research

GLP-1 receptor agonists and substance use p 245

Reporting guidelines for paediatric trials p 248

Protocols and results of post-authorisation studies p 250

What GLP-1 receptor agonists might add to substance use care

ORIGINAL RESEARCH Cohort study

Glucagon-like peptide-1 receptor agonists and risk of substance use disorders among US veterans with type 2 diabetes

Cai M, Choi T, Xie Y, Al-Aly Z

Cite this as: *BMJ* 2026;392:e086886
Find this at doi: 10.1136/bmj-2025-086886

Study question Compared with sodium-glucose cotransporter-2 (SGLT-2) inhibitors, is the initiation of glucagon-like peptide-1 (GLP-1) receptor agonists associated with a lower risk of incident substance use disorders (SUDs) among people without a pre-existing SUD, and with a lower risk of SUD associated adverse clinical events among people with pre-existing SUDs?

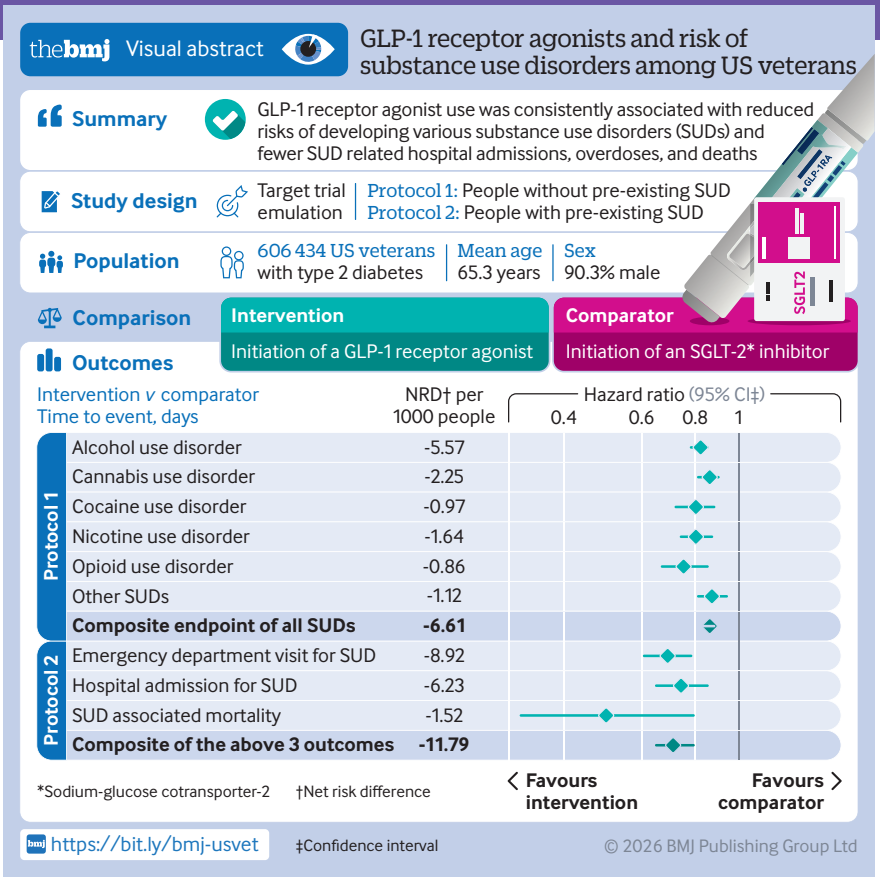
Methods Using electronic health records from the US Department of Veterans Affairs, this study emulated eight parallel, active comparator, new user target trials following 606 434 veterans with type 2 diabetes who initiated a GLP-1 receptor agonist or SGLT-2 inhibitor for three years. Seven trials evaluated incident risks of SUDs related to use of alcohol, cannabis, cocaine, nicotine, or opioids, and to other SUDs, and a composite of these outcomes in participants without a history of SUDs. One trial evaluated SUD related emergency department visits, hospital admissions, mortality, overdose, and suicidal ideation or attempt in participants with pre-existing SUDs. Hazard ratios and three year net risk differences (NRD) per 1000 people were estimated using inverse probability weighted cause specific Cox models.

Study answer and limitations Compared with initiation of SGLT-2 inhibitors, initiation of GLP-1 receptor agonists was associated with reduced risk of disorders related to use of alcohol (hazard ratio 0.82 (95% confidence interval (CI) 0.78 to 0.85); NRD per 1000 people −5.57 (95% CI −6.61 to −4.53)), cannabis (0.86 (0.81 to 0.90), NRD −2.25 (−3.00 to −1.50)), cocaine (0.80 (0.72 to 0.88), NRD −0.97 (−1.37 to −0.57)), nicotine (0.80 (0.74 to 0.87), NRD −1.64 (−2.19 to −1.09)), and opioids (0.75 (0.67 to 0.85), NRD −0.86 (−1.19 to −0.52)), other SUDs (0.87 (0.81 to 0.94), NRD −1.12 (−1.68 to −0.55)), and a composite of these outcomes (0.86 (0.83 to 0.88), NRD −6.61 (−7.95 to −5.26)). Among people with pre-existing SUDs, initiation of GLP-1 receptor agonists was associated with reduced risk of SUD

related emergency department visits (0.69 (0.61 to 0.78), NRD −8.92 (−11.59 to −6.25)), SUD related hospital admissions (0.74 (0.65 to 0.85), NRD −6.23 (−8.73 to −3.74)), SUD related mortality (0.50 (0.32 to 0.79), NRD −1.52 (−2.32 to −0.72)), drug overdose (0.61 (0.42 to 0.88), NRD −1.49 (−2.43 to −0.55)), and suicidal ideation or attempt (0.75 (0.67 to 0.83), NRD −9.95 (−13.14 to −6.77)). The predominantly male veteran population may limit the generalisability of these findings.

What this study adds Use of GLP-1 receptor agonists was consistently associated with reduced risks of developing various incident SUDs, suggesting a broad preventive effect across multiple substance types. Use was also associated with reduced risks of adverse clinical outcomes in people with pre-existing SUDs.

Funding, competing interests, and data sharing
Funded by the US Department of Veterans Affairs. See full paper on bmj.com for competing interests. Veterans Affairs data are made freely available to researchers behind a firewall with an approved Veterans Affairs study protocol.



COMMENTARY Clinical trials and equitable care pathways are needed to build on early evidence of benefit

Substance use disorders (SUDs) are common and burdensome for patients, families, and health systems,[1 2] yet effective albeit underused drugs exist for only some conditions.[2 3] Glucagon-like peptide-1 (GLP-1) receptor agonists, used to treat type 2 diabetes and obesity,[4] have been proposed as anti-craving agents because GLP-1 signalling interacts with brain reward and stress circuits.[5] In their paper, Cai and colleagues tested this hypothesis using routinely collected healthcare data from US veterans with type 2 diabetes.[6]

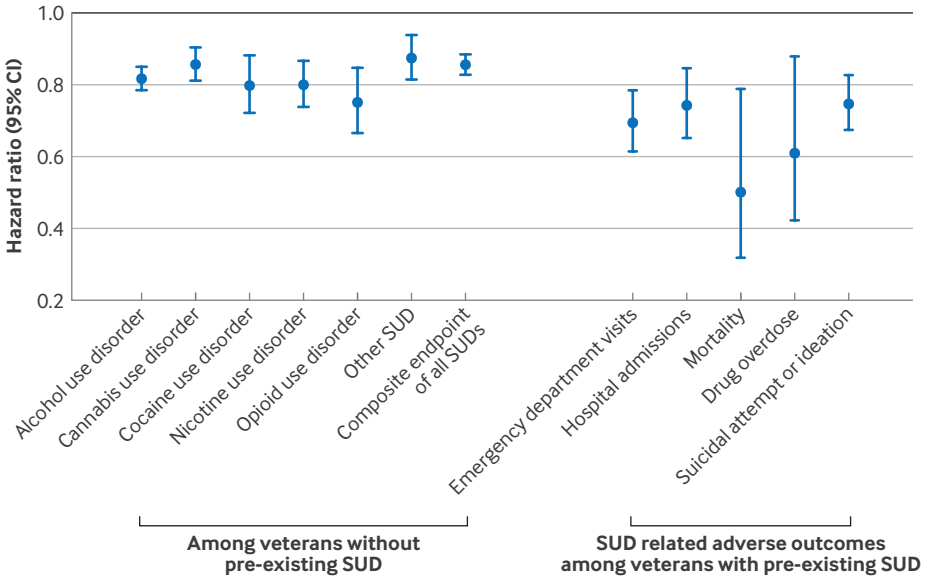
Using Veterans Affairs data, the authors emulated eight parallel target trials[6 7] comparing initiation of a GLP-1 receptor agonist with initiation of a sodium-glucose cotransporter-2 (SGLT-2) inhibitor; an active comparator with similar cardiometabolic indications.

Fares Qeadan
fqeadan@luc.edu
See bmj.com for author details

In veterans without a baseline SUD, initiation of a GLP-1 receptor agonist was associated with lower hazards of incident alcohol (hazard ratio 0.82), cannabis (0.86), cocaine (0.80), nicotine (0.80), opioid (0.75), and other SUDs (0.87) over three years, with net three year risk differences of roughly 1-6 fewer cases per 1000 people.[6] More clinically consequential were the findings among veterans with a pre-existing SUD, shifting the question from prevention to harm reduction. In this group, initiation of a GLP-1 receptor agonist was associated with fewer SUD related emergency department visits (hazard ratio 0.69), hospital admissions (0.74), and mortality (0.50), overdose (0.61), and suicidal ideation or attempt (0.75), translating to about 1-10 fewer events per 1000 people over three years.[6] These results suggest that any potential benefit is not restricted to a single diagnosis or substance and may extend to acute and life threatening consequences of addiction.

Integrated care that addresses both metabolic disease and substance use can reduce avoidable crises

Why might a drug for type 2 diabetes affect addiction outcomes? Preclinical and early clinical evidence suggests GLP-1 receptor activation can reduce reward driven seeking behaviours.[5] A randomised trial of semaglutide in adults with alcohol use disorder reported reductions in alcohol craving and some drinking outcomes over short follow-up,[8] and systematic reviews suggest early trials show signals for alcohol and nicotine outcomes.[9] Observational analyses in other settings have also reported lower risks of alcohol and cannabis use disorders and opioid related outcomes among users of GLP-1 receptor agonists.[10-13] Cai and colleagues' study design strengthens causal interpretation through a new user design, an



Associations between initiation of glucagon-like peptide-1 receptor agonists and risks of incident SUDs in participants without pre-existing SUD and risks of SUD related adverse clinical outcomes in participants with pre-existing SUD, compared with initiation of sodium-glucose cotransporter-2 inhibitors. Other SUDs are related to hallucinogens, inhalants, psychoactive drugs, sedatives or hypnotics, and stimulants. CI=confidence interval; SUD=substance use disorder

active comparator, extensive confounding control, and negative control analyses.[6 7]

Caution is still warranted. Residual confounding is plausible in data (for example, differences in health seeking behaviour, access, or clinician choice). SUDs and overdoses can be underdiagnosed, and ascertainment may differ if groups have different contact with services. The cohort included predominantly older men, so generalisability to women, younger people, and non-US settings is uncertain.[6] Finally, the estimated "net" effect reflects the effect of starting a GLP-1 receptor agonist rather than an SGLT-2 inhibitor; it does not establish benefit versus no treatment or versus evidence based addiction pharmacotherapy.

What should patients and clinicians do now?

For patients with type 2 diabetes who also live with (or are at risk of) a SUD, the key message is not to wait for a single "magic bullet." Evidence based treatments, opioid agonist treatment for opioid use disorder, and pharmacotherapies plus psychosocial support for alcohol use disorder remain the preferred treatments.[2 3] But these results suggest that when GLP-1 receptor agonists are clinically indicated for cardiometabolic reasons, potential benefits for substance related outcomes may be an added consideration in shared decision making.[4] Clinicians in diabetes and obesity services should screen for alcohol and drug use, offer stigma-free support options, and coordinate care with addiction and mental health teams. Families often carry the consequences of relapse and overdose; integrated care that addresses both metabolic disease and substance use can reduce avoidable crises.

If ongoing trials confirm meaningful benefits, affordability and supply will become ethical issues. GLP-1 receptor agonists remain costly, and access is unequal across and within countries; equity should be monitored throughout. A repurposed indication should not widen health inequities or divert supply away from established indications. Instead, it should prompt payers and regulators to invest in integrated models linking metabolic, mental health, and addiction services alongside safety surveillance.

The research agenda is clear

Randomised trials are needed in diverse populations, including people without diabetes and those receiving standard drugs for opioid and alcohol use disorders, to test whether GLP-1 receptor agonists add benefit to patient important outcomes such as functioning.[8 9] Trials should examine dose, duration, and whether effects differ across GLP-1 receptor agonist molecules. Mechanistic studies can clarify whether benefits are mediated by weight loss, improved glycaemic control, reduced inflammation, or direct central nervous system effects. It is also hypothesised that incretin treatments may shift a dysregulated immunometabolic "set point"; an idea to test in studies ranging from basic mechanistic work to pragmatic trials and real world implementation research. Implementation research, codesigned with patients and families, should evaluate how to deliver combined cardiometabolic and addiction care without increasing burden or stigma.

For now, Cai and colleagues' target trial emulation strengthens the case that GLP-1 receptor agonists may influence substance related outcomes in real world practice.[6] The challenge is to translate this signal into trials and equitable care pathways while continuing to scale proved treatments for SUDs.

Cite this as: *BMJ* 2026;392:s325

Find the full version with references at http://dx.doi.org/10.1136/bmj.s325

Making trials in children and adolescents count: why CONSORT-C matters

RESEARCH METHODS AND REPORTING Enhancing the reporting and impact of paediatric RCTs

SPIRIT | CONSORT-Children and Adolescents 2026 extension statements: enhancing the reporting of paediatric RCT protocols and reports

Baba A, Smith M, Potter BK, et al

Cite this as: *BMJ* 2026;392:e085061
Find this at doi: 10.1136/bmj-2025-085061

COLIN CUTHBERT/SPL

Appropriately designed, conducted, and reported randomised controlled trials (RCTs) in children and adolescents inform treatment and healthcare decisions made by young people, families, clinicians, policymakers, researchers, regulators, funders, and other interest holders. To facilitate the planning and implementation of potentially impactful trials, essential paediatric specific detail on the RCTs' aims, design, data collection methods, monitoring, data analysis, and participants' safety should be reported in the trial protocol. Similarly, for the critical appraisal, interpretation, and application of completed paediatric RCTs' results, readers require access to a complete and transparent report of what was planned, done, and found. Harmonised guidance based on evidence and consensus is needed to optimise standardised reporting and reduce research waste in paediatric RCT protocols and reports.

As an extension to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 and Consolidated Standards of Reporting Trials (CONSORT) 2025 statements, the new SPIRIT-Children and Adolescents (SPIRIT-C) 2026 and CONSORT-Children and Adolescents (CONSORT-C) 2026 reporting guideline aim to improve the quality and completeness of reporting of RCT protocols and reports that involve participants aged 0-19 years. SPIRIT-C 2026 and CONSORT-C 2026 were developed following the Enhancing the Quality of Transparency of Health Research (EQUATOR) Network consensus based method. The authors partnered with young people and family caregivers throughout the project and formed a Youth Advisory Group and a Family Caregiver Advisory Group. In a series of Young Person Reporting Guideline workshops, 42 children and adolescents (aged 10-21 years) generated candidate reporting items. 143 international panellists, comprising paediatric clinical trialists, paediatricians, child health researchers, methodologists, journal editors, young people (aged 19-24 years), and family caregivers, completed three rounds of a Delphi study. After a consensus meeting, the explanation and elaboration papers for both the CONSORT-C 2026 extension and the SPIRIT-C 2026 extension were produced (see box for details), and all guideline materials were pilot tested.

SPIRIT-C 2026 comprises 17 unique reporting items and CONSORT-C 2026 comprises 13 unique reporting items that should be reported in a paediatric RCT protocol and report, respectively.

CONSORT-C 2026 AND SPIRIT-C 2026 EXPLANATION AND ELABORATION PAPERS

Baba A, et al. CONSORT-C 2026 explanation and elaboration: recommendations for enhancing the reporting and impact of paediatric randomised trials
BMJ 2026;392:e085063 http://dx.doi.org/10.1136/bmj-2025-085063

Baba A, et al. SPIRIT-C 2026 explanation and elaboration: recommendations for enhancing the reporting and usefulness of paediatric randomised trial protocols
BMJ 2026;392:e085064 http://dx.doi.org/10.1136/bmj-2025-085064

SUMMARY POINTS

- SPIRIT-C 2026 and CONSORT-C 2026 provide harmonised reporting guidance specific to paediatric randomised controlled trial (RCT) protocols and reports, respectively
- Both reporting guidelines were developed following an evidence informed, consensus based method involving end users of paediatric RCTs, which included young people (aged 10-24 years) and family caregivers
- SPIRIT-C 2026 comprises 17 new reporting items specific for paediatric RCT protocols, which include four youth generated and six youth endorsed items
- CONSORT-C 2026 comprises 13 new reporting items specific for paediatric RCT reports, which includes one youth generated and six youth endorsed items
- Uptake and implementation of SPIRIT-C 2026 and CONSORT-C 2026 should lead to comprehensive and transparent reporting, resulting in useful paediatric RCT protocols and impactful RCT reports

Limitations include that the development of these extensions were conducted in English, and despite their efforts, authors could bring in limited perspectives from people in low and middle income countries.

Funding, competing interests, and data sharing
This work was supported by the Canadian Institutes of Health Research (CIHR), Ontario Child Health Support Unit, and CIHR Strategy for Patient-Oriented Research. See full paper on bmj.com for competing interests. Individual, anonymised responses from panellists or pilot testers are available from the corresponding author upon reasonable request.

Randomised clinical trials are at the core of evidence based medicine, yet the evidence base for interventions aimed at children and adolescents remains weaker than for adults. Fewer trials exist, often involving smaller sample sizes, and evidence accumulates more slowly.[1-4] Many trials are discontinued early due to challenges in recruitment and feasibility, while others remain unpublished or incompletely reported.[5 6] The consequences extend beyond academic inconvenience: clinicians are left uncertain about applicability, families struggle to judge relevance and risks, and policymakers and guideline developers must extrapolate from incomplete paediatric evidence and adult data when making recommendations. Inadequate reporting further increases research waste and adds to the ethical cost of involving children and adolescents in research.[7]

Reporting guidelines are one approach to improving the evidence base by supporting accurate and complete reporting of studies. In Baba and colleagues' paper, the first peer reviewed CONSORT (Consolidated Standards of Reporting Trials) reporting guideline specifically targeted at children and adolescents—the CONSORT-Children and Adolescents (CONSORT-C) 2026 extension[8] builds on the recently updated CONSORT 2025 statement.[9 10] CONSORT-C addresses a longstanding gap. Although many CONSORT extensions exist for specific trial designs, interventions, or outcomes, none previously focused on the unique methodological, ethical, and developmental considerations of trials involving children and adolescents. As a result, important aspects such as consent and assent processes, age appropriate outcomes, details of interventions, harms, and burdens on participants, including the impact on age associated activities such as school absenteeism, are often reported inadequately or not at all.[11-13] These omissions limit interpretation and reduce the value of trials for practice and policy.

CONSORT-C introduces 13 additional reporting items for randomised controlled trials in children and adolescents across

The checklist provides a practical tool to ensure paediatric specific problems are reported clearly and consistently

conditions, interventions, and settings. The items are intended as a minimum reporting standard, harmonised with CONSORT 2025, and relevant across the full paediatric age range. The extension specifically draws attention to issues commonly under-reported: how eligibility criteria relate to age and development; whether outcomes reflect the priorities of children, adolescents, and families; how harms, discomfort, and missing data are dealt with; and how baseline characteristics and intervention delivery vary by age.

Added value

The credibility of CONSORT-C is strengthened by its developmental process. The guideline followed the recommendations of the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network, incorporated evidence from systematic reviews and recent literature, and used an international Delphi process with prespecified consensus thresholds. The Delphi process was followed by a consensus meeting, collaborative writing of an explanation and elaboration paper, and pilot testing. Notably, CONSORT-C was developed alongside SPIRIT-C, the corresponding protocol reporting extension.[14] This alignment supports the transparency of a trial's lifecycle and highlights how reporting guidance also influences the planning and conduct of trials.

What most clearly distinguishes CONSORT-C is the active involvement of young people and family caregivers throughout its development. Youth generated and youth endorsed reporting items bring forward perspectives often overlooked, despite children, adolescents, and families bearing the burdens of participation.[15] This approach reframes transparent reporting as a responsibility owed not only to journals, regulators, and colleagues but also to participants and their families. Although CONSORT-C improves transparency around assent and consent, additional support mechanisms, such as peer guidance for adolescents, may further help navigate complex decisions in trials with potentially burdensome or high risk interventions.[16 17] While not strictly a reporting issue, acknowledging these ethical nuances can inform interpretation of enrolment patterns and the perspectives of participants. In doing so, CONSORT-C aligns with wider international efforts to strengthen patient and public involvement, uphold children's and adolescents' rights, and improve ethical accountability in health research related to children and adolescents.

Towards better reporting quality

The implications of CONSORT-C extend across the research community. For researchers, journals, and peer reviewers, the checklist provides a practical tool to ensure paediatric specific problems are reported clearly and consistently. However, endorsement alone is unlikely to be enough, as experience with other reporting guidelines shows that mandatory submission of a checklist and verification by editors or peer reviewers are often required.[18 19] Funders and regulators can use CONSORT-C to set expectations for transparency and completeness, reinforcing reporting quality as a marker of trial value. For clinicians, guideline developers, and systematic reviewers, improved reporting should increase confidence in the relevance and reliability of trial findings. For children, adolescents, and families, it clarifies how evidence informing their care and treatment is generated.

Caution, however, remains necessary. Reporting guidelines cannot correct poor trial designs, inadequate sample sizes, inappropriate outcomes, or ethical or practical challenges in participation. Full implementation may be more challenging for small trials with limited funding or for research teams working in resource constrained settings, where structural factors can hinder adherence to detailed reporting standards.

Despite these challenges, CONSORT-C represents an important step towards reducing research waste and unfruitful burdens on children and adolescents. It makes explicit what should already be expected: that trials involving children and adolescents meet reporting standards that reflect their unique complexity, diversity, and ethical considerations.

Naqash Javaid Sethi
Naqash.javaid.sethi.02@regionh.dk
Ulrikka Nygaard
Kjeld Schmiegelow
Christian Gluud
See bmj.com for author details

Cite this as: *BMJ* 2026;392:s311

Find the full version with references at http://dx.doi.org/10.1136/bmj.s311

Adherence to legislation and recommendations to publicly post protocols and results of post-authorisation studies registered with the European Medicines Agency

Ramezani P, Erviti J, Doshi P, Prugger C

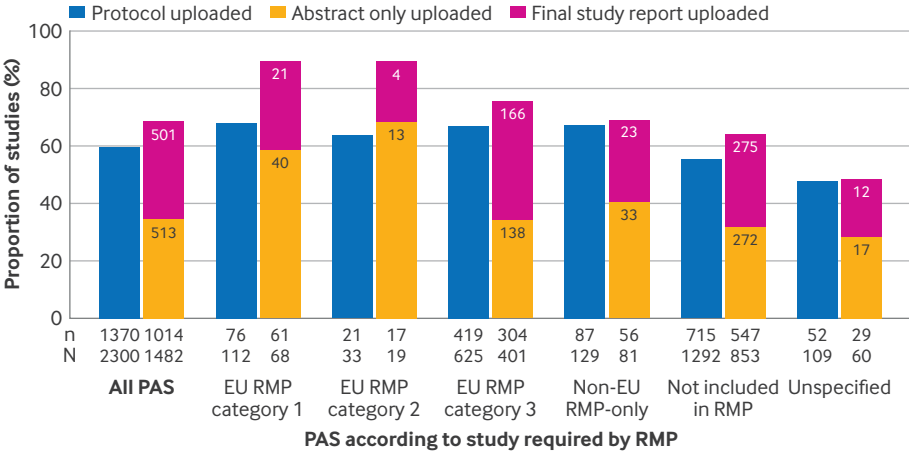
Cite this as: *BMJ* 2026;392:e086693
Find this at doi: 10.1136/bmj-2025-086693

Study question Do post-authorisation studies registered with the European Medicines Agency (EMA) adhere to legislation and recommendations to publicly post protocols and results?

Methods This cross sectional study used data registered since November 2010 and extracted from the EMA Catalogue of real world data studies in February 2024. EU legislation requires EU Risk Management Plan (RMP) category 1 and 2 studies to upload the protocol and results to the catalogue. The EMA also recommends uploading the protocol and results for all other registered post-authorisation studies, including EU RMP category 3 studies, non-EU RMP-only studies, and those not included in an RMP. Main outcome measures were the public availability of protocols (for ongoing and finalised post-authorisation studies) and results (for finalised studies).

Study answer and limitations Overall, protocols were available for 1370 (59.6%) of 2300 ongoing and finalised post-authorisation studies, and results were available for 1014 (68.4%) of 1482 finalised studies. According to RMP requirements, protocols were available for 76 (68%) of 112 EU RMP category 1 studies, 21 (64%) of 33 EU RMP category 2 studies, 419 (67.0%) of 625 EU RMP category 3 studies, 87 (67%) of 129 non-EU RMP-only studies, and 715 (55.3%) of 1292 studies not included in an RMP. Results were available for 61/68 (90%), 17/19 (90%), 304/401 (75.8%), 56/81 (69%), and 547/853 (64.1%) studies, respectively. This study provides only a snapshot of the assessed adherence.

What this study adds Post-authorisation studies registered with the EMA insufficiently adhere to legislation and recommendations to make protocols and results public.



Proportions of finalised and ongoing post-authorisation studies (PAS) that made protocol public and proportions of finalised PAS that made abstract only and final report public. RMP=risk management plan

Funding, competing interests, and data sharing
This study was unfunded. PD has received grants from the US Food and Drug Administration (through University of Maryland M-CERSI) and Arnold Ventures and is senior editor, investigations, at *The BMJ*. Data and code are publicly available.

MORE RESEARCH ON BMJ.COM

Prognosis of respiratory infections
Jordan RE, et al. Prognostic score for predicting respiratory admissions among patients with chronic obstructive pulmonary disease in primary care: development and validation in population cohorts (Birmingham Lung Improvement Studies (BLISS))
BMJ 2026;392:e084521. http://dx.doi.org/10.1136/bmj-2025-084521

Cervical cancer risk after HPV vaccination
Wu S, et al. Extended follow-up of invasive cervical cancer risk after quadrivalent HPV vaccination: nationwide, register based study
BMJ 2026;392:e087326. http://dx.doi.org/10.1136/bmj-2025-087326