An informatics consult approach for generating clinical evidence for treatment decisions

Alvina G. Lai1,2*, Wai Hoong Chang1,2, Constantinos A. Parisinos1, Michail Katsoulis1, Ruth M. Blackburn1,2, Anoop D. Shah1,3,12, Vincent Nguyen1, Spiros Denaxas1,2,3,4, George Davey Smith5,6, Tom R. Gaunt5,6, Krishnarajah Niranthenarukumar2,7, Murray P. Cox8, Donall Forde9, Folkert W. Asselbergs1,2,3,10,11, Steve Harris12, Sylvia Richardson13, Reecha Sofat1,3, Richard J. B. Dobson1,2,14, Aroon Hingorani2,7,11, Riyaz Patel11, Jonathan Sterne6, Amitava Banerjee1,15, Alastair K. Denniston2,16, Simon Ball2,16, Neil J. Sebire17,18, Nigam H. Shah19, Graham R. Foster20, Bryan Williams21,12 and Harry Hemingway1,2

Abstract

Background: An Informatics Consult has been proposed in which clinicians request novel evidence from large scale health data resources, tailored to the treatment of a specific patient. However, the availability of such consultations is lacking. We seek to provide an Informatics Consult for a situation where a treatment indication and contraindication coexist in the same patient, i.e., anti-coagulation use for stroke prevention in a patient with both atrial fibrillation (AF) and liver cirrhosis.

Methods: We examined four sources of evidence for the effect of warfarin on stroke risk or all-cause mortality from: (1) randomised controlled trials (RCTs), (2) meta-analysis of prior observational studies, (3) trial emulation (using population electronic health records (N = 3,854,710) and (4) genetic evidence (Mendelian randomisation). We developed prototype forms to request an Informatics Consult and return of results in electronic health record systems.

Results: We found 0 RCT reports and 0 trials recruiting for patients with AF and cirrhosis. We found broad concordance across the three new sources of evidence we generated. Meta-analysis of prior observational studies showed that warfarin use was associated with lower stroke risk (hazard ratio [HR] = 0.71, CI 0.39–1.29). In a target trial emulation, warfarin was associated with lower all-cause mortality (HR = 0.61, CI 0.49–0.76) and ischaemic stroke (HR = 0.27, CI 0.08–0.91). Mendelian randomisation served as a drug target validation where we found that lower levels of vitamin K1 (warfarin is a vitamin K1 antagonist) are associated with lower stroke risk. A pilot survey with an independent sample of 34 clinicians revealed that 85% of clinicians found information on prognosis useful and that 79% thought that they should have access to the Informatics Consult as a service within their healthcare systems. We identified candidate steps for automation to scale evidence generation and to accelerate the return of results.

Conclusion: We performed a proof-of-concept Informatics Consult for evidence generation, which may inform treatment decisions in situations where there is dearth of randomised trials. Patients are surprised to know that their
Background
Evidence informing treatment decisions traditionally takes years to generate and leaves many clinical uncertainties unaddressed [1]. Especially in patients with two or more conditions (multimorbidity), it has been hard to generate evidence tailored to ‘patients like me’ and embed this evidence in clinical decision making using electronic health records. There are thousands of clinical practice recommendations, but only a small proportion (15–20%) of these recommendations are supported by level A (trial) evidence [1-6]. A systematic review of trial registration records found that 79% of randomised controlled trials (RCTs) excluded patients with concomitant chronic conditions [6]. The United States Food and Drug Administration, Medicines Healthcare Regulatory Authority and European Medicines Agency are increasingly recognising the role of real-world evidence [7] but guidance thus far has not considered its near real-time generation.

The Informatics Consult concept has been proposed [8–11] to produce on-demand evidence in which clinicians request novel evidence based on the care of prior patients to inform the treatment of a specific patient, with return of results in decision-relevant clinical timescales. For example, a hepatologist seeing a patient with cirrhosis in the clinic learns that they have developed atrial fibrillation. What evidence is, or could rapidly be, available to inform a decision on anti-coagulation for stroke prevention? This is an example of a treatment indication and a treatment contra-indication coexisting in the same patient. Initial experience of the Informatics Consult from Stanford University, has focussed on questions of prognosis (rather than treatment decisions) and highlighted analytical and scaling challenges in returning results [11]. However, demonstrators of the Informatics Consult for treatment decisions are lacking.

Our objective was to demonstrate proof of concept of the Informatics Consult using the atrial fibrillation-cirrhosis-warfarin example. Specifically, we sought to (1) develop prototype electronic health record forms for requesting an Informatics Consult and return of results, (2) generate four sources of evidence for an Informatics Consult (evaluate available RCT evidence, meta-analyse prior observational studies, emulate a target trial using electronic health records, and Mendelian randomisation [12, 13]), (3) for each form of evidence, to identify steps necessary for automation to accelerate evidence generation and return of results to clinicians, and scale across multiple exemplars (Additional file 1-1) and (4) explore clinician acceptability of the Informatics Consult.

Methods
Developing prototype electronic health record (EHR) request form and report form
An Informatics Consult is triggered by a request made by a clinician from the electronic health records (EHR) for multiple novel sources of evidence. We developed prototypes for the request form and the report form in consultation with the Chief Clinical Research Informatics Officer and clinicians (cardiologists, hepatologists and clinical pharmacologists). We illustrate possible forms based on an EHR platform, but similar design principles are relevant in EHRs from other vendors, and in other settings, including primary care.

Retrieving information on currently recruiting trials
We searched for previously reported and currently recruiting trials on anticoagulants in patients with atrial fibrillation, with stroke or mortality in the primary outcome using the ClinicalTrials.gov registry. We then used the 8-digit National Clinical Trial numbers to retrieve detailed information on inclusion and exclusion criteria for each trial to identify if any trials included patients with both atrial fibrillation and cirrhosis.

Meta-analysis of prior observational studies
Study identification We searched PubMed for peer-reviewed articles using the keywords “antithrombotic”, “anticoagulant”, “warfarin”, “cirrhosis” and “atrial fibrillation”. We considered eligible studies as those reporting the effects of anticoagulation therapy in patients with both liver cirrhosis and atrial fibrillation. We excluded reviews, single case reports, editorials and small case series (<10 cases). Data extraction We extracted the following variables: author, setting, eligibility criteria, number of patients with atrial fibrillation and cirrhosis, number of patients in treated and untreated groups and summary measures. Analyses were performed following PRISMA guidelines. Outcomes of interest were mortality and ischaemic stroke. Statistical analysis A meta-analysis of associations was performed by pooling hazard ratios (HRs) or odds ratios (ORs) depending on data availability from observational studies using DerSimonian and Laird
random-effects models. We also performed leave-one-out sensitivity analyses.

**Target trial emulation**

We used population-based EHRs to perform a target trial emulation, which is the application of design principles from RCTs to inform analyses on observational data [14, 15]. We obtained informational governance approval from the Medicines Healthcare Regulatory Authority (UK) Independent Scientific Advisory Committee (20_078R) to analyse the Clinical Practice Research Datalink (CPRD) linked to secondary care Hospital Episode Statistics and the Office for National Statistic death registration. The study population was 3,854,710 adults aged ≥ 30 years. Phenotype definitions for atrial fibrillation, cirrhosis and other conditions included as baseline covariates as well as definitions for prescriptions are available at https://caliberrresearch.org/portal and have previously been validated [16, 17]. Phenotypes for primary care records were generated using Read clinical terminology (version 2). Phenotypes for secondary care records were generated using ICD-10 terms.

We developed a target trial protocol where eligibility criteria, treatment assignment, treatment strategy, follow-up period, causal contrast and statistical analyses were specified (Additional file 1-2). Each component of the trial protocol is matched as closely as possible to the design of a randomised trial with minor modifications to accommodate the use of observational data. We employed the intention-to-treat effect as a causal contrast, which was warfarin initiation versus no initiation at baseline. To emulate a target trial, we ensured that individuals are classified as warfarin initiators versus non-initiators at baseline (i.e., using baseline information to assign baseline treatment status). The baseline is defined as the latest date by which a patient has both cirrhosis and atrial fibrillation given that all eligibility criteria are met. As we were interested in assessing the effects of warfarin use on stroke, we have also excluded prevalent cases of ischaemic stroke. Individuals were followed until the development of an outcome of interest, which were all-cause mortality and incident ischaemic stroke. Propensity score matching (PSM) analyses were performed by matching the warfarin initiator and non-initiator groups. PSM was performed using the nearest-neighbour matching method (a 1:3 match was performed where possible) with a caliper width of 0.2 of the standard deviation of the logit of the propensity score. The PSM cohort was subjected to analyses of all-cause mortality and incident stroke using the Kaplan–Meier and logrank test method and the Cox proportional hazard regression model. As patients and clinicians would be interested in understanding risk in specific demographic categories, we performed subgroup analyses for all-cause mortality in patients aged ≤ 65, aged > 65, men, women and in patients with normal international normalise ratio (INR) measurements.

**Genetic evidence: two-sample Mendelian randomisation (MR)**

As an example of drug target validation in the general population, we performed MR to investigate the causal relationship between warfarin use and stroke risk. Vitamin K1 (phyloquinone) is a central component in the production of blood coagulation factors. Warfarin (a vitamin K antagonist) inhibits the activity of vitamin K epoxide reductase to interfere with the recycling of vitamin K and to reduce blood clotting. We considered four single nucleotide polymorphisms (SNPs) that predict circulating phylloquinone (vitamin K1) selected from a genome-wide meta-analysis study on Europeans [18]. Four SNPs, all on separate chromosomes, were selected as they had the strongest association with circulating phylloquinone: rs2108622 (chromosome 19), rs2192574 (chromosome 2), rs4645543 (chromosome 8) and rs6862071 (chromosome 5). We retrieved genome wide association study (GWAS) summarised data for stroke outcomes from the MEGASTROKE study [19]. MR was performed using the “MendelianRandomisation” package in R [20]. We explored four methods for MR: inverse-variance weighted (IVW), MR-Egger, simple median and weighted median.

**Potential for automating the informatics consult**

We tasked a review panel with expertise in health informatics, epidemiology, evidence synthesis and computer science (drawn from co-authors) with two questions: (1) What are the most time-consuming tasks for each of the 4 streams of evidence identification and generation? (2) What automation opportunities might be important for acceleration and scaling.

**Clinician acceptability of the informatics consult**

After the initial development of the Consult, to gain insights into the acceptability and feasibility of the Informatics Consult, we conducted a pilot survey with an independent sample of 34 clinicians who had not taken part in the research.

**Results**

**Prototype EHR request form**

Clinicians wanted the request form (Fig. 1) to include a succinct free text statement of the clinical question, auto propagation of the diagnosis combination from the patient’s EHR, and suggested structured treatment, efficacy and safety outcomes, based on inputs from the survey. Some clinicians wanted to further specify eligibility
criteria for target trial emulation. Interestingly clinicians wanted not only evidence directly related to treatment effectiveness, but also requested national prevalence estimates of cirrhosis and atrial fibrillation, prognosis (1-year mortality), and current treatment variation (proportion of warfarin initiators).

Prototype EHR report
We provide an overall summary report based on new evidence on warfarin use (lower all-cause mortality and lower stroke risk) in patients with atrial fibrillation and cirrhosis (Fig. 2). Through the Consult report, clinicians will have the opportunity to queue patients for RCTs where relevant. We summarise evidence on prevalence, 1-year background mortality risk, meta-analysis of observational studies, target trial emulation results and genetic evidence. The detailed results included in the report for each form of evidence were provided below.

Reported and currently recruiting randomised trials
We did not identify any previous reported RCTs on anticoagulants relevant to patients with cirrhosis. We identified four currently recruiting anticoagulant trials. All four trials reported exclusion criteria related to liver cirrhosis such as contraindication to anticoagulation, i.e., hepatic impairment and elevated liver function tests (Fig. 3).

Meta-analysis of observational studies on warfarin use and ischaemic stroke
We identified 142 articles from PubMed, of which only 4 observational studies remained eligible on full-text review, and were included in the meta-analysis [21–24] (Fig. 4A). The pooled hazard ratio (HR) of warfarin use in patients with atrial fibrillation and cirrhosis on stroke was 0.71, 95% confidence interval [CI] (CI = 0.39–1.29), with high heterogeneity between studies $I^2 = 73\%$ (Fig. 4B). We also performed the leave-one-out sensitivity analysis with HRs ranging from 0.54 (CI = 0.30–1.00) to 0.92 (CI = 0.55–1.54). Only 1 study reported warfarin use and all-cause mortality and found a lower mortality risk (HR = 0.65; CI = 0.55–0.76) [21].

Target trial emulation using population-based EHRs
Per the target trial protocol (Additional file 1-2), a cohort encompassing 1022 individuals fulfilling all eligibility criteria was created (initiators = 443; non-initiators = 579). We performed PSM on 22 baseline covariates and generated a matched cohort involving 235 initiators and 526 non-initiators (Fig. 5A), baseline patient characteristics

---

**Fig. 1** Informatics Consult Electronic health record request form prototype
Clinical question:

Is oral anti-coagulation therapy safe and effective in reducing stroke risk in people with cirrhosis and atrial fibrillation?

Are there existing randomised controlled trials (RCTs) that provide sufficient evidence?

- Previously reported randomised trials on anticoagulants available for patients with cirrhosis = 0
- Currently recruiting anti-coagulant trials with stroke as an outcome = 4
- Currently recruiting trials available for patients with cirrhosis = 0

### Previously completed trials

| Trial number | Trial acronym | Drug comparisons | Inclusion | Exclusion | Primary outcome |
|--------------|--------------|-----------------|-----------|-----------|----------------|
| NCT00262600  | RE-LY        | Dabigatran vs warfarin | Non-valvular atrial fibrillation | Patients with cirrhosis excluded | Stroke or systemic embolic event |
| NCT00403767  | ROCKET AF    | Rivaroxaban vs warfarin | Atrial fibrillation, history of a prior stroke | Patients with cirrhosis excluded | Stroke or systemic embolic event |
| NCT00412984  | ARISTOTLE    | Apixaban vs warfarin | Atrial fibrillation | Patients with cirrhosis excluded | Stroke or systemic embolic event |
| NCT00781391  | ENGAGE AF-TIMI| Edoxaban vs warfarin | Atrial fibrillation | Patients with cirrhosis excluded | Stroke or systemic embolic event |

### Currently recruiting trials

| Trial number | Trial acronym | Drug comparisons | Inclusion | Exclusion | Primary outcome |
|--------------|--------------|-----------------|-----------|-----------|----------------|
| NCT03148457  | ELAN         | Early treatment vs late treatment with rivaroxaban, dabigatran, apixaban or edoxaban | Persistent atrial fibrillation and ischaemic stroke | Patients with cirrhosis excluded | Recurrent stroke, major bleeding, systemic embolic event |
| NCT03559308  | OPTIMAS      | Early treatment vs standard treatment with rivaroxaban, dabigatran, apixaban or edoxaban | Atrial fibrillation and acute stroke | Patients with cirrhosis excluded | Stroke, intracranial haemorrhage and systemic embolic event |
| NCT02618577  | NOAH         | Edoxaban vs aspirin | Atrial High Risk Episodes | Patients with cirrhosis excluded | Stroke, systemic embolic event, cardiovascular death |
| NCT01938248  | ARTESIA      | Apixaban vs aspirin | Sub-clinical atrial fibrillation | Patients with cirrhosis excluded | Stroke or systemic embolic event |

Fig. 2 Informatics Consult Electronic health record report prototype

Fig. 3 Trial evidence and currently recruiting trials of anticoagulation in patients with atrial fibrillation and cirrhosis to reduce stroke risk. A Clinical question and summary of trial evidence. B Previously completed and currently recruiting randomised trials evaluating anticoagulants and stroke outcomes have exclusion criteria related to cirrhosis
before and after PSM are shown in Additional file 1-3. We estimated an intention-to-treat HR for all-cause mortality of 0.61 (CI = 0.49–0.76; \( p < 0.0001 \)) comparing warfarin initiators with non-initiators (Fig. 5B). Warfarin used was associated with lower risk of ischaemic stroke: HR = 0.27 (CI = 0.08–0.91, \( p = 0.034 \)) (Fig. 5B). The 1022 eligible participants for the target trial were categorised into the five subgroups (aged \( \leq 65 \), aged > 65, men, women and patients with normal INR), followed by PSM (Additional file 1-4; Additional file 1-5; Additional file 1-6; Additional file 1-7; Additional file 1-8; Additional file 1-9). Intention-to-treat HRs for all-cause mortality comparing warfarin initiators versus non-initiators were as follow: aged \( \leq 65 \): HR = 0.62 (0.45–0.86, \( p = 0.0041 \)); aged > 65: HR = 0.61 (0.46–0.83, \( p = 0.0015 \)); men: HR = 0.64 (0.49–0.84, \( p = 0.0014 \)); women: HR = 0.53 (0.37–0.77, \( p = 0.00087 \)) and normal INR of < 1.7: HR = 0.62 (0.50–0.78, \( p < 0.0001 \)), where warfarin therapy is associated with lower mortality risk (Additional file 1-4).

Genetic evidence
We found no GWAS summary data for vitamin K1 in patients with atrial fibrillation and cirrhosis, but we did find genetic evidence to indicate that warfarin use is associated with reduced stroke risk. For two-sample MR, we used four methods (inverse-variance weighted (IVW), MR-Egger, simple median and weighted median). The IVW analyses, which assumes no pleiotropy, revealed that higher genetically predicted levels of vitamin K1 were associated with a higher risk of any stroke with an odds ratio (OR) of 1.06 (95% CI 1.00–1.11) per Ln-nmol/L increase in vitamin K1 (Fig. 6). However, these results were not replicated using methods (simple median, weighted median and MR-Egger) which allow for genetic pleiotropy. When considering stroke subtypes, we observed that higher genetically predicted levels of vitamin K1 were associated with a higher risk of large artery atherosclerotic stroke for 3 out of 4 MR methods: simple median (OR = 1.25 [1.03–1.51]) and IVW (OR = 1.29 [1.11–1.50]) (Fig. 6).

Informatics consult report generation
Table 1 shows additional opportunities for pipelining each of the four streams of evidence identification and generation to return the Consult report. Computable EHR phenotypes and computable clinical trial protocols

---

### Table 1

| Study          | Setting            | Eligibility criteria                                                                 | Number of patients with atrial fibrillation and cirrhosis | Warfarin use | No warfarin use | Adjusted estimates | Trial emulation |
|----------------|--------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------|-------------|----------------|--------------------|-----------------|
| Kuo et al (2017) | Population         | CHA2DS2-VASc score \( \geq 2 \)                                                       | 9,056                                                   | 754         | 8,302          | Yes (propensity score) | No              |
| Serper et al (2020) | Population    | Patients without prior venous thromboembolic events                                    | 1,694                                                   | 614         | 1,080          | Yes (propensity score) | No              |
| Lee et al (2015) | Hospital-based     | Patients with non-valvular atrial fibrillation, no previous diagnosis of mitral stenosis or prosthetic heart valve | 321                                                     | 173         | 148            | Yes (multivariate Cox regression) | No              |
| Choi et al (2017) | Hospital-based     | Patients with non-valvular atrial fibrillation                                         | 465                                                     | 113         | 352            | No                 | No              |

---

### Fig. 4

**A** New synthesis of prior observational evidence. Meta-analysis of the association between warfarin use and the risk of ischaemic stroke in observational studies including approaches for automation. A Characteristics of observational studies included in the meta-analysis. B Forest plot depicting the hazard ratios calculated with the DerSimonian and Laird random-effects models. HR = hazard ratio; CI = confidence interval; SE = standard error.

---

### Fig. 6

Hazard ratio for ischaemic stroke

- Overall effect: [0.39; 1.29] 100.0%

---

### Table 1

| Study          | InHR SE InHR | HR 95% CI | Weight |
|----------------|-------------|-----------|--------|
| Lee et al (2015) | -1.20 0.38  | 0.30 [0.14; 0.63] | 23.8% |
| Kuo et al (2017) | -0.34 0.17  | 0.71 [0.51; 0.99] | 33.6% |
| Choi et al (2017) | -0.29 0.66  | 0.75 [0.21; 2.78] | 19.7% |
| Serper et al (2020) | 0.34 0.27  | 1.40 [0.82; 2.38] | 28.9% |

---

### Table 1

| Study          | InHR SE InHR | HR 95% CI | Weight |
|----------------|-------------|-----------|--------|
| Lee et al (2015) | -1.20 0.38  | 0.30 [0.14; 0.63] | 23.8% |
| Kuo et al (2017) | -0.34 0.17  | 0.71 [0.51; 0.99] | 33.6% |
| Choi et al (2017) | -0.29 0.66  | 0.75 [0.21; 2.78] | 19.7% |
| Serper et al (2020) | 0.34 0.27  | 1.40 [0.82; 2.38] | 28.9% |

---

### Table 1

| Study          | InHR SE InHR | HR 95% CI | Weight |
|----------------|-------------|-----------|--------|
| Lee et al (2015) | -1.20 0.38  | 0.30 [0.14; 0.63] | 23.8% |
| Kuo et al (2017) | -0.34 0.17  | 0.71 [0.51; 0.99] | 33.6% |
| Choi et al (2017) | -0.29 0.66  | 0.75 [0.21; 2.78] | 19.7% |
| Serper et al (2020) | 0.34 0.27  | 1.40 [0.82; 2.38] | 28.9% |

---

### Table 1

| Study          | InHR SE InHR | HR 95% CI | Weight |
|----------------|-------------|-----------|--------|
| Lee et al (2015) | -1.20 0.38  | 0.30 [0.14; 0.63] | 23.8% |
| Kuo et al (2017) | -0.34 0.17  | 0.71 [0.51; 0.99] | 33.6% |
| Choi et al (2017) | -0.29 0.66  | 0.75 [0.21; 2.78] | 19.7% |
| Serper et al (2020) | 0.34 0.27  | 1.40 [0.82; 2.38] | 28.9% |

---

### Table 1

| Study          | InHR SE InHR | HR 95% CI | Weight |
|----------------|-------------|-----------|--------|
| Lee et al (2015) | -1.20 0.38  | 0.30 [0.14; 0.63] | 23.8% |
| Kuo et al (2017) | -0.34 0.17  | 0.71 [0.51; 0.99] | 33.6% |
| Choi et al (2017) | -0.29 0.66  | 0.75 [0.21; 2.78] | 19.7% |
| Serper et al (2020) | 0.34 0.27  | 1.40 [0.82; 2.38] | 28.9% |
can be used to automate the process of trial identification and trial recruitment [25, 26]. For meta-analyses of observational studies, approaches for semi-automated systematic reviews [27, 28], batch extraction of data from articles [29, 30] and mapping of SNOMED-CT terms to MeSH descriptors in PubMed [31] can be used in the pipelining process. The DExtER tool can be used for automatic extraction of EHR databases and automated
| Task                                      | Traditional approach                                                                 | Approaches to automate                                                                 |
|-------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| **Evidence from randomised trials**       |                                                                                      |                                                                                        |
| Search for recruiting trials              | Perform search on the clinicaltrials.gov website. Requires manual decisions on relevant search terms | Perform search on the clinicaltrials.gov website using search terms collated from free text input in the Informatics Consult platform. Potential to leverage developments on computable machine-readable trial protocols (https://doi.org/10.1177/009286150704100312) and computable phenotypes (i.e., algorithms to identify clinical characteristics derived from electronic health records) to identify potentially eligible patients for trial recruitment (https://doi.org/10.1161/CIRCOUTCOMES.111.006292). Potential to use sentence embedding and Google BERT as approaches for matching natural language queries with relevant trial protocols |
| Summarise data of recruiting trials       | Download search results from the clinicaltrials.gov website. Manually format tables. Extract additional information not present in downloaded data from the website by inputting NCT numbers | Download search results from the clinicaltrials.gov website. Generate scripts for automated table formatting to retain relevant information. Create a Python web-scraping tool to extract free texts from specific clinical trials and return information on inclusion and exclusion criteria. Note that some websites do not allow web-scraping and exclusions may apply to the clinicaltrials.gov website |
| **Evidence from meta-analysis**           |                                                                                      |                                                                                        |
| Search strategy                           | Requires manual decisions on relevant search terms                                    | Potential for mapping SNOMED-CT terms to MeSH descriptors used in PubMed (PMID:17238584) |
| Identifying existing evidence from published sources and assessing eligibility | Perform searches on PubMed. Manual curation and review of publications. Does not scale | Semi-automated systematic reviews using machine learning and natural language processing for expedited evidence synthesis. For example, using “bag of words” for classifying documents and using learned coefficients for predicting the probability of an unseen document. Examples of platforms for automating evidence synthesis include RobotReviewer and ExaCT, where the latter employs an information extraction engine that identifies and extracts text fragments that describe clinical trial characteristics on unseen articles (https://doi.org/10.1186/s13643-019-1074-9; https://doi.org/10.1186/1472-6947-10-56) |
| Extracting data and performing the meta-analysis | Manual extraction of relevant tables and information. Not practical for batch extraction of data | Semi-automated tool for converting PDF documents to XML using a rule-based system such as PDFX. Batch extraction of data from PDF documents can also be performed using the open-source CyberPDF, which improves the accuracy and efficiency in batch data processing. Extracted data is formatted into data frames for subsequent meta-analysis using the meta package in R or other existing packages. (https://doi.org/10.1145/2494266.2494271; https://doi.org/10.1145/3278576.3281274) |
| **Evidence from target trial emulation**  |                                                                                      |                                                                                        |
| Specifying the target trial protocol      | This process requires a discussion between the clinician and informatician to determine the appropriate criteria, treatment strategies and outcomes | Previous insights on specifying the target trial protocol can be collated automatically and be used to inform future target trial designs |
| Task                                      | Traditional approach                                                                 | Approaches to automate                                                                 |
|-------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Cohort creation based on eligibility criteria in the target trial protocol | Manual cohort creation for each target trial. Does not scale                          | This process can be pipelined using several functions to create cohorts in a consistent format with the covariates of interest. The DExtER tool for automated cohort creation can be employed |
| Propensity score matching to match initiators and non-initiators | Once a cohort is created in the correct format containing all the covariates of interest, propensity score matching can be performed using the MatchIt package | Additional approaches for causal inference analyses, including causal machine learning using the targeted maximum likelihood estimation approach can be investigated and pipelined |
| Descriptive summary of the cohort before and after matching | The tableone package can be used to generate the baseline tables before and after propensity score matching | Previous descriptive summaries on other related studies can be collated and featured in future target trials that investigate related clinical queries |
| Cox regression on the matched cohort      | Cox regression analyses is performed by fitting the coxph function using the survival package | Additional regression analyses can be automated into the pipeline |
| Kaplan Meier analysis on the matched cohort | Survival or cumulative incidence curves are plotted using the survminer package       | This can be pipelined to look at multiple outcomes at a time |
| Scaling to other examples and datasets    | Limited tractability                                                                  | Pipeline scalable to other datasets for cohort generation. Free text input from the Informatics Consult request form and report will inform additional opportunities to scale to other clinical questions |
| Genetic evidence                          | Manual curation of GWAS summary data. Literature search for published genetic variants for the risk factor | The MR-base platform for Mendelian randomisation can be employed to rapidly identify instruments for the exposure and outcome using GWAS summary data from their catalog. Additional GWAS summary data can be obtained from PhenoScanner, EMBL-EBI GWAS catalog and Integrative Epidemiology Unit OpenGWAS database |
| Identifying genetic variants associated with the exposure (e.g., drug) or risk factor in genome-wide association studies (GWAS) | Extract and format data identified above. Run Mendelian randomisation in R | MR-base also includes an analytical platform for performing MR analysis. For exposures and outcomes not available in MR-base, this process can be pipelined to transform the GWAS summary data from other public sources into an analysis-ready format. Mendelian randomisation can be performed using the Mendelian-Randomisation package |
cohort creation for the target trial emulation process [32]. Recent addition of an analytical module to DExtER enables cohort creation, statistical analyses and results visualisation within short time scales for matched cohort studies. Two-sample MR to generate genetic evidence can be automated using the MR-Base platform [33], which returns results within minutes.

Clinician survey on the acceptability and feasibility of the Informatics Consult
We surveyed an independent sample of 34 clinicians from eight specialties with results shown in (Additional file 1-10, Additional file 1-11). Results indicated that 79% of clinicians thought that they should have access to the Informatics Consult as a service within their healthcare systems (21% responded ‘maybe’). Clinicians found each section of the report useful (or ‘maybe useful’) as follows: prognosis [85% useful (12% maybe useful)], a summary of evidence of efficacy and safety [79% useful (21% maybe useful)] and disease prevalence [68% useful (18% maybe useful)]. Only 18% of clinicians thought that they needed to have access to the details of the evidence in the clinic with one clinician stating: “Multi-disciplinary team meetings might benefit from Informatics Consults, this is where difficult cases are discussed and there is time to review newly generated evidence”. When asked whether clinicians found detailed reports on the four sources of evidence useful (or ‘maybe useful’), responses were as follow: randomised trials: 82% useful (15% maybe useful); meta-analysis of prior observational evidence: 76% useful (18% maybe useful); target trial emulation: 62% useful (18% maybe useful) and genetic evidence: 26% useful (24% maybe useful). 74% of clinicians would discuss the Informatics Consult report with their patients (26% answered maybe). Clinicians offered 15 further clinical questions where the Informatics Consult might be of value and made additional comments including: “Ultimately, we practise defensive medicine—would my decision stand up in court based on available data—the Informatics Consult should help with that.” and “Regulators and guideline developers will require replication and quality assurance of evidence generated in clinical timescales”.

Discussion
We demonstrate that the Informatics Consult offers a novel paradigm to generate new clinical evidence. We found that in patients with atrial fibrillation and cirrhosis, initiation of warfarin was common, may be associated with lower all-cause mortality and may be effective in lowering stroke risk. Given the ubiquity of clinical uncertainty where there is little or no evidence, and that current modes of generating new evidence may never be initiated or, if initiated, take years to report, it is imperative to accelerate learning from extant data.

Informatics consult versus traditional approaches for evidence generation and delivery
The Informatics Consult puts the treating clinician and the patient at the centre of evidence generation. Indeed, in seeking to address a range of questions from the clinician and patient, the Informatics Consult, if automation is plausible, could enable the simultaneous delivery of evidence from different sources, rather than employing a one-study-one-design-at-a-time approach. The Consult is embedded within EHR system—making it a form of an electronic consult, which is increasingly being adopted to seek specialist input [34, 35]. Additional information on how the Informatics Consult differs from traditional approaches to evidence generation and use is summarised in Additional file 1-1.

Concordance across sources of evidence identified from the Consult
A primary motivation for requesting an Informatics Consult is to understand how a particular treatment influences an outcome to help guide decision making. We show a degree of concordance across four sources of evidence. RCTs demonstrate the effectiveness of oral anticoagulation in stroke prevention in patients with atrial fibrillation: but as we demonstrate reported and currently recruiting RCTs exclude patients with cirrhosis (i.e., patients having ‘contraindications’ for anticoagulants). This suggests that the prospect of ever mounting, or successfully recruiting to, an RCT in patients with AF and cirrhosis is low. Meta-analysis of observational studies and target trial emulation suggest evidence on the potential benefits of warfarin for stroke reduction, suggesting the significant impact on strokes and deaths averted if these patients are treated with anticoagulant therapy. Although we did not find any relevant GWAS summary data, evidence suggests that lower levels of vitamin K1 (target of warfarin) are associated with lower stroke risk which is corroborated by another study [36].

Returning results on prevalence, prognosis and treatment variation
Interestingly, the clinicians involved in this study recommended that information beyond efficacy and safety should be included as options for the clinician to request in the Informatics Consult. By providing information on the prevalence of cirrhosis and atrial fibrillation, we demonstrate that this pair of conditions is not highly prevalent (although not considered rare). Knowing that the health system has data on diagnosis, treatment and outcomes in an estimated 35,000 individuals (scaled up
to the population of England) with both conditions, highlights the importance of several areas. First, the importance of accessing and learning from nationwide data at scale; any one clinician may have clinical experience of only a handful of such cases, and it is not feasible or scalable to create registries. Second, the clinician likely has never had access before to population-based, contemporary prognostic information on such patients (1-year mortality: 15%), nor the knowledge that in practice 43% of patients were started on warfarin. We anticipate that providing clinicians and patients with this information may stimulate further questions on generating new Consults on a wider range of prognostic outcomes, and predictors of prognosis.

**Need and demand for informatics consult**

Nearly all clinicians are faced with treatment decisions where limited evidence exists where insights might be gained from analysis of large-scale data on ‘patients like me’. Previous studies have employed EHR data for diagnostic consultations [37], and others have created clinical informatics consult services based on the medical literature [38]. But currently, few if any clinicians can request such insights. A clinician from the survey mentioned that evidence from the Informatics Consult is important to help their decision in practicing defensive medicine given that the majority of clinical practice recommendations in professional society guidelines are not supported by RCT evidence. There is limited information on the system-wide frequency of treatment ‘clashes’ where indication and contraindications coexist in the same patient. This is especially relevant for patients with multimorbidity where evidence from RCTs are limited [6], which may result in individuals being subjected to low-quality recommendations. For example, certain targeted cancer therapy such as angiogenesis inhibitors may cause an increase the prevalence of hypertension during treatment, which highlights the importance of considering the impact of cancer therapy on adverse side effects and cardiotoxicity [39]. Our preliminary analyses demonstrate that 26 in 10,000 women have breast cancer and hypertension; these individuals might benefit from the Informatics Consult.

**Developing the informatics consult as a service**

The majority of clinicians in our survey thought that they should have access to the Informatics Consult as a service as their healthcare systems seek to learn from existing data [40]. We have demonstrated the feasibility with this one example. Scaling to other clinical examples, and a service, requires five inter-related challenges to be addressed in clinical standards setting, implementation and evaluation, access to data, informatics, and knowledge management. First, bodies that define standards of care—including clinical practice guideline developers and regulatory and technology assessment bodies—are already considering real-world evidence generated in conventional timescales [7, 41]. In the context of a more rapid generation of evidence, the Informatics Consult raises new questions about replication, open peer review and quality assurance pipelines. Second, development, implementation and evaluation of the impact of the Informatics Consult on clinical decision making in practice are required. Feedback from our survey suggests that multidisciplinary team (MDT) meetings, which concentrate on ‘difficult’ clinical cases may present an opportunity [42]. Third, an Informatics Consult service requires approved, immediate access to large scale, clinically detailed updated data, most likely in a trusted research environment. The coronavirus pandemic offers a new precedent for such information governance approvals, which can not foresee the nature of the next clinician’s question. Fourth, biomedical knowledge (in EHRs, trial protocols, clinical guidelines) needs to become more computable and interoperable. Design and analysis methods need to be improved, standardized and widely distributed. For example, the Observational Health Data Science and Informatics community offers open-source software implementing many routine analyses methods [43]. Fifth, there needs to be an open process of making the knowledge available in an Informatics Consult library. As the library builds, Clinicians might make a request for which a previous consult already provides an answer. The Library might also serve as a platform for connecting ‘patients like me’, registering the frequency of therapeutic dilemmas and potential treatment uncertainties, identifying the need for new RCTs, and informing their design and facilitate targeted recruitment into trials.

**Strengths of the study**

To the best of our knowledge, this is the first demonstration of Informatics Consult for a treatment decision, triangulation of evidence from meta-analyses of observational studies, target trial emulation using EHR data and MR. The breadth, depth and longevity (long follow-up period) of the EHR data, which links primary care, secondary care and the death registry is an advantage. Another significant strength is engagement with an independent sample of clinicians from multiple specialties to gauge the feasibility and acceptability of the Informatics Consult.

**Limitations of the study**

Our study has important limitations. First, although we have prototyped EHR request and report forms based on
feedback from clinicians, these have not yet been implemented in live clinical systems. Second, as initial proof of concept, we have not assessed bleeding outcomes and newer non-vitamin K oral anticoagulants due to current data access limitations. Third, it remains difficult to assess whether there unmeasured confounding despite employing causal inference methods. It is also possible that some prescription data is missing, which means that patients are incorrectly assigned to the control arms. Future analyses on a more recent and larger data-set involving both CPRD Gold and Aurum [44] would be beneficial. Fourth, a limitation of the MR analyses is that access to summarised GWAS data for stroke outcomes in patients with cirrhosis is limited. The advantages of using publicly available GWAS summarised data are speed and transparency, both of which are essential to the Informatics Consult. Although individual-level data would allow more flexibility to conduct analyses in specific patient subgroups and to select which variables to generate the summarised data for, such analyses could not be returned within a clinical timescale that is not scalable and cannot be fully automated. Fifth, although we have identified potential ways to automate the analytic process, these have not been implemented here.

Conclusion
We proposed an Informatics Consult framework to summarize evidence from four sources and have developed a report prototype for answering a treatment question to enable new ways of data-informed decision making. The Informatics Consult may stimulate a conversation among public, professionals and policymakers about more rapidly realising the benefits of health system learning from ‘patients like me’.

Abbreviations
AF: Atrial fibrillation; RCT: Randomised controlled trials; HR: Hazard ratio; EHR: Electronic health record; OR: Odds ratio; CPRD: Clinical Practice Research Data link; PSM: Propensity score matching; INR: International normalise ratio; SNP: Single nucleotide polymorphism, GWAS: Genome wide association study; IVW: Inverse-variance weighted; CI: Confidence interval; MR: Mendelian randomisation; MDT: Multidisciplinary team.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12911-021-01638-z.

Additional file 1. Supplementary data 1 to 11.

Acknowledgements
We thank clinical colleagues who have contributed to the pilot survey and who have consented for their names to be acknowledged: Christopher Tomlinson, Upkar Gill, Paul Harow, Harry Martin, Omer Ahmad, Louise China, Vanessa Taylor, Sai Ambati, Amy Prideaux, Alex May, Ruth Gilbert, Hamish Miller, Bilal Mateen, Rhys Davies, Bu’Hussain Hayee, David Cronin, Katharine Pollock and Philip Oppong.

Authors’ contributions
Research question: AGL, GRF, HH. Funding: AGL, HH. Study design and analysis plan: AGL, WHC, CP, HH. Preparation of data, including electronic health record phenotyping in the CALIBER portal: AGL, WHC, CP, SD. Statistical analysis: AGL, WHC, MK. Drafting initial versions of the manuscript: AGL, HH. Critical review of early and final versions of the manuscript: AGL, WHC, CAP, MK, RMB, ADS, VN, SD, GDS, TRG, KN, MPC, DF, FWA, SH, SR, RS, RUBD, AH, RP, JS, AB, AKD, SB, NJS, NHS, GRF, BW, HH. All authors read and approved the final manuscript.

Funding
AGL is supported by funding from the Wellcome Trust (204841/Z/16/Z), National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre (BRC714/HH/RW/101440), NIHR Great Ormond Street Hospital Biomedical Research Centre (19XR02) and the Health Data Research UK Better Care Catalyst Award (CFCG125). MK is funded by the British Heart Foundation (FS/18/5/33319). RMB is supported by a UKRI Innovation Fellowship funded by the Medical Research Council (Grant No: MR/ S003797/1). ADS is supported by a postdoctoral fellowship from THIS Institute. RUBD is supported by the NIHR Biomedical Research Centres at South London and Maudsley NHS Foundation Trust (SLAM; IS-BRC 1215-200118), Health Data Research UK; UK Research and Innovation (UKRI) London Medical Imaging & Artificial Intelligence Centre for Value Based Healthcare; the BigData@Heart Consortium (Grant No. 116074 of the European Union Horizon 2020 programme); the NIHR BRC and Research Informatics Unit at University College London Hospitals; and the NIHR Applied Research Collaboration South London at KCHFT. GDS and TG are funded by the Medical Research Council Integrative Epidemiology Unit at the University of Bristol MC_UU_00011/1&4. HH is an NIHR Senior Investigator and is funded by the NIHR University College London Hospitals Biomedical Research Centre, supported by Health Data Research UK (LOND1). The funding bodies do not play any roles in the design of the study and collection, analysis, and interpretation of data in writing the manuscript.

Availability of data and materials
Codelists for the conditions included in our study are available on the CALIBER portal (https://www.caliberesearch.org/portal) and can be downloaded in a machine-readable format. The data used in this study are available on successful ethics application to the Clinical Practice Research Data link (CPRD). All summarised data and results are made available as supplementary materials.

Declarations
Ethics approval and consent to participate
We obtained informational governance approval from the Medicines Healthcare Regulatory Authority (UK) Independent Scientific Advisory Committee (20_078R) to analyse the Clinical Practice Research Datalink (CPRD) linked to secondary care Hospital Episode Statistics and the Office for National Statistic death registration. Ethics approval was exempted for the survey as it is classified under service evaluation. Survey participants gave informed consent to participate by returning the completed survey.

Consent to publish
Not applicable.

Competing interests
A8 has received research funding from AstraZeneca for work unrelated to this research. GRF receives funding from companies that manufacture drugs for hepatitis C virus (AbbVie, Gilead, MSD) and consults for GSK, Arbutus and Shionogi in areas unrelated to this research. TRG and GDS have received research funding from GlaxoSmithKline and Biogen for work unrelated to this research.

Author details
1 Institute of Health Informatics, University College London, London, UK. 2 Health Data Research UK, London, UK. 3 University College London Hospitals NIHR Biomedical Research Centre, London, UK. 4 The Alan Turing Institute, London, UK. 5 Medical Research Council Integrative Epidemiology Unit, University
References

1. van Dijk WB, Grobbee DE, de Vries MC, Groenwold RHH, van der Graaf Y. Randomized trials in patients with concomitant chronic conditions in ongoing randomized controlled trials targeting 10 common chronic conditions and registered at ClinicalTrials.gov: a systematic review of registration details. BMJ Open. 2019;301:831–41.

2. Meyer C, Bowers A, Wayant C, Checketts J, Scott J, Musuvathy S, et al. Scientific evidence underlying the American College of Gastroenterology’s clinical practice guidelines. PLoS ONE. 2018;13:e0204720.

3. Koh C, Zhao X, Samarla N, Sakiani S, Liang TJ, Talwalker JA. AASLD clinical practice guidelines: a critical review of scientific evidence and evolving recommendations. Hepatology. 2013;58:2142–52.

4. Fanaroff AC, Califf RM, Windecker S, Smith SC, Lopes RD. Levels of evidence supporting American College of Cardiology/American Heart Association and European Society of Cardiology guidelines. 2008–2018. JAMA. 2019;321:1069–80.

5. Tricco CA, Thomas Lang JM, Kramer JM, Califf RM, Smith SC. Scientific evidence underlying the ACC/AHA clinical practice guidelines. JAMA. 2009;301:831–41.

6. Du Vauvre CB, Dechatelets A, Battin C, Ravaud P, Bouton I. Exclusion of patients with concomitant chronic conditions in ongoing randomised controlled trials: a systematic review and meta-analysis. Eur J Prev Cardiol. 2015;21:323–30.

7. U.S. Food and Drug Administration. Framework for FDA’s real-world evidence program. https://www.fda.gov/science-research/science-research-special-topics/reallworld-evidence. Accessed 16 Nov 2020.

8. Gombar S, Callahan A, Califf R, Harrington R, Shah NH. It is time to learn from patients like mine. npj Digit Med. 2019;2:2018–20. https://doi.org/10.1038/s41746-019-0091-3.

9. Longhurst CA, Harrington RA, Shah NH. A ‘green button’ for using aggregate patient data at the point of care. Health Aff. 2014;33:1.229–35.

10. Callahan A, Gombar S, Jung K, Steinberg E, Harrington R, Shah NH. Delivering on-demand evidence via an informatics consultation service, pp. 3–5.

11. Schuler A, Callahan A, Jung K, Shah NH. Performing an informatics consult: methods and challenges. J Am Coll Radiol. 2018;15:563–8.

12. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ. 2018;362.

13. Burgess S, Davey Smith G, Davies MV, Dudbridge F, Gill D, Glymour MM, et al. Guidelines for performing Mendelian randomization investigations. Wellcome Open Res. 2020;4:186.

14. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol. 2016;183:758–64.

15. Dickerman BA, Hernán MA. Avoidable flaws in observational analyses: an application to statins and cancer. Nat Med. 2019. https://doi.org/10.1038/s41591-019-0597-x.

16. Kuan V, Denaxas S, Gonzalez-Izquierdo A, Direk K, Bhatti O, Hussain S, et al. A chronological map of 308 physical and mental health conditions from 4 million individuals in the English National Health Service. Lancet Digit Heal. 2019;1:e63–77.

17. Denaxas S, Gonzalez-Izquierdo A, Direk K, Fitzpatrick NK, Fatemiwar G, Banerjee A, et al. UK phenomics platform for developing and validating electronic health record phenotypes: CALIBER. J Am Med Informatics Assoc. 2019.

18. Doshi HS, Shea MK, Smith CE, Tanaka T, Hruby A, Richardson K, et al. Meta-analysis of genome-wide association studies for circulating phyto- loquinone concentrations. Am J Clin Nutr. 2014;100:1462–9.

19. Malik R, Chauhan G, Traylor M, Sagarupreemraj M, Okada Y, Mishra A, et al. Multiancestry genome-wide association study of ≥20,000 subjects identifies 32 loci associated with stroke and stroke subtypes. Nat Genet. 2018;50:524–37.

20. Yavorska OO, Burgess S. MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data. Int J Epidemiol. 2017;46:1734–9.

21. Serper M, Weinberg EM, Cohen JB, Reese PP, Taddei TH, Kaplan DE. Mortality and hepatic decomposition in patients with cirrhosis and atrial fibrillation treated with anticoagulation. Hepatology. 2020;0–3.

22. Choi J, Kim J, Shim JH, Kim M, Nam GB. Risks versus benefits of anticoagula- tion for atrial fibrillation in cirrhotic patients. J Cardiovasc Pharmacol. 2017;70:255–62.

23. Kuo L, Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Liver cirrhosis in patients with atrial fibrillation: would oral anticoagulation have a net clinical benefit for stroke prevention? J Am Heart Assoc. 2017;6.

24. Lee SJ, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B. The safety and efficacy of vitamin K antagonist in patients with atrial fibrillation and liver cirrho- sis. Int J Cardiol. 2015;180:185–91.

25. Ahmed FS, Ricket IM, Hammill BG, Eskensazi L, Robertson HR, Curtis LH, et al. Computable phenotype implementation for a national, multicenter pragmatic clinical trial: lessons learned from ADAPTABLE. Circ Cardiovasc Qual Outcomes. 2020;CIRCOUTCOMES–119.

26. Willoughby C, Fridsma D, Chattejee L, Speakman J, Evans J, Kush R. A standard computable clinical trial protocol: the role of the BRIDG model. Drug Inf J DIU/Drug Inf Assoc. 2007;41:383–92.

27. Marshall II, Wallace BC. Toward systematic review automation: a practical guide to using machine learning tools in research synthesis. Syst Rev. 2019;8:163.

28. Kiritchenko S, De Bruijn B, Carini S, Martin J, Sim I. ExaCT: automatic extraction of clinical trial characteristics from journal publications. BMC Med Inform Decis Mak. 2010;10:56.

29. Constantin A, Pettifer S, Voronkov A. PDFX: fully automated-PDF-to-XML conversion of scientific literature. In: Proceedings of the 2013 ACM symposium on Document engineering. 2013. pp. 177–80.

30. Parizi RM, Guo L, Bian Y, Azzoodeh A, Dehgahantaha A, Choo KKR. CyberPDF: smart and secure coordinate-based automated health PDF data batch extraction. In: 2018 IEEE/ACM international conference on connected health: applications, systems and engineering technologies (CHASE). 2018. pp. 106–11.

31. Jacobs AK, Quinn TA, Nelson SJ. Mapping SNOMED-CT concepts to MeSH concepts. In: AMIA annual symposium proceedings. 2006. p. 965.

32. Gokhale KM, Chandan JS, Toikus G, Kourous G, Tino P, Niranthinarakum K. Data extraction for epidemiological research (DEXEHR): a novel tool for automated clinical epidemiology studies. Eur J Epidemiol. 2020;36:1–14.

33. Heimani G, Zheng J, Ellisworth B, Wade KH, Haberland V, Baird D, et al. The MR-Base platform supports systematic causal inference across the human phenotype. Elife. 2018;7:e44008.

34. Vimalananda VG, Gupta G, Saraj SM, Orlander J, Berlowitz D, Fincke BG, et al. Electronic consultations (e-consults) to improve access to specialty care: a systematic review and narrative synthesis. J Telemed Telecare. 2015;21:106–11.

35. Informatics Consultation Service at Stanford. http://greenbutton.stanford.edu. Accessed 17 Dec 2020.

36. Larsson SC, Traylor M, Markus HS. Circulating vitamin K1 levels in relation to ischemic stroke and its subtypes: a Mendelian randomization study. Nutrients. 2018;10:1–7.

37. Li Y-C, Haug PJ, Lincoln MJ, Turner CW, Pryor TA, Warner HH. Assessing the behavioral impact of a diagnostic decision support system. In: Proceedings of the annual symposium on computer application in medical care. 1995. p. 805.
38. Plante DA, Kassirer JP, Zarin DA, Pauker SG. Clinical decision consultation service. Am J Med. 1986;80:1169–76.
39. Mouhayar E, Salahudeen A. Hypertension in cancer patients. Texas Heart Inst J. 2011;38:263.
40. Budrionis A, Bellika JG. The learning healthcare system: Where are we now? A systematic review. J Biomed Inform. 2016;64:87–92.
41. European Medicines Agency. Guideline on registry-based studies. https://www.ema.europa.eu/en/guideline-registry-based-studies. Accessed 15 Dec 2020.
42. National Guideline Centre (UK). Emergency and acute medical care in over 16s: service delivery and organisation. London: National Institute for Health and Care Excellence (UK); 2018 Mar. (NICE Guideline, No. 94.) Chapter 29, Multidisciplinary team meeting.
43. Observational Health Data Sciences and Informatics Methods Library. https://www.ohdsi.org/methods-library/. Accessed 07 Dec 2020.
44. Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) aurum. Int J Epidemiol. 2019;48:1740–1740g.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.