Case Studies

COVID-19 Longitudinal Health and Wellbeing National Core Study

2021-22

Case Studies

The integration of emerging scientific understanding into policy or practice at pace

- Long Covid- Definition and symptom groups
- OpenSAFELY-Vaccination and Treatment
- Mental Health Cabinet Reports
- Society and Health Cabinet Reports
- Healthcare Disruption- National GP Alert
- Serology- Importance of the booster

The co-ordinating of research to answer specific policy questions at pace

- Rapid response bespoke survey when plan B emerged.
- OpenSAFELY tools for collaborative working
- Increased risk of blood clots one year after infection
- HealthCare Disruption, measured using UK LLC

The novel approach to team science that prepares us for future pandemics

- The LH&W collaborative is itself a novel approach to team science
- Bidirectional relationships with policymakers
- UK LLC: The legacy of this work is a responsive system
- Modern approaches to Open Science
- Prospective alignment of Longitudinal Population Studies

The integration of emerging scientific understanding into policy or practice at pace

Long Covid

The LH&W NCS Long Covid research has improved diagnostic precision for research and informed strategies for care provision by being directly reported to:

Policymakers: via the Scientific Advisory Group for Emergencies (SAGE) reports, meetings and a Cabinet Office Teach in session
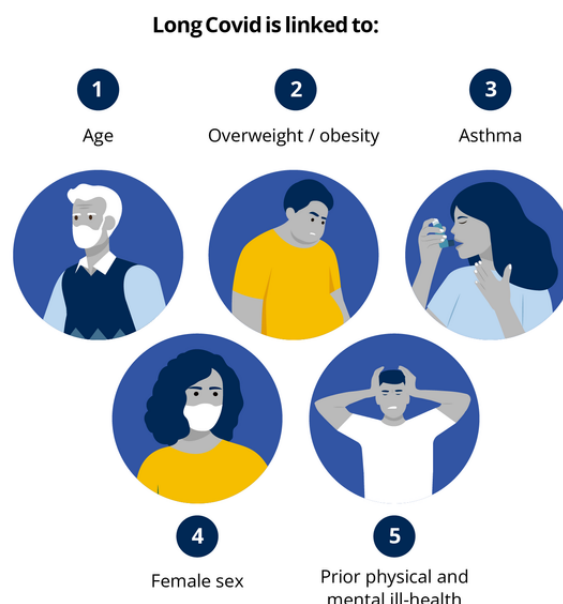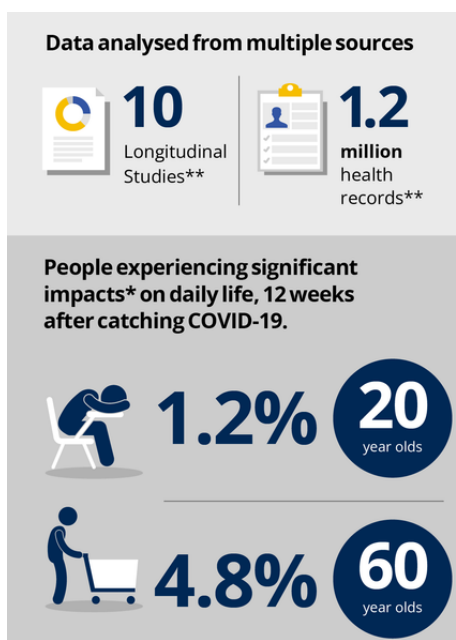**The NHS:** via NHSE/I presentations
NICE: to provide evidence for living guidelines.

This work included findings on risk factors, symptom clustering and healthcare access issues.

Risk Factors for Long Covid in 10 LPS and OpenSAFELY were consistent and included increasing age, female sex, white ethnicity, poor pre-pandemic general and mental health, overweight/ obesity, and asthma.

Symptoms and Clustering in 9 LPS (n=42,000) of largely non-hospitalised people, symptoms include fatigue, shortness of breath, muscle pain or aches, difficulty concentrating and chest tightness. Cluster analysis supported two distinct symptom patterns, representing high and low symptom burden. The identified patterns among individuals with COVID-19 > 12 weeks ago were strongly associated with self-reported length of time unable to function as normal due to symptoms.

Data analysed from multiple sources

10 Longitudinal Studies**

1.2 million health records**

People experiencing significant impacts* on daily life, 12 weeks after catching COVID-19.

1.2% 20 year olds

4.8% 60 year olds

Long Covid is linked to:

1 Age
2 Overweight / obesity
3 Asthma
4 Female sex
5 Prior physical and mental ill-health

Long Covid

Low Long Covid Coding: OpenSAFELY described the early use of GP codes for long Covid, and identified generally low use of the codes compared to survey-based estimates, as well as substantial geographic variation, and different levels of coding depending on the electronic health record software that practices used. This led to a substantial discussion with NICE about how our findings might impact their subsequent revision of Long Covid guidance. OpenSAFELY also shared the results with electronic health record software providers to discuss how their software might affect recording of these details. Since our initial publication, we have continued to monitor recording of long COVID, and have seen gradual increases in recording over time.

Poor Access to Health Care: 40 interviews were conducted by the team with people with Long Covid alongside 12 interviews with healthcare professionals providing Long Covid support in Bradford, as part of a UK wide Qualitative Longitudinal Study. Those living with Long Covid had a large degree of difficulty in accessing healthcare services for Long Covid support. The team categorised the healthcare access experiences of participants into five main types: 1) being unable to access primary care 2) accessing primary care but receiving (perceived) inadequate support 3) extreme persistence 4) alternatives to mainstream healthcare 5) positive experiences. There was a severe lack of access to specialist Long Covid services. Ethnic minority participants faced a further barrier of mistrust and fear of services deterring them from accessing support. Healthcare professionals discussed systemic barriers to delivering services. This work has been passed onto NHSE/I Long Covid Taskforce.

Vaccination

OpenSAFELY has played a key role in several parts of COVID-19 vaccine delivery in the UK, specifically in prioritisation, delivery, and measurement of safety and effectiveness. The early COVID mortality risk stratification work was a critical part of creating the prioritisation groups, with the UK Joint Committee on Vaccination and Immunisation (JCVI) requesting that OpenSAFELY present data on several occasions.

Vaccination disparities: Once vaccination had started, we rapidly published a series of updating reports on the rate at which groups in the eligible population were receiving vaccines. This, to our knowledge, was the first indication that there were large disparities in vaccination rate between demographic groups, with for example 68% of eligible black people vaccinated compared to 96% of eligible white people at the time of our first paper on the subject.

Ethnic differences in vaccine uptake: In parallel to this work, SAGE asked Understanding Society to analyse information on the take-up of the COVID vaccines, with a particular emphasis on how different ethnic groups view the vaccination programme. In November 2020 participants were asked whether they planned to have a COVID vaccine. Overall, there was a high number of people who were planning to be vaccinated, with 82% of participants stating that they were likely or very likely to have the vaccine. However, after stratification by ethnic group wide variations were seen: 72% of Black or Black British people said that they were unlikely or very unlikely to be vaccinated against COVID. Pakistani and Bangladeshi groups were the next most hesitant minority ethnic group, with 42% unlikely or very unlikely to be vaccinated. In contrast, people from Indian groups were less hesitant, with 21% not willing to be vaccinated. The main reason for vaccine hesitancy was concern over the future unknown effects of a vaccine, with 43% of people of unwilling to take a vaccine stating this as their main worry. Black and Black British people were particularly concerned about a lack of trust in vaccines in general, with 29% of the vaccine hesitant stating this as a reason not to take the COVID vaccine. Pakistani and Bangladeshi participants were more concerned about possible side effects and the future unknown effects of the vaccine

Vaccination

Effectiveness and Safety: The remaining pieces of the COVID vaccine puzzle are effectiveness and safety. Following early reports of neurological events thought to be associated with COVID-19 vaccination, OpenSAFELY carried out a study that found elevated rates of some events after ChAdOx1 vaccination, though absolute risks remained low. While effectiveness studies are methodologically challenging in routinely collected data, a broad collaborative OpenSAFELY group has carefully defined methods to describe the comparative effectiveness of initial vaccines, how that effectiveness has changed over time, and effectiveness of booster vaccination.

COVID-19 Treatment: Following the emergence of new treatments for COVID-19, the team were quickly able to link data on who received such treatments into OpenSAFELY. As with vaccination administration, we initially described which patient groups were being given the treatments, finding large regional variation, with particularly low administration in socioeconomically deprived areas and care homes. We have since been working on describing the real world effectiveness of these treatments, initially comparing two of the first used treatments, molnupiravir and sotrovimab. We have demonstrated that data about roll out of new treatments can be rapidly linked to primary care and other data, to monitor drug coverage and effects in near-real time and produce unbiased estimates of drug effectiveness. This data has been used to inform NICE, NHSE prescribing guidance and is being reviewed by the WHO as part of their review of the recent guidance they produced. It shows the possibility of better use of linked data to conduct or emulate low-cost, rapid RCTs – particularly when drug effectiveness is likely to be changing rapidly, as at present.

Mentod Health

The LH&W NCS highlighted the wider impacts of the pandemic on those with prior poor mental health in terms of non-covid outcomes, including healthcare and economic disruptions.

Careful analyses of longitudinal data from before and during different phases of the pandemic indicated that **mental health deteriorated** during the early stages of the pandemic, with severity varying by demographics and mental and physical health history, all of which were prospectively measured.

These were rapid responses taken early in the pandemic and then used in official UK government reports. Our evolving results from multiple and well-time questionnaires produced timely and regular updates to HDRUK, which then fed into SAGE and other cabinet reports.

Further collaborative work showed the **long-term impact of COVID mental health, even when lockdown was lifted in summer 2020** (in contrary to evidence from online convenience samples).

We also provide some of the first evidence from population based longitudinal studies on the mental health impacts of mild and moderate covid-19 infection, as most other investigations to-date were focused on mental health consequences of more severe COVID-19 infections and hospitalisations and recorded mental health conditions.

It demonstrates the crucial use of longitudinal studies, linked population surveys and EHRs and health records to provide a more rounded understanding of mental health during a pandemic and highlights the benefits of using well characterised existing longitudinal data rather than starting convenience samples during pandemics (or other shocks) to avoid a very biased picture of population mental health.

Inequality between those with and without mental health problems should be considered when providing current and post-pandemic health, economic and well-being support.

Society and Health

FURLOUGHED

The LH&W NCS investigated the impact that furlough and home working had on mental health and health behaviours. These results were passed onto policy makers via cabinet reports.

Furlough and mental health: The team found that compared with furloughed workers, those who lost their jobs were more likely to report psychological distress, poor health, low life satisfaction and loneliness. But when compared with those who remained working, furloughed workers were at greater risk of each of these outcomes. In other words, the study shows that furlough occupies an intermediate position between employment and unemployment. Furlough had a protective effect for those who were at risk of losing their job, but was not as beneficial as remaining at work.

Furlough and health behaviour: Those furloughed exhibited similar health behaviours to those who remained in employment during the initial stages of the pandemic. There was little evidence to suggest that adoption of such social protection policies in the post-pandemic recovery period had adverse effects on population health behaviours.

Home working and its association with social and mental wellbeing: No clear evidence of an association between home working and mental wellbeing was found, but differences across sub-groups may exist. Longer term shifts to home working might not have adverse impacts on population wellbeing in the absence of pandemic restrictions but further monitoring of health inequalities is required

Long COVID and financial disruption: We have shown that long COVID can lead to worsening individual finances in the UK. We found that long COVID was associated with worse subjective financial wellbeing, new benefit claims and decreased household income. Extending employment protection and financial support to people with long COVID may be warranted.

The evidence shows that social protection policies should be implemented in the post-pandemic recovery period and during future economic crises.

Healthcare Disruption

National GP Alert

On behalf of NHS England, we conducted a population-based cohort study investigating the association between warfarin and COVID-19 outcomes compared with direct oral anticoagulants (DOACs). We used the OpenSAFELY platform to analyse primary care data and pseudonymously linked SARS-CoV-2 antigen testing data, hospital admissions and death records from England. We found that during lockdown, some individuals were inappropriately switched from warfarin to DOACs, this led to a national alert to GPs.
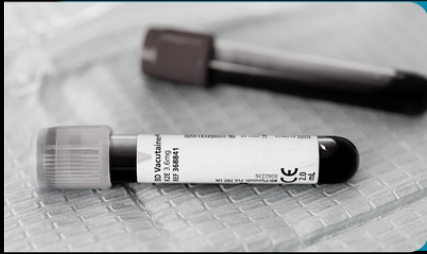
Serology

The Importance of the Booster The Serology team have been looking at SARS-CoV-2 antibody levels to assess immune responses following either natural infection or vaccination.

From cross-sectional antibody testing of 9,361 individuals from TwinsUK and ALSPAC UK population-based longitudinal studies (jointly in April-May 2021, and TwinsUK only in November 2021-January 2022), we tested associations between antibody levels following vaccination and: (1) SARS-CoV-2 infection following vaccination(s); (2) health, socio-demographic, SARS-CoV-2 infection and SARS-CoV-2 vaccination variables. Within TwinsUK, single-vaccinated individuals with the lowest 20% of anti-Spike antibody levels at initial testing had 3-fold greater odds of SARS-CoV-2 infection over the next six to nine months, compared to the top 20%.

In TwinsUK and ALSPAC, individuals identified as at increased risk of COVID-19 complication through the UK "Shielded Patient List" had consistently greater odds (2 to 4-fold) of having antibody levels in the lowest 10%. **Third vaccination increased absolute antibody levels for almost all individuals, and reduced relative disparities compared with earlier vaccinations.** These findings quantify the association between antibody level and risk of subsequent infection and **support a policy of triple vaccination for the generation of protective antibodies.**

The LPS are also playing a key role in the Immunology NCS, (https://www.uk-cic.org) where cohorts are charting the immune response to infection in the real world, longitudinally and in great detail, rather than hospitalised cases

Historical samples are now being used for the development of new tests for new infections. Only with these resources available can one then chip in to analyses and comparisons of the work ongoing to explore new infections ("Development and evaluation of low-volume tests to detect and characterize antibodies to SARS-CoV-2").

Next steps for the third round of serological data are based around using truth observations from cohorts with data to ask about the modelled impact of heterogeneity in infection/vaccination exposure by risk factors for infection outcome (age) and also from existing data across cohorts, the calibration of antibody responses to symptoms, infection risks and outcomes.

The co-ordinating of research to answer specific policy questions at pace

The importance of the Cohorts

Rapid response bespoke survey when plan B emerged.

As a mark of translation of pandemic research into policy output, cohort material has continued to be included in influential outputs. Early on, this included examples such as an early report from the Department for Education on grandparental care, (SAGE 37 on 19 May 2020). This has matured to include evidence in key reports and reviews (as shown in the appendix, Table 1). Examples of this include the bringing together information for the SAGE report on long Covid and latterly the Goldacre Review where ALSPAC is used as an exemplar of data use inside a TRE, helping to support the review's key recommendations related to greater investment in the development of TREs for health data research.

Most recently, coordinated cohort activity was able to react to the shifting pandemic situation and with **SPI-M** members to undertake a bespoke survey of participant behaviour in light of the omicron rise, "Plan B" and Christmas planning. As an **example of dynamic response and connection to policy need**, this work led to a working data set on >2800 participant responses within 3 weeks and the presentation of findings to SPI-M (22 December 21 and 12 January 22) and the Welsh Government Technical Advisory Cell (21 January). The subsequent report was circulated to SAGE (meeting 103 on 13 January) and throughout government including No.10 and the Cabinet Office, informing the Welsh cabinet's 21 day review. We concluded that **voluntary measures have substantially reduced the projected impact of the SARS-CoV-2 Omicron variant but that voluntary measures alone would be unlikely to completely control transmission.**
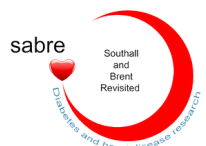
OpenSAFELY tools for collaborative working

The NCS collaboration has led to a huge increase in the depth of collaborations between different research groups, in order to answer critical questions quickly. We have developed a range of **OpenSAFELY tools** to facilitate collaborative working, for example:

OpenCodelists.org – a tool for creating and openly sharing codelists that are used to define diseases, so that they can be checked and reused by new studies.
All code run in OpenSAFELY must be shared on **github.com/opensafely**, a platform for sharing and reviewing code, tracking changes and discussing issues.

·**OpenSAFELY Reusable Action**s allow teams of researchers to share common analytic code and maintain it in a central place.

Together, these tools have enabled geographically disparate groups like the OpenSAFELY vaccines working group, from Oxford, Bristol, LSHTM and other institutions to collaborate on several studies, including describing the comparative effectiveness of COVID vaccines, or the COVID treatments working group to describe the use and comparative effectiveness of emerging COVID treatments.

Increased risk of blood clots one year after infection

In collaboration with the **BHF Data Science Centre**, the LH&W NCS Team found that COVID-19 infection increases the risk of potentially life-threatening blood clots for at least 49 weeks.

These results used health records of 48 million unvaccinated adults from the first wave of the pandemic. They support policies and practice to prevent severe consequences of COVID-19 by means of COVID-19 vaccines, early review of cardiovascular risk after discharge, risk factor control, and use of secondary preventive agents, such as giving medication to lower blood pressure and serum cholesterol in high-risk patients.

Quantifying the impact of COVID-19 infection on incidence of vascular disease enhances the ability of public health professionals to design targeted, effective, evidence-based policy, and minimise the impacts of COVID-19. The ultimate impact is in influencing public behaviour, cost savings to the health and social care system and improved patient outcomes.

This research informed NHSE and gained widespread media attention – see https://ahajournals.altmetric.com/details/136134452).

Data Science Centre

Led by HDR UK
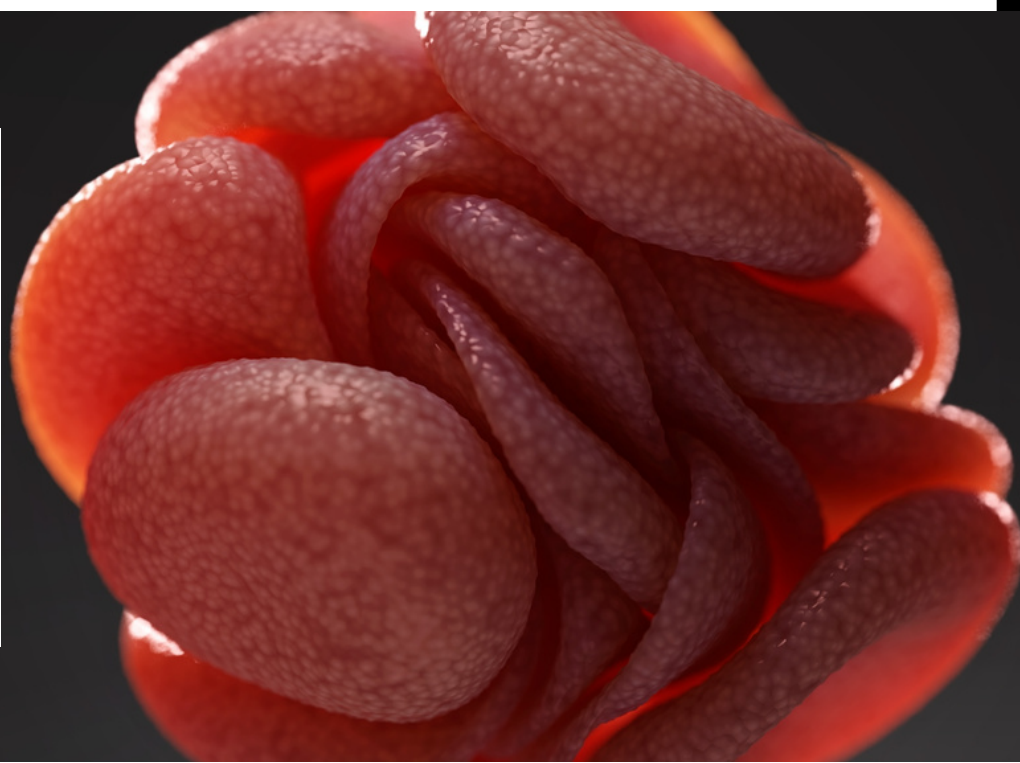
HealthCare Disruption, measured using UK LLC

Pandemic mitigation measures led to inevitable disruption of healthcare provision. Possible effects of this disruption have been published in the media and widely discussed however empirical evidence has largely derived from modelling exercises making reasonable assumptions and ecological studies describing changing patterns of health outcomes in relation to phases of the pandemic and associated mitigation measures - this evidence presents a mixed picture.

The Longitudinal Linkage Collaboration (UK LLC) - a new national data asset created as part of the LH&W NCS allows linkage of individual reports of experience of disrupted healthcare to health outcomes in the EHRs of the same individuals across several large cohort studies.

This has allowed us to show that **individuals exposed to disrupted care had approximately double the risk of avoidable hospital admission,** that this effect was most marked in relation to disrupted appointments and procedures and that the effect was more substantial the sicker the baseline health of the individual. (This work is unpublished).

UK Longitudinal Linkage Collaboration

The novel approach to team science that prepares us for future pandemics

The LH&W NCS Collaborative

LH&W is an excellent example of **multidisciplinary team science** at its best on a scale never seen before. The LH&W NCS is a unique, **cross-institution**, collaboration of biomedical, social and data scientists, spanning **cohorts, electronic health records**, quantitative and qualitative analysts, detailed clinical investigations, and policy groups such as NICE. LH&W created a collaborative of 12 population cohorts (200k participants) – enhanced by questionnaire and serological measures and linked to both health and administrative data. This team science approach ensures that results are robust and representative. We have shown that data from many diverse LPS can be rapidly harmonised to answer policy relevant questions with more statistical power than ever before.

The NCS have also established the UK as a **world leader in harnessing the power of national electronic health record platforms**, such as OpenSAFELY and the NHS Digital TRE established by the BHF Data Science Centre. These and the new Longitudinal Linkage Collaboration linked dataset will provide unprecedented opportunities for research that improves population health in the coming years.

The LH&W collaborative is a target driven team that operates using work trackers across 15 institutions who have aligned complementary resources and brought together of linkage/EHRs and cohorts at a scale never seen before. Early Career researchers have been given the opportunity to lead areas of research and gain valuable experience working in a large collaboration. The LH&W team have also trained a **new generation of data scientists**, both from within the collaborating institutions, and secondees across the country, in the use of these unique, complex and highly informative datasets.

Bidirectional relationship with policy makers

The "clearing house model" which has emerged enables rapid transfer of policy relevant science directly to policymakers but also enables policy makers to approach the team with questions.

Examples include the SAGE reports mentioned in section a, the vaccination evidence, the Cabinet Office Teach In Session and the rapid survey deployed for SPI-M during Plan B. Table 1 documents policy documents that feature LH&W NCS findings.

Long Covid SAGE Reports

SAGE Report on the take-up of the COVID vaccines, with a particular emphasis on how different ethnic groups view the vaccination programme

Evidence to NHSE on Long Covid GP coding and access and the use of anti-virals to treat COVID-19

SPI-M Rapid Response Bespoke Survey, when plan B emerged

Presenting Vaccine evidence on request to the UK Joint Committee on Vaccination and Immunisation (JCVI)

UK Longitudinal Linkage Collaboration

Legacy Infrastructure: As part of the LH&W NCS, the **UK LLC** has established a new national trusted research environment (TRE) for longitudinal research. For the first time, a considerable proportion of the interdisciplinary UK longitudinal community have committed to a new-way-of-working based on a centralised Trusted Research Environment: UK LLC.

UK LLC has cut through previously intangible governance challenges by establishing a centralised service for 'record linkage' and FAIR data access based on cutting edge Data Science principles. This includes a single overarching governance framework; a single pipeline linking many studies to NHS and Government records; and, a single pathway for efficient and predictable researcher access. This means that the burden of record linkage on studies and data owners is reduced, that turnaround times from project application to data access have been slashed to 8 weeks, and new scientific opportunities relating to pooling longitudinal study data are improving the fairness of longitudinal research by enabling research into harder to reach populations.
This model has already made significant and tangible differences to how major UK Governments are engaging with requests from LPSs to link data:

280,000 participants from 24 longitudinal studies are linked to comprehensive NHS Digital records through one agreement and a new sustainable and efficient data pipeline – generating substantial efficiencies for the NHS and UKRI and delivery a prospectively harmonised dataset

UK LLC now have Ministerial and Departmental approval to link to employment, earnings, welfare benefits and education records from HMRC, DWP and DfE. This is a significant development, given that DWP have not provided similar permissions for over 18 years to any study – and is built on UK LLC's unified governance framework and collaborative approach which minimised departmental burden and UK LLC's highly secure model and regulatory compliance. UK LLC is now acting as a 'pathfinder' Trusted Research Environment for the UK – working with Health Data Research UK, the NHS and Administrative Research UK to set precedents and principles for pan-UK and cross-cutting sharing of data. Our active Public Involvement activities ensure a public voice is baked into our design. UK LLC now provides a transformational resource to enable the UK research community rapidly respond to pressing government policy-relevant questions and provides the flexibility to ensure the longitudinal community can contribute to a 100 day mission to respond to future crises.

Open Science

The team have embraced, **modern open approaches to data science**: sharing code openly to the whole community, as the bedrock of deep technical collaboration; working closely with research software engineers - who have decades of skill in writing code - alongside traditional domain experts with research knowledge; and moving away from "manual labour" on datasets towards "reproducible analytic pathways", with well tested and re-executable code, in line with best practice in data science. These sound like dry technical details - and they are - but they are the hidden bedrock of efficient, high quality research.

They have also developed **new methods** for preserving patients' privacy which allowed an unprecedented scale of data access - using 58 million patients' full GP records in research for the first time ever - earning active and positive support from privacy campaigners who have previously blocked access on this scale by other means.

Better, Broader, Safer: Using Health Data for Research and Analysis

April 2022

Prospective alignment of Longitudinal Population Studies

Prospective alignment of LPS is essential to provide rapid responses in times of future crises.

Building on the success of the LH&W NCS coordinated LPS questionnaires and response to a "clearing house" model to policy questions, LPS now are aligning more closely to their regional and national policy questions.

The LPS should be actively deployed as a set of research/measurement tools and connections to the public and participants in the future.