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Observational research in epidemic settings: a roadmap to reform

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ABSTRACT

Observational studies are critical tools in clinical research and public health response, but challenges arise in ensuring the data produced by these studies are scientifically robust and socially valuable. Resolving these challenges requires careful attention to prioritising the most valuable research questions, ensuring robust study design, strong data management practices, expansive community engagement, and access and benefit sharing of results and research materials. This paper opens with a discussion of how well-designed observational studies contribute to biomedical evidence and provides examples from across the clinical literature of how these methods generate hypotheses for future research and uncover otherwise unattainable insights by providing examples from across the clinical literature. Then, we present obstacles that remain in ensuring observational studies are optimally designed, conducted and communicated.

INTRODUCTION

High-quality biomedical research is key for ensuring effective treatment and epidemic response: poor-quality evidence harms patients, undermines public trust and diverts resources. While randomised controlled trials (RCTs) are the gold standard for answering questions about treatment efficacy in tightly controlled settings, high-quality observational studies offer valuable advantages for answering an array of clinical questions. First, observational studies deliver evidence rapidly, efficiently and ethically in settings where RCTs are impractical or raise ethical concerns.[1] Second, observational studies' scope of inquiry extends beyond quantifying potentially causal associations to address non-experimental questions that hold direct relevance to patient care and epidemic response.[2] As with ongoing developments in RCT methodology, significant resources are needed to strengthen observational research methods, particularly in epidemic settings, where the urgent nature of an unfolding crisis demands robust evidence on which to base public health and policy recommendations. By harnessing the full potential of both observational and experimental approaches, we can substantially enhance the quality and generalisability of clinical evidence for global benefit.

This paper opens with a discussion of how well-designed observational studies contribute to biomedical evidence and provides examples from across the clinical literature of how these methods generate hypotheses for future research and uncover otherwise unattainable insights by providing examples from across the clinical literature. Then, we present obstacles that remain in ensuring observational studies are optimally designed, conducted and communicated. These challenges occur throughout the research lifecycle ranging from technical questions of study design to dwindling community engagement during and after outbreaks. Finally, we provide actionable solutions to many of these problems.

Where does high-quality clinical evidence come from?

The classic 'evidence hierarchy' pyramid places observational studies at the bottom, then experimental trials, which are topped by critical appraisals (primarily of RCTs) (figure 1A). This structure implies study designs lower on the pyramid are less reliable due to the influence of confounding and other biases. Research insights derived from RCTs are considered unequivocally higher quality than those from observational studies, since randomisation substantially reduces confounding for assessing claims of causality between exposure(s) and outcome(s). Indeed, the influence of confounding is an important

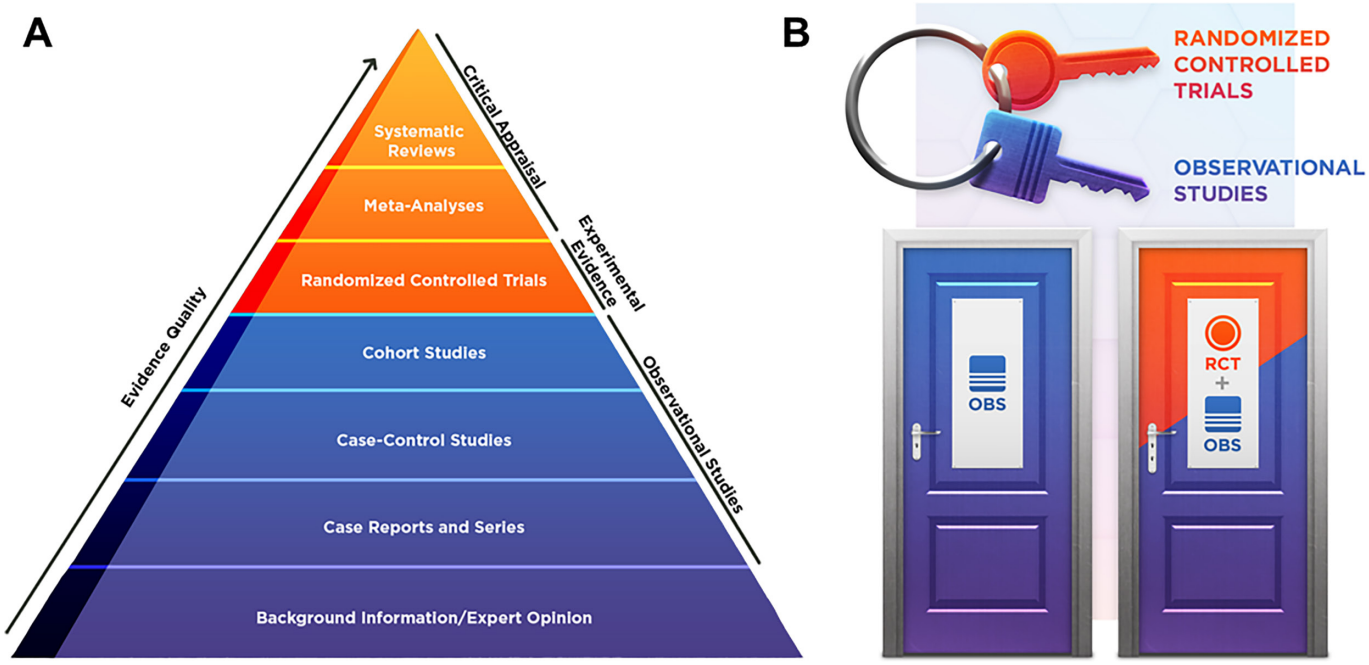

Figure 1 Sources of clinical evidence. (A) Traditional 'hierarchy of evidence pyramid' with evidence quality increasing from lowest at the bottom (background information/expert opinion) to highest (critical appraisal methods). (B) In this representation of evidence, observational studies (OBS) 'unlock' their own information, but they also are needed to 'unlock' evidence from randomised controlled trials (RCT).

consideration when assessing observational studies, especially those proposing causal relationships, as is the fact that it is not always possible to infer causality from observational data. However, RCTs, like observational studies, can exhibit bias from insufficient blinding of treatment assignment, measurement error, selection bias and residual confounding, among others, leading to invalid effect estimates that could be catastrophic if incorporated into clinical care or policy (eg, medical reversal).[3]

Substantial work has gone into developing analytical methods to reduce the impact of biases that may occur in observational research[4] and to overcome challenges of identifying causal relationships in observational studies. In fact, explicit comparisons demonstrate that well-conducted observational studies produce results comparable to RCTs, emphasising the importance of study quality over study design.[5–7] Here, we expand on the strengths of observational studies and their benefits to biomedical knowledge, particularly during epidemics.

The case for observational studies: more than just RCT alternatives

Observational studies have a well-established role in expanding our understanding of human health, generating novel hypotheses and informing the generalisability of RCT findings to real-world clinical practice. For example, natural history studies, a type of cohort study, provide information about clinical progression and generate longitudinal biological samples, leading to insights about the underlying processes and improved diagnostic tools and interventions. Natural history studies are crucial for learning basic information about a disease and characterising its long-term impact on health, particularly those in special populations. One of the world's largest natural history studies with over 1000 individuals enrolled as of 2022 has been instrumental in describing rare brain and spine tumours.[8]

Observational studies may provide evidence of an intervention's clinical benefit when RCTs are not available. Indeed, many lifesaving medications were initially tested using observational studies. For example, following Alexander Fleming's discovery of *Penicillium* mould's antibacterial properties, a case series reported the positive effects of penicillin in 10 British patients with *Staphylococcal* or *Streptococcal* infections. This series, plus the subsequent treatment and remarkable recovery of the first American patient to be treated with penicillin, convinced the pharmaceutical industry to mass produce the drug. Only then did the increased supply pave the way for RCTs.[9]

Clinically actionable data can be derived from observational studies in cases where randomisation of an exposure or intervention is ethically or practically infeasible. Non-pharmaceutical interventions (NPIs), like wearing face masks and social/physical distancing, present unique challenges to randomisation.[10] Blinding participants and providers to the intervention arm can be difficult, potentially introducing bias. Furthermore, participant non-adherence and the possibility of control group contamination through intervention spillover can obscure true effect sizes. And in practical terms, it is simply difficult to precisely measure how well and how

often participants wear masks during everyday life when social pressures regarding mask wearing may be at odds with the behaviour that participants are randomised to. These issues are particularly magnified for exposures like NPIs where the primary benefit manifests at the population level rather than on an individual basis, potentially weakening the overall evidence for its efficacy. One solution for this is carefully designed observational studies, basic research and thoughtful clinical judgement.

A particular strength of observational studies is their capacity to identify variables associated with an exposure and/or outcome that would otherwise be masked by or impossible to measure because of randomisation in an RCT. Case-control and cohort studies are especially useful for identifying disease biomarkers and factors influencing their levels. The Investigation of Profile Related Evidence Determining Individualized Cancer Therapy (I-PREDICT) cohort study serves as an example, elucidating molecular biomarker profiles that informed personalised cancer therapies, which correlated with improved outcomes.[11] Observational studies have yielded crucial insights that would likely be missed by RCTs due to stringent exclusion criteria such as the association between hepatitis C/HIV coinfection with heightened immune activation.[12] This link was only revealed through observational studies, as coinfection with hepatitis C was generally an exclusion factor in HIV treatment trials.

Finally, postmarket surveillance and real-world evidence of approved medical therapeutics rely on observational study methods to generate data. These studies provide additional insight into an intervention's longitudinal efficacy and outcomes as well as rare side effects and drug interactions. In addition, they characterise the real-world effectiveness of interventions at the population level, expanding our understanding of a treatment's benefits beyond the limited understanding of efficacy that is gained in tightly controlled research settings. They can further identify additional clinical endpoints that were unstudied or underpowered in the RCT(s) facilitating regulatory approval. For example, after the U.S. Food and Drug Administration approved ivacaftor, a transmembrane conductance regulator potentiator for the treatment of G551D-positive cystic fibrosis, observational studies uncovered an added benefit: ivacaftor usage reduced the incidence of pathogenic bacteria in these patients.[13] Moreover, drug utilisation studies, another form of postapproval observational studies, can reveal usage trends in understudied populations, including determining whether prescription patterns indicate potential drug abuse or improper prescribing.[14]

Observational studies in epidemic settings

The stakes involved in conducting research in epidemic settings are extremely high owing to the rapid spread of disease and the strain on resources and infrastructure. These unique pressures often necessitate observational studies as the cornerstone of early epidemic research. In this context, observational methods yield critical information that can influence policy decisions that would be otherwise unobtainable through experimental designs.

Observational studies can track disease spread by analysing demographics, travel history and contacts of infected persons. Transmission patterns of emerging diseases can be characterised by observational research, especially in early and well-defined clusters when the need for insights into transmission is paramount. During the emergence of SARS in 2003, the study of Amoy Gardens residents provided concrete evidence of SARS-CoV-1 transmission via airborne respiratory droplets in the absence of RCTs, and arguably in a context in which RCTs would have fared poorly as a strategy.[15] The use of epidemiological modelling provided evidence of the relevant transmission pathways, guiding control and prevention efforts.

Where RCTs are designed to assess outcomes over a shorter period, observational studies allow long-term observation of an infectious disease or its treatment. During the 2014–2016 Ebola virus (EBOV) outbreak, several longitudinal cohort studies of Ebola survivors demonstrated persistent EBOV RNA in semen, even up to 40 months post infection. Indeed, the Partnership for Research on Ebola Virus in Liberia longitudinal study detected intermittent EBOV PCR positivity following two negative tests, challenging the WHO's recommendation of when to discontinue semen testing in survivors.[16]

Observational studies with the appropriate methodology can also provide evidence of causality in epidemic settings where RCTs would be difficult to conduct. For example, the association between maternal Zika virus infection and infant microcephaly was first suspected in October 2015 given the contemporaneous increase in reports of these medical conditions in Brazilian surveillance data. Because causality could not be assessed using an RCT, Rasmussen *et al* proposed that 'the determination of a causal relationship would be expected to emerge from various lines of evidence, each of which suggests, but does not on its own prove, that prenatal Zika virus infection can cause adverse outcomes.'[17] Given the accumulation of observational evidence, the WHO declared Zika-related microcephaly a public health emergency of international concern in February 2016.

Based on this evidence, observational studies clearly have a vital and complementary role to RCTs for advancing biomedical knowledge (figure 1B). Their strengths lie in generating rapid, real-world evidence, addressing broad research questions and providing insights unobtainable through RCTs alone. Observational studies are often the only viable option for studying rare diseases, ethically challenging exposures, hard-to-reach populations and emerging epidemics. However, the diminished attention paid to strengthening observational studies' design and conduct in epidemic settings presents an inherent challenge to achieving insights robust enough to advance science and justify appropriate

Table 1 Challenges and recommendations for reforming observational trials in epidemic settings

Topic	Challenges	Recommendations
Research Priorities	► No current consensus on prioritising study funding and questions, leading to research duplication and waste. ► Need clear, early triggers for initiation and funding of observational research to answer priority questions.	► Convene a high-level stakeholder group to develop a primary set of pathogen-agnostic consensus questions for infectious disease epidemics and create a secondary set for each common pathogen type or transmission route, Funding agencies should revise mechanisms to prioritise funding of observational studies that align with priority research questions and be empowered to begin research early through well-articulated pre-emergency triggers through or continuing rapid funding mechanisms.
Study design	► Protocols and data standards used for observational studies can be significantly heterogeneous, decreasing the ability to compare results across settings. ► Observational studies can be prone to bias and inadequate size, resulting in low-quality, untrustworthy data. ► Need improved reporting processes for observational study methods and results, including how to convey limitations.	► Funding agencies should encourage participation in, or development of, research networks to standardise protocols and data standards, increase sample size and reduce duplication. ► Develop a broadly accessible, concise prestudy checklist to aid observational study design and bias assessment to select appropriate design, data standards and analysis methods before data collection begins. ► Study teams should develop standardised after-action reviews modelled after those used by the disaster response community to help assess successes, failures and areas for improvement.
Data management	► Absence of data standards, lack of dedicated data managers and insufficient technology/infrastructure to ensure data quality. ► Little or no dedicated funding to facilitate data collection, storage and availability for observational studies.	► Convene a high-level stakeholder group to define data elements and collaborate with data standards organisations for their development and implementation. ► Funding agencies should make available grant supplements to support data management activities, including dedicated data managers, appropriate software and storage and sharing costs.
Community engagement	► Observational research needs to engage with relevant community groups regarding study purpose, outcomes and research processes. ► Community trust for current and future studies can be jeopardised if trust building and trust management are overlooked by study team.	► Form an open, centralised collection of existing resources for researchers to better engage and involve communities in observational research. ► Educate researchers on opportunities for engagement, eliciting community participation and results dissemination beyond scientific publication.
Access and benefit sharing	► No clear, equitable and binding benefits (eg, data, samples, intellectual property) access and sharing agreements between researchers, funders and communities/countries where research is conducted. ► Absence of standardised templates for material/data transfer agreements can delay observational research and subsequent benefits development.	► Funding agencies should maintain centralised, open catalogue of the locations where all datasets from a grant were shared across its lifetime and require this information in awardee final reports. ► WHO pandemic treaty states parties and non-governmental organisations should develop standardised transfer agreement templates for use ahead of the next substantial outbreak.

policy changes. We next discuss the most pressing challenges to observational studies and provide examples and recommendations to overcome them (table 1). Achieving these reforms before future epidemics will aid the scientific community in producing robust, actionable data for policy-making and public health.

Develop harmonised research priorities

As examined above, observational studies can be vital early in epidemic settings for identifying key information such as risk factors for severe outcomes. However, formal methods to prioritise which studies get funded and what questions are answered are currently lacking. While this is also a problem for RCTs, the speed, ease

and reduced cost with which observational studies can be deployed relative to experimental trials is more likely to result in early study duplication. Consensus priority questions would decrease misallocation of resources and duplication of effort by targeting new observational studies to questions of importance or realigning existing studies and research networks to ensure adequate statistical power through fewer large studies instead of many underpowered ones. Research waste is a perennial issue in biomedical research,[18] but in the case of large epidemics, research waste and duplication of effort are particularly concerning given the limited availability of time and resources.

Priority setting requires (1) determining the most urgent and/or critical unknowns in an epidemic and (2) facilitating the conduct of fewer, highly robust studies to rapidly answer those questions. A high-level group (eg, WHO, InterAcademy Partnership) should develop a consensus list of research priorities answerable via observational studies as part of future updates to their preparedness plans (eg, WHO R&D Blueprint for Action to Prevent Epidemics). Top-down priority setting should be paired with bottom-up consultation with state and local public health agencies, who can provide guidance on research priorities that best address local public health needs at the onset of outbreaks. Public health emergency funding should then prioritise studies specifically addressing such questions. Furthermore, funding agencies should revise their mechanisms for when and how to allocate funds during epidemics. The US National Science Foundation's rapid response research grants are a longstanding initiative designed for urgent, priority research, including in emergencies and disasters, and several US National Institutes of Health institutes have similar mechanisms.[19] Finally, given the local nature of early outbreaks, empowering and funding local public health agencies to conduct observational research as cases arise could provide outsized benefits for disease containment and public health. Given the health and economic consequences of delayed action and the relatively low cost of observational research, pre-emergency triggers activated by funders (for higher-level response) and local agencies (for community-based response) rather than state or federal declarations could be developed to facilitate early studies targeting priority research questions.

Improve study design

Observational studies lacking careful design can be prone to concerns like methodological choices that bias estimates or fail to answer the stated question in the study population, findings that do not generalise to populations of interest, unstandardised data collection and processing, and incomplete reporting when published. The impact of low-quality observational data on epidemic response was illustrated by an early report on hydroxychloroquine that erroneously concluded the drug effectively treated COVID-19.[20] Extensive resources were spent attempting to replicate the results of the eventually retracted study, and many people received ineffective treatment.[21] Improving observational study design is key to improving future epidemic research.

Study quality can be improved through participation in and utilisation of research networks with unified protocols and data standards. Increased sample size and participant diversity achieved through such multisite studies would reduce the number of low-quality studies reporting conflicting results. Where heterogeneity exists, site-specific analyses can be used to identify local trends. Repurposing extant research networks and large cohort studies to understand new outbreaks is beneficial, as participants are already recruited and frequently have stored samples.[22] The rapid establishment of new networks can also be successful, as demonstrated during the COVID-19 pandemic.[23 24]

We also recommend the creation and adoption of a prestudy checklist that researchers could use during observational study design to facilitate standardisation and reduce bias, in addition to consulting or including epidemiologists and statisticians in the design process. Modelled after tools used to assess bias ex post,[4] an ex ante checklist would provide researchers with guidance from epidemiology and biostatistics in design and analytic approaches to decrease bias.[25 26] Such a checklist should be concise and comprehensible to researchers from other fields for maximum impact. Journals, which have previously demonstrated their leadership in improving the quality of clinical research and statistical reporting, could require researchers reporting observational studies to confirm that these tools have been used to guide study design.

Finally, to improve observational study quality, study teams must understand their own past successes, failures and areas for improvement. We recommend the widespread adoption of rigorous after-action reviews (AARs), which are standard practice in humanitarian response and preparedness communities and can improve team effectiveness.[27 28] AARs break down the procedures, protocols and analyses that did not work and highlight successful study design and analytic decisions. They also contain lessons learnt, which could help other researchers improve their own future activities. Funding agencies could require that AARs are submitted at the end of a grant at minimum, to ensure compliance.

Invest in data management

Data quality is a vital component of conducting and reporting observational studies, but dedicated funding, time and personnel for data management to guarantee high-quality data are often neglected.[29] These issues are compounded in resource-constrained locations and when data are collected by epidemic response personnel whose training in data collection varies in quality and who are already overburdened by their principal duties. Data collected for non-research purposes and absent or disconnected IT infrastructure make capturing

observational data challenging and its repurposing for research difficult to impossible.[30] Standardised data elements and electronic report forms, the lack of which is a longstanding challenge, may take months to develop and implement at an outbreak's onset. A 2022 report by the US Government Accountability Office highlighted the lack of common data standards, data interoperability and public health IT infrastructure as key challenges impacting national pandemic response.[31] Improving data collection and management for observational studies, and epidemic research more generally, will require heavy investments of time, money and physical and human resources.[29 32] However, in the short term, changes in how the research community approaches data management can lead to improvement in the quality and trustworthiness of observational data.

In line with the creation of research priorities and improving study design, we recommend the development of standardised data elements and collection forms in this inter-pandemic period, in addition to curated and annotated analytical code for data cleaning and processing alongside the data. Existing initiatives such as the 'first few hundred' strategy adopted by the UK in the 2009 influenza pandemic, which sets out primary and secondary research questions along with standard data elements for emerging outbreaks,[33] could be used by a high-level group convening to set research priorities as the basis for incorporating data management into their mission. Once a consensus list of data elements has been created, standards development organisations like the Clinical Data Interchange Standards Consortium could enable the development of data definitions and collection forms. Uptake and use of the created standards will require dedicated funding for investigators who will need to invest in the personnel and technology needed to implement these changes. We recommend the adoption of a grant supplement model by funding agencies, similar to those for climate network development[34] or data harmonisation for existing repositories.[35] These funds should be dedicated to providing ongoing data management throughout the lifetime of the grant and to support capacity development for quality data collection and management, including the transfer of skills, technology and equipment.

Require community engagement

Producing high-quality observational research requires active and continuous community engagement, especially in socially and economically disadvantaged populations that may be harder hit by epidemics. Researchers should seek input from affected populations regarding study objectives, design and implementation.[36] Scientists must meaningfully involve potential participants as equal partners in research, especially in epidemic settings where distrust of political and medical authorities or inconsistent public health messaging may hinder research. In some cases, a lack of inclusion can have serious consequences for a community that may have been obviated with greater patient involvement. For example, the exclusion of patients with hepatitis in HIV/AIDS antiretroviral trials led to long-term harms for patients with an extremely common coinfection as people living with HIV/AIDS began to live longer lives.[37] While it is improbable that scientists will be conducting research in the exact community where the next outbreak first occurs, the broader goals of science are advanced by promoting productive communication and collaboration with communities likely to be impacted by an epidemic. It is rarely enough that knowledge can be trusted by scientific standards alone; the organisations that produce that knowledge must also earn their position as trustworthy authorities, not only by fellow scientists but also—and especially so—in the eyes of the impacted communities.[38]

Given that observational studies are often conducted early in an outbreak, establishing and honouring community priorities and shared goals in any proposed research are key to building trust and sustaining researcher–community relationships.[39] This can be particularly important for observational studies because the community benefit may be less immediately obvious than, for example, a person receiving treatment in a clinical trial. Before fielding observational studies, researchers should plan to assess community knowledge and elicit feedback on study aims and output. Currently, available resources for improving community engagement more generally[40 41] can be leveraged for this purpose and, where possible, resources that are specific to, and have been influenced by, the priorities of the communities of interest should be employed.[42] We recommend forming an open collection of existing community engagement resources and educating researchers on opportunities for engagement beyond simply returning scientific results. Including experts from the social, behavioural and humanistic sciences can help ensure the collected resources are appropriate and useful, while not hindering rapid data collection in an emergency setting.

Prioritise access and benefit sharing

Almost a decade after the Nagoya Protocol on Access and Benefit Sharing[43] entered into force, the international consensus is that nations have material rights to their biological resources, including samples collected during research. Yet generating global, equitable benefits from observational studies in epidemic settings presents conflicting challenges. Removing data and samples from countries for research generally requires the development of material and data transfer use agreements (DTA/MTAs) which can slow data collection and analysis and, ultimately, the development of effective interventions. Conversely, the absence of equitable and binding access agreements can alienate communities or even lead to a breakdown in research altogether, as in 2007 when Indonesia refused to share samples of H5N1 influenza.[44] Therefore, researchers and funders must ensure that countries in which research is conducted receive timely

and equitable sharing of benefits such as tests, vaccines, therapeutics and data.

While many granting bodies have data sharing requirements to increase the scientific community's knowledge about and access to data, we recommend that funding agencies (1) require the location of all data shared throughout a grant's lifetime be listed in final reports, and (2) create and maintain an open, online catalogue of this information. Additionally, grant recipients and research institutions should engage relevant stakeholders in developing DTA/MTAs ahead of the next epidemic. For example, the WHO uses a Standard MTA for sharing human influenza viruses with pandemic potential,[45] which includes the terms of future use of resources and return of benefits derived from use of the samples to the provider. Standardised transfer agreement templates, which could be developed as part of the currently undernegotiation WHO treaty on pandemic prevention, preparedness and response would allow rapid deployment of observational studies while ensuring that data and biological materials are accessed on fair terms and used in a way that prioritises provider nations' needs.

CONCLUSIONS

These recommendations cover a range of strategies that, once addressed, will help strengthen observational studies that inform epidemic preparedness and response. Achieving them requires global action from investigators to institutions, national governments and international agencies. Given the importance of observational studies for providing critical early evidence, we believe the benefits of these reforms far outweigh their costs. Many of these policies, moreover, will improve the global observational study landscape outside of an epidemic, which will have important benefits for human and animal health. In the interpandemic world, reforming observational studies is a scientific, policy and ethical imperative.

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