Public Health England

Protecting and improving the nation's health

NHS England

Case-mix adjusted 30-day mortality post systemic anti-cancer therapy rates for acute lymphoblastic leukaemia in children, teenagers and young adults (CTYA)

A companion brief to support the interpretation of this data

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing and reduce health inequalities. We do this through world-leading science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000
www.gov.uk/phe
Twitter: @PHE_uk
www.facebook.com/PublicHealthEngland

Published May 2021
PHE publications

PHE supports the UN
Sustainable Development Goals

Contents

Summary

In March 2021, the National Disease Registration Service (NDRS) team, as part of the SACT-NHSE Partnership at Public Health England (PHE), produced a workbook documenting case-mix adjusted 30-day mortality post systemic anti-cancer therapy (SACT) rates (CMAR) for Acute Lymphoblastic Leukaemia (ALL) in children, teenagers and young adults (CTYA). These CMAR were calculated for Principal Treatment Centres (PTCs).

The data is case-mix adjusted to allow for comparisons to be made between PTCs and within one PTC over time. A pre-release of the workbook was circulated to all PTCs in early March 2021. PTCs were able to request NHS numbers of patients who had died within 30 days of receiving SACT at their centre. We provided all PTCs the opportunity to comment on their data. Comments are included at the end of this document, published May 2021.

Context and interpretation

We acknowledge a current lack of clarity as to whether 30-day post-SACT mortality analysis is a good quality indicator in this age group. Prescribing practices for children and young people towards the end of life may be different to those used for the majority of the (generally much older) cancer population, and certain indicators such as performance status are less relevant than in older people. We developed this information to support clinical governance and potentially identify areas where clinical care could be improved.

Ascertainment of data for this age group is challenging. The SACT team are currently completing an evaluation on the level of ascertainment in the SACT dataset compared with other resources and we hope to publish these findings in the near future. We are aware that the data presented for the CMAR CTYA ALL may not be complete, however it is a starting point upon which we wish to build upon.

Key messages

- The workbook is being published with the aim of identifying whether case-mix adjusted 30-day mortality post SACT rates are a useful metric for Principal Treatment Centres (PTC).
- The average case-mix adjusted 30-day PTC mortality rate post SACT was 6.3%.
- Case-mix adjusted 30-day mortality post SACT rates varied from 0 to 19.5%.
- No Principal Treatment Centres were identified as outliers.
- The number of patients included in the analyses from different Principal Treatment Centres ranged from 5 to 179, which may reflect different caseloads, but also potentially different levels of case ascertainment in the SACT dataset.

Background

In 2016, the SACT team at PHE published a paper in the Lancet Oncology providing 30-day mortality post-SACT rates for breast and lung cancer. NHS trusts, NHS England and the clinical community fed back to PHE that this work had been beneficial in terms of setting a national benchmark, identifying variation in clinical practice between trusts and identifying areas where patient care could have been improved. This information helped to inform advancements to clinical practice.

In December 2018, the SACT team released a workbook to trusts providing crude rates for 30-day mortality post-SACT for all cancers combined and breakdowns for Acute Myeloid Leukaemia, Breast, Colon, Children's Teenagers and Young Adults (CTYA), Small Cell Lung Cancer, Non-Small Cell Lung Cancer, Upper Gastro-Intestinal Oesophageal.

Feedback generated from this release highlighted the need for 30-day mortality data which was more timely to support clinical audit, as well as case-mix adjusted which would facilitate the comparison of performance between trusts. Unfortunately, these two needs cannot be met in a single data feed. Case-mix adjusted data cannot be produced soon enough after treatment activity to support clinical audit as it requires linkage to the National Cancer Registration Dataset for England to provide supplementary patient information which operates at an approximate 18-month time lag, and additional analytical time to conduct the work. Furthermore, for rarer cancer types, case-mix adjustment may only be possible when several years of data have accrued to provide a sufficient cohort size to support analysis. The SACT team have therefore met these two needs through two outputs: the Rapid Data Review (RDR) and the CMAR workbook. The RDR provides a quarterly data feed to all NHS trusts in England providing key information on patients who died within 30 days of receiving SACT at their trust. This aims to inform 'mortality and morbidity' meetings and develop communications between trusts on initiatives undertaken to reduce 30-day mortality. The CMAR produces 30-day mortality post-SACT rates that are adjusted for key variables which means that rates can be compared between trusts and within trusts over time.

In August 2020 and November 2020, the SACT-NHSE partnership team released workbooks containing case-mix adjusted 30-day post-SACT mortality rates for adults (aged 18+) for a range of cancer sites; the data for these workbooks are now available as an interactive web application at https://cancerdata.nhs.uk/sact/cmarreport. This presents all cancer sites from these workbooks in one output and enables new functionality; such as displaying trust name, number of patients treated, and case-mix adjusted 30-day mortality rate when hovering over datapoints on the funnel plot. The August 2020 CMAR workbook reviewed patients aged 18+ diagnosed between 2010 and 2017 treated for lung, gastric, pancreatic cancer, and cancer of unknown primary (CUP) in 2017-2018 (depending on the site). The November 2020 CMAR workbook reviewed patients aged 18+ diagnosed between 2010 and 2018 treated for bowel, breast, myeloma and ovarian in 2018-2019 (depending on the site).

Two further workbooks were released publicly in May 2021. The first reviewed patients aged 18+ diagnosed between 2010 and 2018 and treated for acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) in 2017-2019 (depending on the site). The second reviewed patients aged 18+ diagnosed between 2010 and 2018 and treated for prostate cancer in 2018-2019.

Case-mix adjusted 30-day mortality post-SACT for acute lymphoblastic leukaemia in children, teenagers and young adults (CTYA)

Each workbook was based on data reported by NHS trusts in England through their monthly routine SACT data uploads. In advance of these publications the adult workbooks were sent to the NHS Trusts for review, giving them the opportunity to provide a statement to accompany their data. These statements have been included in the companion reports released with the August 2020, and November 2020 and May 2021 CMAR workbooks.

For further information on the SACT data reports please see http://www.chemodataset.nhs.uk/reports/

Workbook

The workbook is based on routine data submitted by NHS trusts to the SACT dataset and includes patients aged 0-24 at diagnosis, diagnosed with acute lymphoblastic leukaemia (ALL) in England between 2010 and 2018, treated with SACT in England between January 2017 and December 2019[1]. Patients were only included if they received their last treatment during the treatment period (i.e. patients still receiving treatment in 2020 were excluded).

Patients were aged between 0 and 24 at the time of diagnosis, with a median age of 7. At the time of their last treatment, 72.4% of patients were in the 0-15 age-group, and 25.4% of patients in the 16-24 age-group. There is a small difference in the age at diagnosis and age at last treatment, which has meant that 20 patients (2.2%) in the analysis were aged between 25 and 31 at the time of their last treatment.

Each patient was allocated to the trust where they received their final treatment, regardless of any prior treatment received at other trusts, and was assigned to their associated Principal Treatment Centre (PTC) for the analysis. For Liverpool, Manchester, Sheffield and Birmingham, where there is a clearer distinction between designated children's vs teenager and young adult (TYA) hospitals, the PTC for children and TYA are grouped separately. Please see the 'List of trusts included' tab in the workbook for the list of trusts and caseload (number treated) which were included in the analysis for each PTC.

Table 1. ICD-10 code and treatment activity covered

Cancer site	ICD-10 code	Period of treatment activity
Acute Lymphoblastic Leukaemia (ALL)	C91.0	Jan 2017 – Dec 2019

The National Cancer Registration and Analysis Service (NCRAS), part of Public Health England (PHE), is the population-based cancer registry for England. It receives data from across the National Health Service (NHS) and produces the National Cancer Registration Dataset for England. At the time of this release, the National Cancer Registration Dataset was complete up to the end of 2018.The SACT dataset collects systemic anti-cancer therapy activity from all NHS England providers. For the purposes of the analysis, patients were selected from the National Cancer Registration Dataset. This cohort of patients was then linked to the SACT dataset on NHS number in order to retrieve the latest treatment records for these patients. Certain restrictions were applied to the data to ensure the appropriate patients and treatments were selected. These restrictions mean that some trusts may have no data included in the workbook because their patients and patients' treatment activity did not fit the criteria applied. The restrictions applied to the data are outlined below.

[1] All patients treated during the selected time frame were included – not only those who started treatment during the period of interest.

Case-mix adjusted 30-day mortality post-SACT for acute lymphoblastic leukaemia in children, teenagers and young adults (CTYA)

Cancer restrictions

- Diagnosis was restricted to cancers diagnosed between 2010 and 2018.
- Patients whose most recent cancer diagnosis was the cancer site of interest were selected. If patients had more than one cancer diagnosed on the same day, the ALL diagnosis was selected.

It is important to note that in some cases, the cancer diagnosis recorded in the National Cancer Registration Dataset may differ from that recorded by the trust.

If you would like support in improving the quality of the data feed into the NCRAS then please contact NDRSdatasets@phe.gov.uk

Data completeness restrictions

No data completeness restrictions were applied in the analysis as all key variables had near 100% completeness (ethnicity had 5 cases of missing data). Age, sex, ethnicity and deprivation status were sourced from the National Cancer Registration Dataset. The adult analyses we have produced exclude trusts with less than 70% completeness for the key variables: performance status, co-morbidity score, and stage data where possible. These variables are not included in the ALL CTYA analysis and thus restrictions were not required.

Data consistency restrictions

- The trust at which final SACT treatment was completed is important for calculating the CMAR. Any patients whose final SACT treatment was recorded at two different trusts on the same day have therefore been removed from the analysis.
- Any patients who had a record of SACT treatment after death were removed from the analysis.

These were not common events in the data.

Age restrictions

- The cohort was restricted to those aged 0-24 at diagnosis.

30-day SACT mortality restrictions

We count deaths (for any reason) within 30 days of the date that the last SACT treatment was administered. For oral treatments the 30-day window starts 28 days after the last administration date recorded in SACT, as most oral treatments have a prescription length of 28 days. Please see the CDF methodology document[2] for further details. The current method of setting all oral treatments as lasting 28 days is being reviewed for future SACT outputs.

Treatment restrictions

For the purposes of the analysis, and to ensure treatment data was relevant to the cancer site, the following rules were applied when linking SACT data to the cohort of patients identified from the National Cancer Registration Dataset:

1. For those patients with only one cancer diagnosed, all treatment records within the relevant time frame were selected.

[2] Appendix links for the CDF methodology document: Appendix A (oral treatment duration calculations) and Appendix B (caveats associated with oral treatment duration calculations)

2. For those patients with more than one cancer diagnosed, treatment records were selected if they fit the following criteria:
    a. Within the relevant timeframe (January 2017-December 2019).
    b. The first three characters of the primary diagnosis recorded in SACT for that treatment record matched the first three characters of the cancer site identified in the registration data.
3. For those patients with treatment records that did not fall within categories 1 and 2 outlined above, treatment records were selected if they were within the relevant timeframe and fell within 31 days before and 456 days after the diagnosis of interest. The decision to restrict based on the time between treatment and diagnosis is in accordance with the Linking treatment tables – chemotherapy, tumour resections and radiotherapy' standard operating procedure. The timeframes used ensure that treatment given soon after diagnosis is included for those patients where the diagnosis codes recorded in the National Cancer Registration Dataset are not an exact match to those recorded in SACT. This is particularly relevant for some cancers where coding of the cancer site sometimes differs between data sources.

Treatment regimens

Non-harmful, supportive treatments, hormones and non-chemo drugs excluded from the analysis. The excluded regimens are listed below. These were selected for exclusion in consultation with clinicians and pharmacists and are reviewed on a site-specific basis for every release.

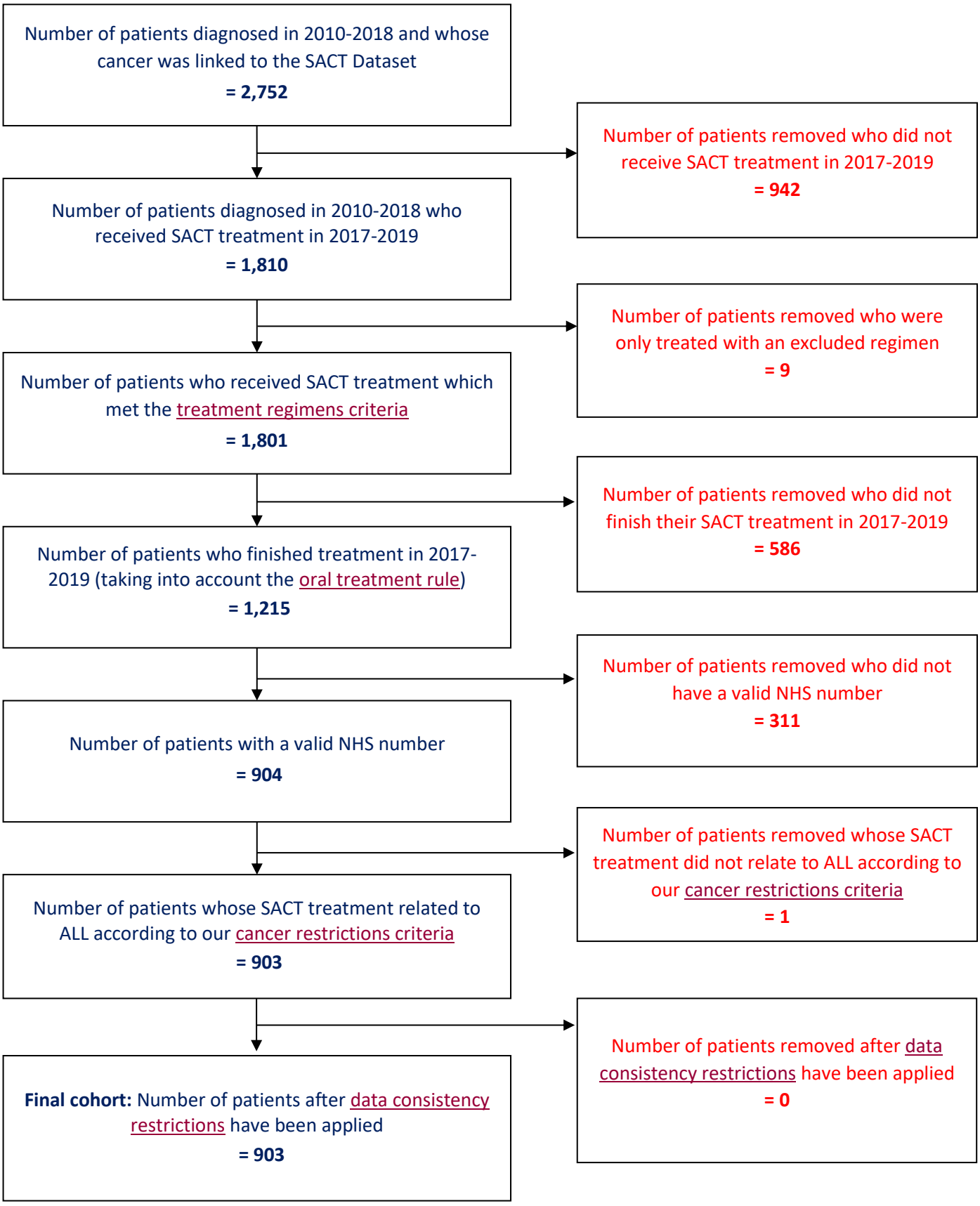
- Not Chemo
- Trial
- Anagrelide
- Anastrozole
- Anti-Emetics
- Anti-Histamines
- APML
- B12
- Bisphosphonates
- Denosumab
- Exemestane
- Folinic Acid
- CGSF
- Goserelin
- Hepatoblastoma
- Ibandronic Acid
- Lanreotide
- Letrozole
- Medroxyprogesterone
- Megestrol
- Octreotide
- Pamidronate
- Pasireotide
- Progesterone
- Retinoblastoma
- Sandostatin

Case-mix adjusted 30-day mortality post-SACT for acute lymphoblastic leukaemia in children, teenagers and young adults (CTYA)

- Signifor
- Somatostatin
- Somatuline
- Steroid[3]
- Stilbestrol
- Stilboestrol
- Tamoxifen
- Vitamin
- Zoledronic Acid

[3] A sensitivity analysis with steroid treatments included in the analysis showed that the inclusion of this treatment regimen did not change the results.

CMAR ALL CTYA analysis flowchart



Implications of methodological approach

To get detailed information on the cancer diagnosis, patient and cancer characteristics, cancers recorded in the National Cancer Registration Dataset are linked to those in the Systemic Anti-Cancer Therapy (SACT) datasets. This requires analytical decisions to be made. In particular, the recording of primary diagnoses in the SACT dataset are known to not always exactly match the cancer site recorded in the National Cancer Registration Dataset (the gold standard), so linking records on patient identifiers and cancer site would mean many cancers and their associated SACT treatment could be missed.

The treatment restrictions detailed on the treatment restrictions section, are therefore designed to balance the risks of erroneously excluding patients from the cohort because of errors in the recording of primary diagnosis in the SACT dataset (or errors in the mapping of regimens), with the risk of incorrectly including SACT treatment records that do not relate to the cancer site under consideration in the CMAR report.

In cases where the primary diagnoses recorded in the two datasets differ, we use the time between cancer diagnosis and treatment along with the timeframes cited in the 'Linking treatment tables – chemotherapy, tumour restrictions and radiotherapy' standard operating procedure, to infer whether the treatment captured in the SACT dataset is likely to relate to the tumour of interest. For acute lymphoblastic leukaemia the recommended window is between 31 days before the recorded date of diagnosis and 456 days after, so it is quite a long window.

The COVID-19 pandemic has unfortunately led to an increased lag in the availability of National Cancer Registration Dataset data, which has meant cancer diagnoses made in 2019 are not yet available. Patients who received a second primary cancer diagnosis in 2019 will therefore been captured as having just acute lymphoblastic leukaemia. We have included treatment information up to the end of 2019 as SACT data is more timely.

We follow the approach used for the Cancer Drugs Fund reports for oral treatments, where we estimate how long the patient is 'on treatment' for, by adding days relating to the typical prescription length to the last administration date recorded in the SACT dataset. 28 days was found to be a reasonable proxy for most treatments. Therefore, we add 28 days to the administration date for all oral treatments. This is then taken into account when retrieving the final treatment date for each patient. This may differ from methodologies used within trusts themselves. We are currently reviewing our methodology to consider which approach is of greatest value to trusts.

We are conservative in our approach to excluding regimens from the analyses, to avoid excluding regimens that have been incorrectly mapped. This can, however, result in SACT treatment for cancer sites other than the site of interest being included.

Interpretation of the data

Case-mix adjusted rates (CMAR) of 30-day mortality post systemic anti-cancer therapy (SACT) are reported in this workbook. Each Principal Treatment Centre (PTC) will see and treat a wide variety of patients depending on the population they serve and the services they provide. The case-mix adjusted rates take into account these differences by producing rates that are based on an average group of patients as opposed to the PTC's own group of patients. The rates can then be compared between PTCs and within a PTC over time. This was done using statistical modelling (in this case, a mixed effects logistic regression model). Please see the accompanying FAQ document for further technical information on calculating CMAR.

The following variables were adjusted for in the analysis:

- Age calculated as of the 1st January 2019
- Deprivation status[4]
- Ethnicity[5]
- Principal Treatment Centre (as a random effect[6])
- Sex

These variables were chosen because they are known to influence 30-day post-SACT mortality and have sufficient completeness. For paediatric patients, comorbidities and performance status would only exceptionally influence treatment decisions, so neither were included in the risk-adjustment model. Furthermore, there is low completeness for performance status for CTYA patients in the SACT dataset. Stage was not adjusted for as there is no TNM staging data for this cancer.

It is important to note that due to the absence of any information on critical factors such as patient/parent choice and clinical factors such as liver function tests, the case-mix adjustment may not fully correct for the differences in caseload between trusts.

The funnel plot[7] presented in the workbook is a means of visualising 30-day mortality post-SACT rates for the PTCs in England.

- The volume of patients is on the horizontal axis. The more patients treated by your PTC, the further to the right your PTC will be.
- The 30-day mortality post-SACT is on the vertical axis. The higher the mortality post-SACT rate at your PTC, the further up the graph it will appear.
- The solid red horizontal line shows the average mortality post-SACT rate of all PTCs.
- The selected PTC is indicated by the yellow diamond, other PTCs are represented by the blue diamonds.

[4] Using the income domain of the Index of Multiple Deprivation. IMD data from 2015 was used for tumours diagnosed between 2010 and 2013 and IMD data from 2019 was used for tumours diagnosed between 2014 and 2018.
[5] Grouped into White, non-White and Unknown categories for analysis as there were insufficient numbers in the other ethnic groups for robust analysis.
[6] In a model, a random effect is usually a grouping factor (e.g. general practice, school, university), in this case the PTC, for which we are trying to control and which we expect to be influencing the pattern of 30-day mortality.
[7] More information on funnel plot uses and interpretation can be found on the PHE Technical Guide and Tower Hamlets Clinical Commissioning Group Guide

Case-mix adjusted 30-day mortality post-SACT for acute lymphoblastic leukaemia in children, teenagers and young adults (CTYA)

- The dotted lines represent the ±2 standard deviations (SDs) (roughly equivalent to 95% confidence intervals); the dashed lines represent the ±3 standard deviations (SDs) (roughly equivalent to 99.8% confidence intervals). They are higher on the left because when a PTC treats a smaller number of patients, chance will have a greater impact on the rate, and therefore the confidence intervals will be wider to reflect this.

The confidence intervals presented in the workbook reflect the distribution of PTC mortality post-SACT rates around the national average. The workbook highlights the mortality post-SACT rates for ±2 standard deviations (SDs) (roughly equivalent to 95% confidence intervals) and ±3 standard deviations (SDs) (roughly equivalent to 99.8% confidence intervals). PTCs with rates above the upper, +3SD will be identified as outliers.

- PTCs with rates above the upper, +3SD have a significantly higher than average 30-day post-SACT mortality rate.
- PTCs with rates below the lower, −3SD have a significantly lower than average 30-day post-SACT mortality rate.
- PTCs with rates within the confidence limits have an average 30-day post-SACT mortality rate.

Excluded PTCs and outlying PTCs

No Principal Treatment Centres (PTCs) were excluded from the analysis, as all PTCs had near complete data for all the variables used in the risk-adjustment model.

No PTCs had a case-mix adjusted rate above the 3 standard deviation limit, so no PTCs were identified as outliers.

Principal Treatment Centre comments

PTCs were invited to comment on their results. We received the following comment:

Alder Hey Children's NHS Foundation Trust

We welcome attempts to provide meaningful outcome data for our service and that of other principal treatment centres, to enable focus on practise and comparison with other providers.

We do however have a number of concerns both regarding the data from our own trust but also for that from other trusts;

1. The total number of leukaemia patients used for Alder Hey data set appears to be less than the actual number of patients treated during the time period covered by this report. It is difficult to ascertain why this is.
2. A few patients may have been missed due to an incomplete SACT dataset during the early part of the time period analysed and a few others will be excluded due to transfer to Manchester for transplant and CAR-T

We note a similar discrepancy may exist for other trusts given numbers recorded, which are not consistent with expected numbers for many centres. It is difficult to cross check the accuracy of numbers given the methodology and it would be good to see a more detailed breakdown of the figures used to compile the dataset so we can try and address the discrepancies for future analysis.

We would make the following suggestions;

- The context of death is clarified (disease versus treatment related)
- Analysis of relapse rates
- It is of concern that incorrect data with respect to patient numbers and mortality (for patients treated at Alder Hey and other Principal treatment centres) may be accessible in the public domain

Communication of the workbook

The SACT helpdesk at PHE (SACT@phe.gov.uk) compiled a list of named contacts at each Principal Treatment Centre (PTC) including the SACT uploader, lead cancer clinician, the regimen mapper, CEO and medical director, unless we were otherwise notified.

The workbook was sent to these named contacts at the relevant PTC. There was no patient identifiable data included in the workbook. PTCs were invited to request the NHS numbers of patients in their data who died within 30 days of receiving SACT. NHS numbers were only provided via secure means following a request from the PTC. This aims to restrict the circulation of this sensitive information to individuals who intend to use it for clinical audit and local governance processes.

We informed PTCs that we would be making the acute lymphoblastic leukaemia (ALL) CTYA workbook covering those aged 0-24 publicly available on the SACT website[8] in May 2021 and invited them to provide a statement for inclusion in this companion report.

Trusts were invited to provide a statement for inclusion across all other published CMAR reports. Other reports published on the SACT website[8] in May 2021:

- Acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) workbook covering those aged 18+
- Prostate workbook covering those aged 18+

Each release will be publicised through a range of channels, including the SACT and the National Disease Registration Service (NDRS) newsletters.

If you have any questions regarding this work, please contact the SACT Helpdesk (SACT@phe.gov.uk).

[8] SACT website: http://www.chemodataset.nhs.uk/