Comparative Effectiveness Research 3

Ethical Implications of Poor Comparative Effectiveness Evidence: Obligations in Industry-Research Partnerships

Ilina Singh, PhD[1]
Huseyin Naci, MHS PhD[2]
Jennifer Miller, PhD[3]
Arthur Caplan, PhD[4]
Andrea Cipriani, MD PhD[1,5]

1. Department of Psychiatry and Wellcome Centre for Ethics & Humanities, University of Oxford, Oxford, UK
2. Department of Health Policy, London School of Economics and Political Science, London, UK
3. Yale School of Medicine, Yale University, New Haven, CT, USA
4. Division of Medical Ethics, New York University, Grossman School of Medicine New York, NY, USA
5. Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

Correspondence to

Professor Ilina Singh
Department of Psychiatry
University of Oxford
Warneford Hospital
OX3 7JX Oxford
UK
Email: ilina.singh@psych.ox.ac.uk

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Which treatment is best for me? This question is the beating heart of the clinical consultation. And yet, too often, the question is not answerable using currently available medical evidence on drugs and devices.

The first two articles in this Series documented the shortcomings of the current process for regulatory approval in incentivising the generation of comparative effectiveness evidence that is useful for patients, clinicians, and the wider health care system [reference to Papers 1 and 2]. The paucity of meaningful comparative data on drugs and devices before and after market entry means that clinicians and patients are both compromised in a crucial decision-making moment. In this commentary, we argue that measurable ethical obligations to patients should form the core of future comparative effectiveness research in an era of personalised medicine.

Trustworthy evidence is a foundational ethical obligation to patients and clinicians. In the clinical relationship, trust, evidence and respect for patient autonomy are critical to support an ethical process of shared decision-making and to achieve personalised guidance on the best treatment for each patient. A lack of evidence on comparative benefits and harms of multiple treatment alternatives means that clinicians are unable to provide patients with key information in the decision-making process. However, a lack of *trustworthy* evidence is potentially more harmful than a lack of evidence. When there is no evidence, clinicians may rightly draw on their clinical experience in offering guidance.[1] But when there is the appearance of evidence, where the methodology underpinning that evidence is in fact weak or, even worse, misleading, clinicians might feel obliged to override clinical experience to follow treatment algorithms.

Treatment algorithms have enabled advances in many fields of medicine,[3] and computerised decision systems can provide ongoing assistance to clinicians.[4] Developing trustworthy and valid treatment algorithms, however, is complex. Much has been written about the technical problems of algorithms (rubbish in, rubbish out).[5] Algorithms have also been criticised for perpetuating other biases found in science, including racial, ethnic and gender biases.[6] The 'black box' of the machine-learning algorithm means that clinicians cannot judge the strength or applicability of the evidence that is provided to inform decisions in the clinic. Nevertheless, the *trustworthiness* of the available supporting evidence is critical to effective use of treatment algorithms in the processes of patient and clinician decision-making.

Accountability to patients presents a further challenge when the trustworthiness of underlying evidence for treatments is obscure. Algorithms can often occlude the absence of comparative effectiveness evidence on drugs and devices.This raises the risk of wrong clinical decisions, which can further erode patient trust. It also risks the inefficient use of scarce resources. What can be done? One route is to build more robust and transparent partnerships with patients. Recent years have witnessed unprecedented involvement and engagement of patients in research. Rather than being viewed simply as passive recipients of medical expertise, patients are increasingly seen as partners in the development and appraisal of relevant and trustworthy evidence.[8] Governments and national funders are backing this view by mandating 'patient and public involvement and engagement' (PPIE) in research. Although it was never ethical to prioritise profit over patients, the PPIE mandate provides new authority to the ethical position that economic interests must be balanced against patient interests. Moreover, the process of balancing must be transparent. Therefore, if robust pre- and/or post-market research on rapidly approved new drugs and devices is not conducted, or if it is conducted hastily or badly, then patients have a right to know this, and they have a right to know who to hold accountable.

We encourage industry actors to take responsibility and to ensure that pre- and post-market research delivers quality, timely comparative evidence on their drugs and devices. Granted, industry has a primary obligation to its shareholders. Yet industry has and continues to benefit from partnering in collaborative research with public institutions, such as universities and national funders. A chief benefit for industry is access provided to patients for clinical trials. As a partner in research collaborations that are mandated to put patient interests at the heart of a research strategy, industry shares the obligation to invest in PPIE. Therefore, industry has an obligation to also heavily invest in the design of robust and relevant comparative studies. From the perspective of patients and the public, who may be sceptical of industry priorities, collaborations with industry in research are valuable only if they are also seen as ethical. The health care industry has unique moral duties to those in need. Industry actors must fulfil their accountability to public stakeholders beyond what they owe to financial shareholders.

Industry cannot and should not act alone in this regard. As outlined in the first two papers of this Series, regulators, governments, and payers also have obligations to public stakeholders [reference to Papers 1 and 2]. Moreover, patient organisations, consumer advocacy groups, researchers and academic institutions have roles to play. Ethics must be integrated in future collaborative partnerships. This is not an argument for 'ethics oversight' or support for obtaining research ethics committee approvals. It is an argument for recognising barriers to responsible and relevant research, and for conducting ethical analyses that will help to inform the negotiations required for industry-research collaborations to meet their obligations to patients.

One way to help ensure ethics is operationalised across the research landscape is to develop ethics measures and use them to benchmark the ethics performance of stakeholders. Studies have shown that benchmarking works, with one study finding pharmaceutical companies will improve their ethics-related practices within 30 days of receiving a low evaluation.[9] In many

universities, partnerships with industry are conceived as a business development opportunity. Increasingly this is also true of patient groups, who can receive substantial funding in exchange for collaborating with industry in designing trials. Bringing ethics into this infrastructure means that the public interest can be continually represented and that economic interests are not prioritised at the expense of patient interests or societal needs for better comparative evidence.

A sustainable infrastructure that supports ethics and governance of health data collection and data sharing should be required, and evaluated, as part of industry – academic research partnerships. Such an infrastructure will help to identify, anticipate and tackle challenges that create barriers to overcoming significant lapses in evidence. The generation of robust comparative studies to address patient need, using meaningful outcomes pre and post-marketing, is one pressing challenge. [reference to Papers 1 and 2]. Patients must be involved in work to make progress on this challenge, particularly in developing policies on personal health data obtained through digital and electronic sources.

Patient and public trust are essential to delivering the future of personalised medicine.[10] Trust is intrinsically important as well as practically essential: without trust, patients and their families will not be willing to share personal health data, and without such data, algorithms will not improve in their capacity to support personalised treatment decision-making in real-world clinical settings.

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Contributors

IS, HN and ACi conceived and designed the study. IS and HN wrote the first draft of the manuscript. ACi, ACa and JM contributed to the writing of the final version of the manuscript. All authors agreed with the results and conclusions of this Article.

Declaration of interest

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