinical need for studying the impact of trial recruitment in younger patients is less than in the TYA group and unfortunately we do not have the resource to perform this analysis.
Rates of inclusion of teenagers and young adults in England into National Cancer Research Network clinical trials: report from the National Cancer Research Institute (NCRI) Teenage and Young Adult Clinical Studies Development Group.
Fern L, Davies S, Eden T, Feltbower R, Grant R, Hawkins M, Lewis I, Loucaides E, Rowntree C, Stenning S, Whelan J; National Cancer Research Institute (NCRI) Teenage and Young Adult Clinical Studies Development Group.

Br J Cancer. 2008 Dec 16;99(12):1967-74. doi: 10.1038/sj.bjc.6604751. Epub 2008 Nov 25.

#2. In page 17, authors insisted that "the prevalence of Ph+ve ALL in UKALL2003 overall was only 1.8% and the observed difference between groups was smaller in the older patients". However, the difference of survival in the 20-24 age group did not reach statistical significance mainly due to smaller sample size compared to the 15-19 age group.
This is clarified in the manuscript – 'smaller' is changed to 'non-significant' (page 18, line 23)

#3. Could authors provide information of treating physician (pediatric or adult background) for non-trial cases?
Unfortunately it is not possible to identify the training of treating physicians (paediatric, TYA or adult) using the registry data available for the study period.
A statement clarifying this has been added to the results section (page 15, line 15). In our analysis we have reported completion of a TYAC form as a surrogate for patients receiving care within the commissioned TYA pathways. The more recently developed national SACT dataset prospectively records the GMC number of treating physicians, which would allow this question to be asked in future analyses.

Reviewer: 2
Reviewer Name: Josep-Maria Ribera
Institution and Country: ICO-Hospital germans Trias i Pujol, Badalona, Spain Please state any competing interests or state 'None declared': No competing interest

Please leave your comments for the authors below The paper by Hough et al addresses a very important aspect in the outcome of TYA: the inclusion into clinical trials. This is an interesting and very difficult-to-perform study. The methodology of selection of patients is accurate and the groups of comparison have been well selected. The statistical methodology seems appropriate (although I have limitations in understanding the selection of the statistical methods), the results are sound and the discussion is well performed, with special emphasis in the limitations and potential biases of the study.
Specific comments to authors:
1. Although I assume that the clinical and biologic characteristics of ALL in TYA not in trial are difficult to obtain, a minimum data apart of age could be retrieved (eg, gender, T vs. B ALL and even the WBC count at diagnosis). It would be desirable if these data could be retrieved to provide more insights on the comparability of the two groups. These were not recorded, incomplete
We agree that this is an important limitation of the study. Unfortunately the national registry dataset available for the study period did not include variables of prognostic importance in ALL and we cannot, therefore, compare clinical features at presentation between groups. Currently, the national registry is collecting some, although not all, prognostic variables in ALL patients. However, completion of these fields by treating centres is poor and mechanisms for improving the quality of data submission are being explored. A sentence highlighting this limitation has been added to the discussion (page 16, line 21-24)

2. The discussion of the potential bias by the Ph chromosome status is very well addressed in the Discussion section. However, data on the number of TYA patients included in the specific trials for Ph ALL activated during the study period could be provided in order to know the proportion of Ph-ve and Ph+ve TYA patients included in clinical trials
Patients with Ph+ve ALL were treated on UKALL2003 induction and then recruited to either the ESPHALL or UKALLXII trials for post induction therapy or treated off trial. The trial consent forms for

ESPHALL and UKALLXII did not include explicit consent for data sharing with the national registries and thus we have been unable to access detailed information from these trial databases. However, the clinical trials units were able to provide us with the overall number of UK patients recruited to these trials within our study period; 3 patients aged 15-17 years were recruited to ESPHALL and 100 patients aged 15-24 years were recruited to UKALL XII. However, this does not provide us with accurate information regarding the proportions of Ph+ve and Ph-ve disease for the following reasons;
a) because of the consent limitations, we could only access numbers of UK patients recruited rather than those treated in England (ie the cohort reported in our manuscript)
b) although ESPHALL was a trial specifically open to only those with Ph+ve disease, UKALL XII recruited both Ph+ve and Ph-ve ALL patients. The lower age limit for UKALL XII for Ph-ve ALL was sequentially increased from 15 years to 20 years in 2006 and 24 years in 2007. Thus the highest proportion of patients recruited to UKALL XII will be those with Ph-ve disease in the older age group and may have contributed to the smaller difference in outcomes between those on UKALL2003 compared to those not on this trial in the 20-24 year old age group.
Clarification of trial entry into ESPHALL and UKALLXII has been added to the methods (page 7 lines 21-24). The number of patients recruited to these 2 trials has been included in the results section (page 13-14). The potential impact of recruitment to UKALL XII on lack of significant difference in the 20-24 year olds has been included in the discussion (page 19, lines 10-15).

3. Was this study evaluated by and IRB?. If yes, this information should be included in the Patients and Methods section IRB not required, consent not required for registry explicit consent for trial
Clarification regarding the consent requirements for trial recruitment and data submission to the national registries has been included in the patients and methods section (page 10, line 1-6).

4. The ways by which an implementation of the trials is notified to all the English centers should be included in the Patients and Methods section. Depending of that, the failure of broad communication of activation of national clinical trials could be included as another potential reason for the lack of recruitment of some patients.
The change in age criteria for our national ALL studies were extensively publicised at annual national (NCRI) paediatric and adult leukaemia update meetings and by newsletters circulated via the clinical trials units. The NIHR also hosts a clinical trial database, which is searchable by any clinician. Although lack of awareness was probably not a major factor in recruitment rates, it may have contributed in the older patients and has been added to the methods (page 8, line 4-8) and discussion (page 20, lines 11-12).

5. Although I assume that is very difficult to know details about the treatment administered to the TYA patients not in trial, it is possible that some of them could receive the same treatment as that of the UKAL2003 trial, but were not included in the trial. This possibility should be mentioned in the discussion
The dataset available to the registry for the study period did not include treatment regimen for those not on trial. It is probable that a substantial proportion of patients were treated with the same regimen off trial. Treatment regimen is now routinely collected in the SACT dataset and will be available for interrogation in the future. This is now clarified in the discussion (page 19, line 12-14)

Reviewer: 3
Reviewer Name: Helene Hallböök
Institution and Country: Dept of Medical Sciences, Haematology, Uppsala University, Uppsala, Sweden Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below This an interesting and well written manuscript discussing the impact of clinical trials on treatment outcome, in this case regarding young adults with ALL.

Major comments:
The survival rates after leukemia treatment is probably multifactorial which is discussed in the manuscript, however the effectiveness of the treatment protocol itself (UKALL 2003) versus contemporary ALL protocols used for non trial patients could be a very important factor for outcome. Even if the non trial treatments used is not known this could be considered as an important confounding factor and could be discussed.
This potential confounding variable has been included in the discussion (page 17, line 11 and page 19, line 12-14).

Discussion (p18, line 26-47). The confounding factor of participating in other clinical trials as in UKALLXII is discussed. As the recruitment to this trial stopped in 2007 for the <25y patients, and the majority of 20-24y patients in the present trial was diagnosed from 2008, a subgroup analysis 2008-2010 could be of value (even if the numbers are small). As presented now, it's difficult to draw firm conclusions for the 20-24y age group.

A subgroup analysis has now been performed (see below). The results for 2008-10 are similar to those for the whole study period: 20-24 year olds in the trial had a two-year survival 10.2% better than those not in the trial, but this did not reach statistical significance p = 0.393. This statement has been added to the results section (page 14, line 17-20).

Trial Status Age group Number of patients Deaths Survival (%) 95% CI P value
1-year survival
Trial 15-19 104 7 93.3 86.4-96.8 0.005
Non-Trial 31 8 74.2 55.0-86.2
Trial 20-24 32 4 87.5 70.1-95.2 0.504
Non-Trial 38 3 92.2 77.5-97.4
Trial 15-24 136 11 91.9 85.9-95.5 0.095
Non-Trial 69 11 84.1 73.1-90.9
2-year conditional on 1-year survival
Trial 15-19 97 5 94.9 88.1-97.9 0.523
Non-Trial 23 2 91.4 69.5-97.8
Trial 20-24 28 2 93.0 74.4-98.3 0.126
Non-Trial 35 8 77.2 59.5-87.9
Trial 15-24 125 7 94.5 88.7-97.4 0.018
Non-Trial 58 10 82.8 70.4-90.4
2-year survival
Trial 15-19 104 12 88.5 80.6-93.3 0.005
Non-Trial 31 10 67.8 48.4-81.2
Trial 20-24 32 6 81.3 63.0-91.2 0.393
Non-Trial 38 11 71.1 53.9-82.9
Trial 15-24 136 18 86.8 79.9-91.5 0.004
Non-Trial 69 21 69.6 57.3-79.0

Minor:
RESULTS: Study population (p12, line 22). The discrepancy between UKALL and NCDR databases regarding diagnosis is a bit unclear regarding confirmed diagnosis. Could it be clarified that the

UKALL database diagnosis was confirmed/reviewed?
Clarification has been added to the methods section - discrepancy is difficult to resolve as there was no central verification of diagnosis (page 8, lines 13-14)

DISCUSSION: (p15, line 44) ”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.” This way of describing the survival benefit might be unintuitive for the reader to understand.
This has been changed in the discussion to the more conventional terminology of 17.9% higher survival in those on trial (page 16, line 7).

VERSION 2 – REVIEW

REVIEWER	Motohiro Kato MD, PhD National Center for Child Health and Development, Japan
REVIEW RETURNED	18-Jun-2017

GENERAL COMMENTS	The authors responded to the comments adequately, thank you.

REVIEWER	Helene Hallböök Dep of Medical Sciences, Uppsala University, Sweden
REVIEW RETURNED	25-Jun-2017

GENERAL COMMENTS	All point raised in previous review have been met, and even if some difficulties remain due to the nature of the material, the study is of interest, well performed and addresses an important topic. I have no further comments.

VERSION 2 – AUTHOR RESPONSE

Thank you very much for your positive response to our manuscript. As requested, we have made the following changes;

a) The title has been revised
b) The STROBE checklist has been included as a supplementary file and the methods section now includes a statement confirming that the STOBE guidelines have been followed
c) The strengths and limitation section has been expanded to include statements regarding the methods and potential confounding variables
d) The reference style has been reformatted