

The impact of COVID-19 on prescribing of pancreatic enzyme replacement therapy for people with unresectable pancreatic cancer in England. A cohort study using OpenSafely-TPP

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Abstract

Background: Cancer treatments were variably disrupted during the COVID-19 pandemic. Despite UK national guidelines recommending pancreatic enzyme replacement therapy to all people with unresectable pancreatic cancer, observational studies demonstrate under-prescribing.

Aim: To investigate the impact of the COVID-19 pandemic on the prescribing of pancreatic enzyme replacement to people with unresectable pancreatic cancer.

Methods: With the approval of NHS England, we conducted a cohort study using 24 million health records through the OpenSAFELY-TPP research platform. We modelled the effect of COVID-19 with multivariable linear regression.

Results: We found no reduction in pancreatic enzyme replacement therapy during the COVID-19 pandemic. Overall, since 2015, the rates of prescribing increased steadily over time by 1% every year. The national rates ranged from 41% in 2015 to 48% in 2022. There was substantial regional variation. The highest rates of 50% to 60% were in the West Midlands and the lowest (20% to 30%) were in London.

Conclusions: In contrast to many other treatments, prescribing of pancreatic enzyme replacement therapy was not affected during the COVID-19 pandemic. Although overall rates increased over time, substantial under-prescribing existed at the end of this study (March 2022). At just under 50% in 2022, the rates were still below the recommended 100% standard. Prior work evaluating quality of care in this area relied on manual audits which come at increased cost and reduced frequency of updates. With the methodological advantage of OpenSAFELY, we established an automated audit which allows for regular updates.

Keywords: Electronic healthcare records, COVID-19, prescribing audit, pancreatic cancer, pancreatic cancer, quality of care, pancreatic enzyme insufficiency, pancreatic cancer enzyme replacement

Key messages

What is already known on this topic

- Cancer treatments were disrupted by the COVID-19 pandemic.
- Pancreatic enzyme replacement therapy (PERT) is underused in people with pancreatic cancer.

What this study adds

- Prescribing of PERT was not affected by the COVID-19 disruption.
- Since 2015, the rates of PERT in England increased by 1% every year.
- At just under 50% in 2022, the national rates were significantly below the recommended 100% standard for people with unresectable pancreatic cancer.
- We also showed substantial regional variation.

How this study might affect research, practice or policy

- Research is needed to understand barriers to prescribing of PERT.
- Our automated audit will allow regular data updates for the evaluation of healthcare interventions to improve prescribing of PERT.

Background

Worldwide, there are around half a million new pancreatic cancer diagnoses every year (including 10,000 in the UK and 60,000 in the US) [1, 2]. Currently, surgery is the only curative option, but with 85-90% of people diagnosed too late for surgical resection, pancreatic cancer has the lowest (9%) 5-year survival rate among all the cancers [2]. Treatment options available to people with unresectable pancreatic cancer are palliative in nature and include symptom and pain management. Deficiency in the endo- and exocrine functions of the pancreas has implications for pancreatic cancer care. Diabetes presents commonly, and there are well established treatment pathways. Pancreatic exocrine failure, or insufficiency, is less well treated [3-5].

There is clear evidence that untreated insufficient digestive enzyme production results in dramatic weight loss, malnutrition, impaired quality of life via gastrointestinal symptoms and, in pancreatic cancer, contributes to cachexia and frailty [6, 7]. In pancreatic cancer, pancreatic enzyme replacement therapy (PERT) can help to improve nutritional status and wellbeing and, as a result, the ability to tolerate the disease and treatment [3, 8-10]. A meta-analysis of the effect of PERT demonstrated a survival benefit of several months among patients with unresectable pancreatic cancer [11]. This survival advantage is of similar magnitude to that associated with palliative chemotherapy [11]. The first UK pancreatic cancer guidelines published by the National Institute for Health and Care Excellence (NICE) in February 2018, recommend PERT to people with pancreatic cancer [12]. Subsequently, a Quality Standard (QS177 #4) was published by NICE in December 2018 to ensure that all adults with unresectable pancreatic cancer receive PERT [13].

Despite the clear evidence of the benefits, as well as relatively low risks and few contraindications of PERT, the therapy remains underutilised in pancreatic cancer management [3-5]. In addition, the recent healthcare disruption associated with the COVID-19 pandemic, was shown to affect both primary care prescribing [14] and cancer care [15]. Given that PERT prescribing was suboptimal prior to COVID-19, and that rationing of pancreatic cancer diagnostics and treatment has been reported during the pandemic across the UK, there is a concern that this patient population would be further disadvantaged during the pandemic.

We therefore set out to evaluate the impact of the COVID-19 pandemic on the rates of PERT prescribing in England. Previous work in this area, such as the largest (until this study) national audit undertaken by the RICOCHET Study Group in 2018 [16], relied on manual audits of patient records. This is a resource intensive and limiting (e.g., duration and frequency of audits) process. The methodological advance of OpenSAFELY offers an improved monitoring approach. OpenSAFELY facilitates the opportunity for transparent and reproducible automated audits which can be regularly updated with limited additional resource.

Methods

Study design

We used a cohort study design to assess the proportion of adults with unresectable pancreatic cancer receiving PERT from 1st January 2015 to 31st March 2022. The national target was 100%, as per the NCIE (2018) Quality Standard [13].

Data Source

All data were linked, stored and analysed securely within the OpenSAFELY platform: opensafely.org. Primary care records managed by the GP software provider TPP were linked to Office of National Statistics (ONS) death data and to Secondary Uses Service (SUS) hospital procedures data through OpenSAFELY, a data analytics platform created by our team on behalf of NHS England to address urgent COVID-19 research questions (opensafely.org). OpenSAFELY provides a secure software interface allowing the analysis of pseudonymized primary care patient records from England in near real-time within the EHR vendor's highly secure data centre, avoiding the need for large volumes of potentially disclosive pseudonymized patient data to be transferred off-site. This, in addition to other technical and organisational controls, minimises any risk of re-identification. The dataset was based on 24 million people currently registered with GP practices that use TPP's SystmOne software (covering over 40% of England's population). It included pseudonymized data such as coded diagnoses, medications and physiological parameters. It did not include free text data.

Study population and study measures

Between 1st January 2015 and 31st March 2022, each month we identified individuals receiving PERT (numerator) among adults with unresectable pancreatic cancer (denominator). PERT was defined using a list of medications compiled from the British National Formulary (BNF, bnf.org) and coded using NHS Dictionary of Medicines and Devices, the nationally mandated NHS terminology. Individuals were classified each month as receiving PERT if they had a prescription between the 1st day of that month and 61 days after. This was because 86% of prescriptions are issued for durations of one or two months [17]. Adults with unresectable pancreatic cancer were defined by a presence of SNOMED-CT codes for pancreatic cancer and an absence of OPCS-4 codes indicating a surgical resection procedure after pancreatic cancer diagnosis. The study flowchart explaining inclusion criteria is presented in Figure 1.

Statistical methods

The overall trends in prescribing, and by regions in England, were visualised over time. Monthly rates were presented as the proportion of individuals receiving PERT per 100 people with unresectable pancreatic cancer (%). Generalised linear model (GLM) was fitted to the data to model the overall trend in prescribing over time, the effect of COVID-19, and predict the expected rates in prescribing as if the pandemic had not occurred. The time was included as a continuous variable to allow change in prescribing rates over time. The seasonality effect (month) was not accounted for. A variable that represented the COVID-19 period was included together with its time interaction term to allow varying slope. The 95% confidence intervals of the predicted values were used to estimate the significance of the difference between the predicted and observed values (to estimate the effect of the COVID-19 pandemic).

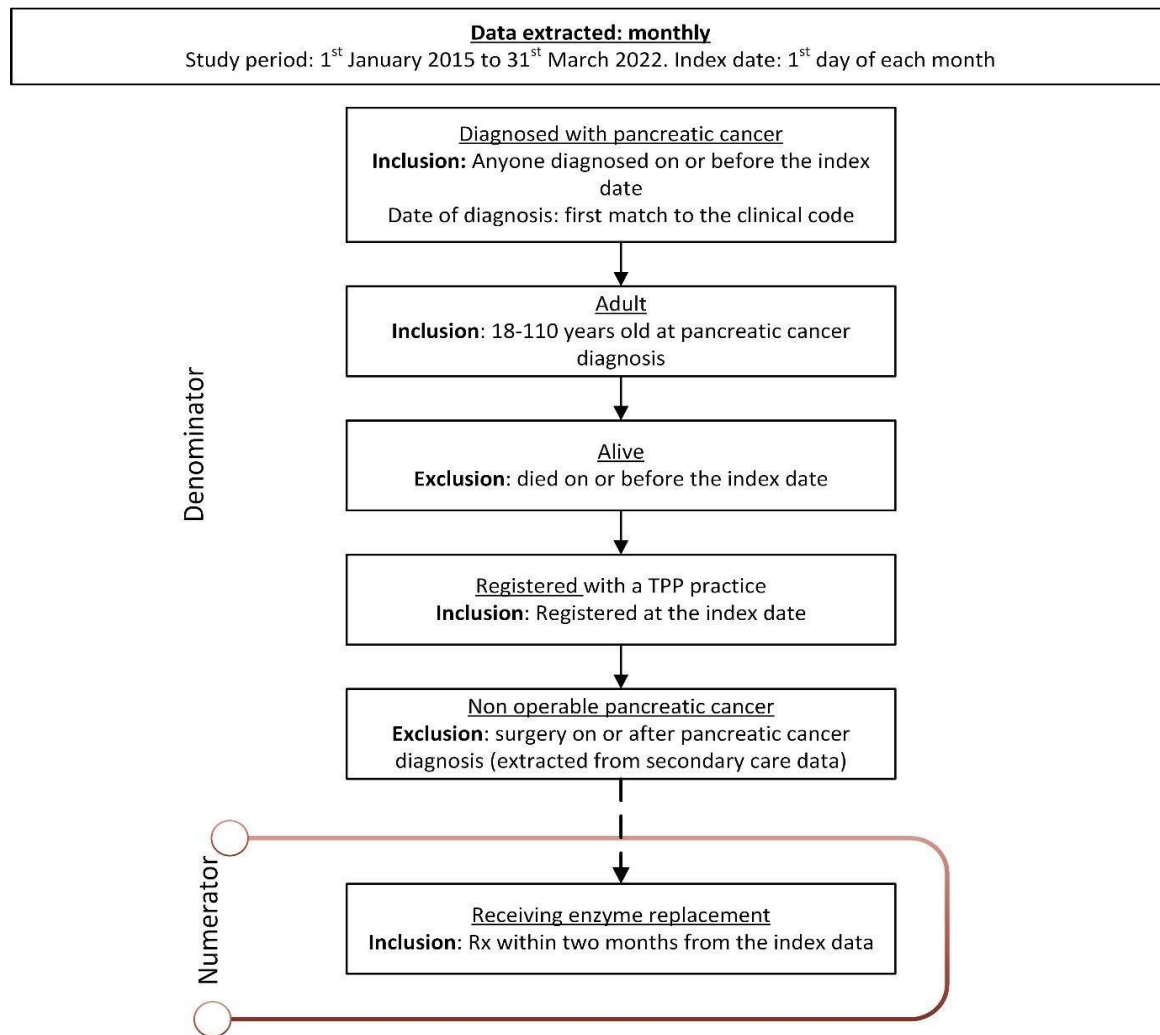


Figure 1. Study flowchart explaining inclusion and exclusion criteria for the study. Each month a rate of people receiving pancreatic enzyme replacement therapy among people with unresectable pancreatic cancer was calculated.

Software and reproducibility

Data management was performed using Python 3.8 and analysis carried out using R 4.0.2. Software for data management and analysis is available online via github.com/opensafely/PaCa_Enzyme_Rx. Code lists are available via opencodelists.org.

Patient and public involvement

OpenSAFELY has developed a publicly available website <https://opensafely.org/> through which they invite any patient or member of the public to make contact regarding the broader OpenSAFELY project.

Results

The effect of COVID-19

Figure 2 shows the rates in prescribing over time in England. Overall, the COVID-19 pandemic did not affect PERT prescribing to people with unresectable pancreatic cancer. A small decrease in treatment rates, by about 3% (from 46% to 43%), was observed at the beginning of the COVID-19 pandemic from March to July 2020. This dip in rates could potentially be associated with the effect of the COVID-19 healthcare crisis. However, the rates of prescribing recovered by September 2020 to rates that would be expected if the pandemic had not occurred.

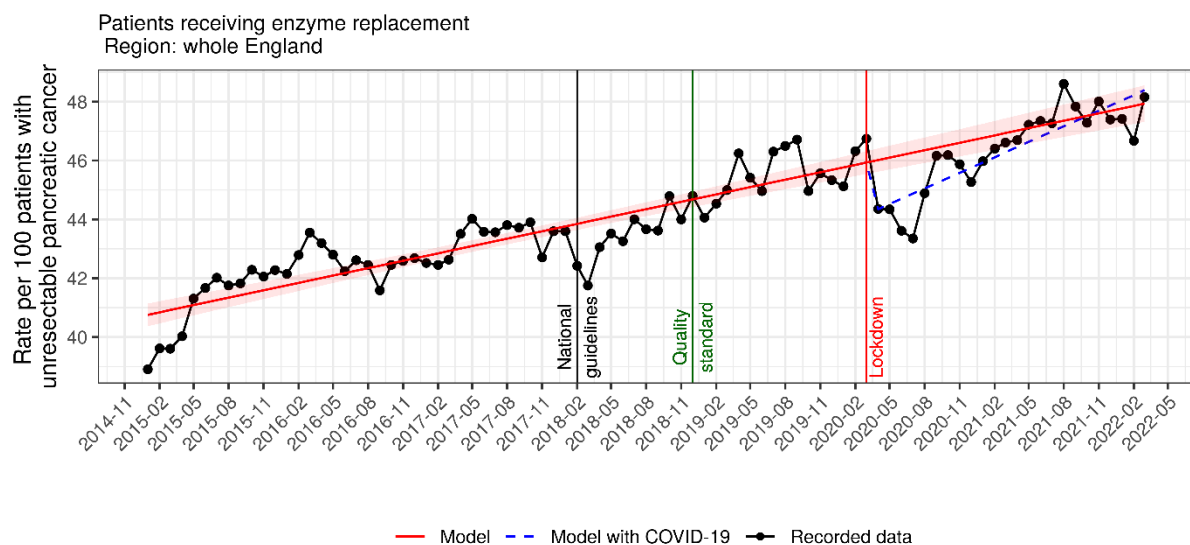


Figure 2. National rates of prescribing of pancreatic enzyme replacement therapy to people with unresectable pancreatic cancer in England between 1st January 2015 and 31st March 2022. Vertical lines indicate points in time of interest to the study; black line, February 2018: publication of the National Institute for Health and Care Excellence (NICE) first UK national guidelines [12] recommending pancreatic enzyme replacement therapy to people with pancreatic cancer; green line, December 2018: publication of the NICE Quality Standard 4 [13] published to ensure that all adults with unresectable pancreatic cancer receive pancreatic enzyme supplementation; red line, March 2020: beginning of the COVID-19-related national restrictions.

National and regional trends

In view of the national target rate of 100%, the national trend increased gradually over time on average by 1% every year, ranging from 41% in 2015 to 48% in 2022 (Figure 2). Figure 3 shows the rates in prescribing by regions in England. The highest rates, achieving values between 50% and 60% from 2018 onwards were in the West Midlands region. Throughout the study period, the lowest rates of between 20% to 30% were in the London region. The effect of COVID-19 was the most pronounced in the West Midlands area with a dip in rates by nearly 10% (from 50% to 40%) in July 2020. This recovered by September 2020 to higher than the pre-pandemic levels.

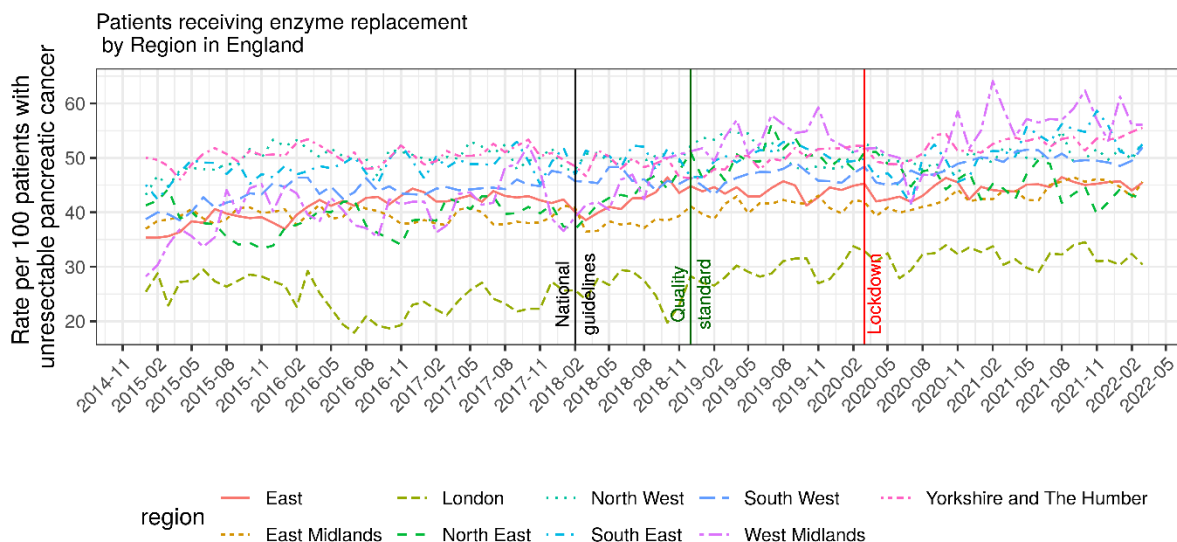


Figure 3. Regional rates of prescribing of pancreatic enzyme replacement therapy to people with unresectable pancreatic cancer in England between 1st January 2015 and 31st March 2022. Vertical lines indicate points in time of interest to the study; black line, February 2018: publication of the National Institute for Health and Care Excellence (NICE) first UK national guidelines [12] recommending pancreatic enzyme replacement therapy to people with pancreatic cancer; green line, December 2018: publication of the NICE Quality Standard 4 [13] published to ensure that all adults with unresectable pancreatic cancer receive pancreatic enzyme supplementation; red line, March 2020: beginning of the COVID-19-related national restrictions.

Discussion

Summary

Reassuringly, despite the challenges of the COVID-19 pandemic, clinicians ensured continuity of care in this area. Overall, there was no change in prescribing of PERT to people with unresectable pancreatic cancer during the COVID-19 pandemic. We did observe a small and temporary decrease in prescribing rates from March to July 2020, which recovered fully by September 2020 to rates that would be expected if the pandemic had not happened. However, with the target prescribing rate of 100% (all adults with unresectable pancreatic cancer are to be prescribed PERT) [13], we also found that despite the clear benefits, PERT remained under-prescribed in this group of patients.

Findings in context

The delivery of cancer services was severely impacted by the COVID-19 pandemic. Effects upon cancer surgery [18, 19], chemotherapy [20] and cancer research [21] have been well described. In pancreatic cancer, centres have described impact upon the entire pathway, including diagnostic, staging as well as treatment delivery [22]. In contrast, in this study we show that prescribing of PERT to people with unresectable pancreatic cancer was not affected during the COVID-19 pandemic.

A previous national UK study, undertaken between 2001 and 2015, demonstrated an overall prescribing rate of PERT to people with pancreatic cancer at 21% [3]. A regional UK study observed a prescribing rate of 22% between 2010 and 2012 [4]. More recently, the national RICOCHET audit conducted April to August 2018, six months after the introduction of the national pancreatic cancer guidelines, demonstrated rates of 74% for patients with resectable and 45% with unresectable disease [16]. The current study demonstrated rates consistent with the RICOCHET audit. However an important finding is that although increasing over time, at just under 50% in 2022, the rates were still below the recommended 100% quality standard [13].

Strengths and limitations

The key strength of this population-based study is the large size (40% of the population in England) and completeness of the underlying raw EHR data in OpenSAFELY [23]. In addition, because the OpenSAFELY platform provides analysis directly on the servers of the healthcare records administrator (TPP), we access near real-time data while prioritising patient privacy (no need for data transfers). The national audit undertaken by the RICOCHET Study Group [16], relied on manual audits of patient records by many local teams in the UK, following by compilation of the results centrally. By contrast, the automated audit method that we developed, enables frequent and cost-effective re-execution of the analysis at regular audit cycles. In addition, because with OpenSAFELY we are able to access the full set of patients' records, we provided a longitudinal view of trends in prescribing since 2015. This allowed us to investigate the effect of the COVID-19 pandemic. All analytics software and code lists are shared openly and are available for inspection and re-use, providing opportunity for reproduction of this report to support recovery from the COVID-19 pandemic and reducing duplicative efforts.

We also note some limitations. We note that our data will only include prescriptions issued in primary care, it is possible that some hospitals supply the medicines directly to patients when they attend the hospital. We have written extensively [24, 25] on the availability of hospital prescriptions and NHS Digital have recently made some of this hospital medication data available for a small subset of hospitals [26]. We will seek to incorporate this in any future work. In addition, pancreatic

cancer was defined by coding in primary care, rather than via linkage with cancer registry, the gold standard for cancer diagnoses.

Policy Implications and future research

Across the UK, pancreatic cancer care has been centralised since 2001, largely due to a need to reduce perioperative mortality. This, however, has created a potential disconnect between specialist and non-specialist sites. Patients with unresectable pancreatic cancer are typically treated at their local hospital, which for most patients will not be a specialist site, and will receive regular repeat prescriptions from their general practitioner. The RICOCHET audit of pancreatic cancer and PERT prescribing demonstrated that rates of PERT prescribing were highest within specialist sites, regardless of tumour stage and treatment intent [16]. It also demonstrated that high prescribing rates were shared within hospitals (i.e., if there was high prescribing in resectable cancer, there was high prescribing in unresectable cancer and vice versa), but not across each local network which consisted of the central specialist surgical unit and their referring non specialist sites (i.e., prescribing rates in each specialist centre did not correlate with those within each centres network of referring non-specialist sites). The geographic variation observed in the present study contrasts with that data. Given that RICOCHET was a snapshot of a 3-month cohort of patients, the present study is much better placed to observe regional variation in practice. Understanding why regions have differing rates of prescribing could help overcome barriers to PERT prescribing. Additionally, qualitative research, beyond the scope of this study, is needed to understand barriers to the implementation of NICE guidelines and quality standards.

More broadly, the implications of this study for data usage to improve NHS services are very substantial. Previously, practical and privacy challenges around accessing GP data meant that the largest study to date in this area, RICOCHET, relied on manual audits by many local teams at a single point in time. This manual approach imposes a substantial resource burden on local teams collecting data as well as being hard to reproduce on an ongoing basis. Using the OpenSAFELY framework we were able to execute a single analysis in OpenSAFELY-TPP for 40% of the population in near real-time, whilst leaving the data in situ preserving trust. OpenSAFELY was the single most trusted COVID-19 data project in a rigorous Citizen's Jury sponsored by the NHS and the National Data Guardian [27]. We can extend this analysis to OpenSAFELY-EMIS, increasing coverage to 99% of English general practices, as well as providing fine grained demographic (e.g., ethnicity) or clinical sub-populations. OpenSAFELY tools can facilitate cost-effective, ongoing and near real-time audits and feedback to NHS organisations. This presents an important opportunity in the context of rapidly evolving pressures on the health service during the COVID-19 recovery period.

Conclusions

The COVID-19 pandemic did not affect PERT prescribing in unresectable pancreatic cancer. However, despite national guidelines, under-prescribing of PERT continues and has improved only marginally since their publication. This could be an important missed opportunity to reduce morbidity for patients. The research into the effect of COVID-19 as well as barriers to prescribing of PERT and geographic variation is urgently needed to improve quality of care.

List of abbreviations

COVID-19	Coronavirus disease 2019
EHR	Electronic healthcare records
GP	General practice
NHS	National Health Service
PERT	Pancreatic enzyme replacement therapy
RICOCHET	Receipt of curative resection or palliative care for hepatopancreaticobiliary tumours

Declarations

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Conflicts of Interest

BG received research funding from the Laura and John Arnold Foundation, the NHS National Institute for Health Research (NIHR), the NIHR School of Primary Care Research, NHS England, the NIHR Oxford Biomedical Research Centre, the Mohn-Westlake Foundation, NIHR Applied Research Collaboration Oxford and Thames Valley, the Wellcome Trust, the Good Thinking Foundation, Health Data Research UK, the Health Foundation, the World Health Organisation, UKRI MRC, Asthma UK, the British Lung Foundation, and the Longitudinal Health and Wellbeing strand of the National Core Studies programme; he is a Non-Executive Director at NHS Digital; he also receives personal income from speaking and writing for lay audiences on the misuse of science. BMK is employed as a pharmacist by NHS England and seconded to the Bennett Institute.

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Funders had no role in the study design, collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Ethical approval

The study was approved by the Health Research Authority (Research Ethics Committee reference 20/LO/0651) and the London School of Hygiene and Tropical Medicine (London, UK) Ethics Board (reference 21863).

Information governance

NHS England is the data controller for OpenSAFELY-TPP; TPP is the data processor; all study authors using OpenSAFELY have the approval of NHS England. This implementation of OpenSAFELY is hosted

within the TPP environment which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant [28].

Patient data have been pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is via a virtual private network (VPN) connection, restricted to a small group of researchers; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts [29].

The OpenSAFELY research platform adheres to the obligations of the UK General Data Protection Regulation (GDPR) and the Data Protection Act 2018. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure; this sets aside the requirement for patient consent [30].

Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform.

Data access and verification

Access to the underlying identifiable and potentially re-identifiable pseudonymised electronic health record data is tightly governed by various legislative and regulatory frameworks, and restricted by best practice. The data in OpenSAFELY is drawn from General Practice data across England where TPP is the data processor. TPP developers initiate an automated process to create pseudonymised records in the core OpenSAFELY database, which are copies of key structured data tables in the identifiable records. These pseudonymised records are linked onto key external data resources that have also been pseudonymised via SHA-512 one-way hashing of NHS numbers using a shared salt. Bennett Institute for Applied Data Science developers and PIs holding contracts with NHS England have access to the OpenSAFELY pseudonymised data tables as needed to develop the OpenSAFELY tools. These tools in turn enable researchers with OpenSAFELY data access agreements to write and execute code for data management and data analysis without direct access to the underlying raw pseudonymised patient data, and to review the outputs of this code. All code for the full data management pipeline—from raw data to completed results for this analysis—and for the OpenSAFELY platform as a whole is available for review at github.com/OpenSAFELY. The data management and analysis code for this paper was led by AL and contributed to by CA.

Data Sharing

Detailed pseudonymised patient data are potentially re-identifiable and therefore not shared. The process for external users to request access to data via the OpenSAFELY platform is described on opensafely.org.

List of figures

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