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Access to Patient-Level Trial Data — A Boon to Drug Developers

Hans-Georg Eichler, M.D., Frank Pétavy, M.Sc., Francesco Pignatti, M.D., and Guido Rasi, M.D.

The provision of access to clinical trial results that include patient-level data is generating much debate. A growing chorus of transparency advocates is pushing for open access to these data,

making a case on the basis of respect for patients' altruism, the need to safeguard public health, and distrust in the integrity and completeness of published trial information.[1] We at the European Medicines Agency (EMA) have been actively engaged in this debate, and the EMA has recently published a draft of a policy that would make patient-level data in its possession publicly accessible. The principle of privacy protection will inform the EMA's policy and activities; robust and proportionate measures will be adopted to safeguard patients' privacy, in compliance with applicable data-protection legislation.[2]

Pharmaceutical-industry organizations, however, have expressed concern that "one of the risks to innovation is disclosure to competitors of companies' trade secrets and proprietary information that could allow others to 'free ride' off of the substantial investments of innovators"; they fear "degradation of incentives for companies to invest in biomedical research."[3]

Industry leaders have rightly complained about the unsustainability of the current drug development and business model. The timelines and costs of clinical drug development are increasing relentlessly, and the attrition rate of assets in development remains high. At the same time, growing cost pressures in all health care environments are forcing restrictions on drug use, aiming to limit coverage only to patients who can be expected to benefit from a given intervention and for whom that intervention is clearly cost-effective.

Contrary to industry fears, we argue that access to full — though appropriately deidentified — data sets from clinical trials will benefit the research-based biopharmaceutical industry. We predict that it will help to increase the efficiency of drug development, improve cost-effectiveness, improve comparative-effectiveness analysis, and reduce duplication of effort among trial sponsors.

First, access to the full data sets of completed studies will lead to improvements in the design and analysis of subsequent trials. For example, available information about numerous variables can be used to identify and validate prognostic factors. Relevant validated prognostic factors can then be selected for use in the stratification of subsequent trials to reduce unwanted variability, minimize type I and type II error rates, and inform prespecification of statistical modeling and

subgroup analyses. The identification and validation of factors that predict a response to treatment also allow subsequent trials to use active sampling (or "enrichment") to avoid having a treatment appear ineffective because the trial has been conducted in a diluted population; enrichment can effectively reduce the necessary sample size, since it makes larger treatment effects easier to detect.

The inclusion of patient-level data can result in comprehensive, quality-controlled databases that may inform future projects and research questions. Meta-analyses of patient-level data can suggest that a trial is not needed because of the weight of existing evidence; such analyses have been essential in validating surrogate end points and speeding up the clinical development of subsequent drugs for HIV and colorectal cancer, have reduced the need for blinded independent central review in cancer trials, and may lead to shorter efficacy trials of drugs to treat schizophrenia.[4] The availability of such data would also allow well-characterized historical controls to be used in drug development when randomized, controlled trials are not feasible because a disease is rare.

Second, lessons from past trials about the heterogeneity of treatment effects not only will streamline drug development but also may enhance a drug's value in the marketplace. Identification of a population with high unmet need in which a new treatment may be more cost-effective than other available treatments can aid sponsors during reimbursement negotiations.

Third, since several possible treatments for one medical condition are often available, comparative-effectiveness information is important to patients, prescribers, and sponsors seeking to position their products. Head-to-head randomized, controlled trials are considered the standard for assessing comparative effectiveness, but a dearth of such trials has led to increased use of indirect comparison methods that rely on data from placebo-controlled regulatory trials. Data from individual patients on both outcomes and covariates can alleviate some of the weaknesses of this approach, such as the need to make assumptions about heterogeneity and consistency of effect on the basis of the summary data that are currently in the public domain. In particular, within-trial and between-trial relationships among covariates and outcomes can be more clearly distinguished, and confounding by individual-level covariates can be investigated. Thus, wider access to patient-level data will allow sponsors to present more robust comparative-effectiveness information about their product soon after licensing and at a very limited cost as compared with that of head-to-head trials.

Finally, one of the inherent inefficiencies of data secrecy is the repetition of trials and projects that are doomed from the outset; drug developers may continue to pursue a given target even though clinical trials conducted by others have demonstrated the effort's futility. In at least one documented case, the availability of data from completed trials could have spared trial subjects a potential health risk and saved millions of research dollars.[5] With patients' health at risk and with limited resources for research, the high opportunity cost of clinical-data firewalls is difficult to justify.

The array of potential uses of patient-level data suggests that their wide availability will facilitate research and drug development. Thus, it is surprising that few drug developers have been sharing data voluntarily. Commonly voiced concerns have included the risk of jeopardizing the privacy of patients, the risk of misinterpretation of clinical trials due to inappropriate analyses, and the risk of disclosing commercially confidential information. We argue that standards for deidentifying personal data are available and continue to evolve to ensure adequate protection. Legally binding data-sharing agreements can provide an additional level of protection. We agree that a truly open approach carries a risk of inappropriate secondary data analysis and inappropriate conclusions — a risk that exists for any type of secondary analysis, regardless of the nature of the data. Two-way transparency is crucial to address this risk, since it allows critical review of any secondary analysis by the public and the EMA. Strong safeguards must be in place to ensure that the clinical investments and intellectual property of innovators are not jeopardized by "free riders."

Clearly, however, legitimate interests in intellectual property and the protection of private investments must be weighed against other legitimate interests, such as transparency regarding the outcomes of clinical trials and the protection of public health. Striking the right balance among all such interests is a duty for all responsible stakeholders involved, not just for regulators.

A managed-release environment that allows sharing of patient-level data while ensuring patient privacy would create a

level playing field for all stakeholders. What is sometimes labeled as "free riding" may ultimately pay dividends for innovative companies and for public health. It is ironic that the organizations that most resist wider access to data are the ones that stand to benefit so much from greater transparency.

The views expressed in this article are those of the authors and do not necessarily reflect those of the European Medicines Agency or any of its committees.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

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The randomized trial is one of the most powerful tools clinical researchers possess, a tool that enables them to evaluate the effectiveness of new (or established) therapies while accounting for the effects of unmeasured confounders and selection bias by indication. Randomized trials, especially huge megatrials, have transformed medical practice. Thanks to randomized trials, we no longer, for example, treat acute myocardial infarction with lidocaine and nitrates. Instead we use rapid revascularization, anticoagulants, and antiplatelet agents, and during long-term follow-up we routinely prescribe statins, beta-blockers, and angiotensin-converting–enzyme inhibitors. But the reputation of randomized trials has suffered of late,[1] owing to reasonable concern about excess complexity, expense, and time required to recruit study participants, as well as inadequate representativeness. What good are trials if the results aren't applicable to real-world patients and if, because of excessive expense, they can be used to answer only a tiny fraction of our important clinical questions?

One possible solution is to look to observational registries for answers. Over the past 20 to 30 years, a number of professional societies, government agencies, private corporations, and independent researchers have established high-quality registries that collect standardized data from patients seen in a variety of settings. In cardiovascular medicine, for example, registries in the United States and abroad have collected vast amounts of data from patients with acute coronary syndromes, stable coronary disease, and heart failure, as well as from patients with rare diseases such as hypertrophic cardiomyopathy and patients referred for surgery, percutaneous invasive procedures, and device implantation. Investigators and public health officials use registries to describe practice patterns and trends, to identify outliers, and to detect safety signals. They often use registries to assess comparative effectiveness, too, but are forced to admit that purely observational findings may not be internally valid owing to the absence of randomization.

As debates about comparative-effectiveness research have intensified over the past few years, we find ourselves in a kind of intellectual trap: yes, in theory we would like to conduct more randomized trials, but in practice they are too complex and difficult to apply to many clinical questions. And, yes, in theory we could answer many questions at