Frank W. Moler, M.D.
Faye S. Silverstein, M.D.
University of Michigan
Ann Arbor, MI
fmoler@med.umich.edu
J. Michael Dean, M.D.
University of Utah
Salt Lake City, UT

Since publication of their article, the authors report no further potential conflict of interest.

1. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic–ischemic encephalopathy. N Engl J Med 2005;353:1574-84.

DOI: 10.1056/NEJMc1702364

Challenges for Small Biopharmaceutical Companies

TO THE EDITOR: Moscicki and Tandon (Feb. 2 issue)[1] present the challenges faced by small biopharmaceutical companies, particularly the small number of patients available for clinical trials involving rare diseases. In our opinion, these challenges are relevant across the whole spectrum of diseases, even the common ones. The "-omics" technologies are leading to an ever-better molecular characterization of diseases, taking into account not only clinical characteristics but also genomic and epigenomic ones. For example, for decades colorectal cancer was considered to be a homogeneous entity and was treated as such. However, as colorectal cancer becomes better categorized by its molecular characteristics (e.g., *KRAS* negative–*BRAF* V600E positive), we may end up with many different types of colorectal cancer, some of which have been discovered and are now being treated according to their molecular status.[2] In effect, this new understanding of colorectal cancer means that in the future each of these distinctive cancers could qualify as a rare disease, making the recruitment of patients for trials difficult and thereby triggering the need for new drug-development strategies.[3]

Nikolaos Evangelatos, M.D.
Paracelsus Medical University
Nuremberg, Germany
nikos.evangelatos@gmail.com
Angela Brand, M.D.
Maastricht University
Maastricht, the Netherlands

No potential conflict of interest relevant to this letter was reported.

1. Moscicki RA, Tandon PK. Drug-development challenges for small biopharmaceutical companies. N Engl J Med 2017;376:469-74.
2. Perkins G, Pilati C, Blons H, Laurent-Puig P. Beyond KRAS status and response to anti-EGFR therapy in metastatic colorectal cancer. Pharmacogenomics 2014;15:1043-52.
3. Evangelatos N, Reumann M, Lehrach H, Brand A. Clinical trial data as public goods: fair trade and the Virtual Knowledge Bank as a solution to the free rider problem — a framework for the promotion of innovation by facilitation of clinical trial data sharing among biopharmaceutical companies in the era of Omics and Big Data. Public Health Genomics 2016;19:211-9.

DOI: 10.1056/NEJMc1702644

TO THE EDITOR: Moscicki and Tandon suggest that small companies might use historical controls or surrogate end points to demonstrate the efficacy of a drug with small samples. However, the diseases they presented as possible targets for such an approach — Pompe's disease, Fabry's disease, and cystic fibrosis — support the principles of drug evaluation as now applied to rare diseases in adequately calibrated, randomized, controlled trials (RCTs). Sample size depends on effect size. When the effect size is large, a very small sample allows measurement of efficacy: there is no need to conduct an RCT to evaluate the efficacy of a parachute. Similarly, the use of an intermediate (surrogate) end point may be convincing when the treatment effect for this end point is so huge that there is almost no doubt that it will translate to clinical benefit for patients.

We believe that there need not be exceptions to the quality of an RCT because of the size of the pharmaceutical company conducting it or because the disease is rare. Experimental designs and modeling techniques that optimize trial designs should be developed[1,2]; regulatory agencies might encourage high-quality research in this area.

Catherine Cornu, M.D.
Behrouz Kassaï-Koupai, M.D., Ph.D.
Hospices Civils de Lyon
Lyon, France
catherine.cornu@chu-lyon.fr

Michel Cucherat, M.D., Ph.D.
Université Lyon 1
Lyon, France

No potential conflict of interest relevant to this letter was reported.

1. Cornu C, Kassai B, Fisch R, et al. Experimental designs for small randomised clinical trials: an algorithm for choice. Orphanet J Rare Dis 2013;8:48.
2. Nony P, Kurbatova P, Bajard A, et al. A methodological framework for drug development in rare diseases. Orphanet J Rare Dis 2014;9:164.

DOI: 10.1056/NEJMc1702644

THE AUTHORS REPLY: We agree with Evangelatos and Brand that the promise of "-omics" profiling for therapeutic decision making is exciting. It is also true that high-throughput "-omics" technologies may allow for more informative characterizations of disease that will better predict both the clinical course of an individual patient and the treatment effect derived from new and existing therapeutic interventions.[1] This point is illustrated in our article in the discussion of cystic fibrosis. However, significant challenges remain regarding the clinical application of molecular tumor profiling, especially for situations in which the mutation of interest is infrequently detected. Currently, various clinical trial designs are being developed to address both the statistical and the clinical challenges involved in the treatment of cancer.[2,3]

In response to Cornu et al.: We are concerned that there may be a misperception that we meant to imply that small biopharmaceutical companies can simply use historical controls or surrogate end points to demonstrate the safety and efficacy of their products. Rather, we agree with Cornu et al. that the RCT should always be the preferred choice when the goal is to demonstrate the safety and efficacy of a therapeutic intervention, irrespective of the size of the biopharmaceutical company. Our goal in the article was to present the variety of approaches (including the use of historical controls and surrogate end points in studies of rare diseases) that have been used by small biopharmaceutical companies. Regarding the use of historical controls, these are useful only in special circumstances, when placebo controls are particularly problematic, when an objective, well-defined, end point is available, and when a large treatment effect is anticipated. It should also be noted that historically, small biopharmaceutical companies have turned to the treatment of rare diseases because the development of related trials is perceived to be less costly and regulatory authorities may exercise greater flexibility when reviewing clinical development programs for rare diseases.[4]

Richard A. Moscicki, M.D.
Food and Drug Administration
Silver Spring, MD
richard.moscicki@fda.hhs.gov

P.K. Tandon, Ph.D.
Ultragenyx Pharmaceutical
Novato, CA

Since publication of their article, Dr. Tandon reports being an employee of Ultragenyx Pharmaceuticals. No further potential conflict of interest was reported.

1. Michael CM, Nass SJ, Omenn GS, eds. Evolution of translational Omics: lessons learned and the path forward. Washington, DC: National Academic Press, 2012 (https://www.nap.edu/catalog/13297/evolution-of-translational-omics-lessons-learned-and-the-path-forward).
2. Polley MY, Freidlin B, Korn EL, Conley BA, Abrams JS, McShane LM. Statistical and practical considerations for clinical evaluation of predictive biomarkers. J Natl Cancer Inst 2013;105:1677-83.
3. Kummar S, Williams PM, Lih CJ, et al. Application of molecular profiling in clinical trials for advanced metastatic cancers. J Natl Cancer Inst 2015;107(4):djv003.
4. Sasinowski FJ. Quantum of effectiveness evidence in FDA's approval of orphan drugs. Ther Innov Regul Sci 2012;46:238-63.

DOI: 10.1056/NEJMc1702644

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere.

Letters accepted for publication will appear in print, on our website at NEJM.org, or both.

Please note the following:

- Letters in reference to a *Journal* article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article.
- Letters not related to a *Journal* article must not exceed 400 words.
- A letter can have no more than five references and one figure or table.
- A letter can be signed by no more than three authors.
- Financial associations or other possible conflicts of interest must be disclosed. Disclosures will be published with the letters. (For authors of *Journal* articles who are responding to letters, we will only publish new relevant relationships that have developed since publication of the article.)
- Include your full mailing address, telephone number, fax number, and e-mail address with your letter.
- All letters must be submitted at authors.NEJM.org.

Letters that do not adhere to these instructions will not be considered. We will notify you when we have made a decision about possible publication. Letters regarding a recent *Journal* article may be shared with the authors of that article. We are unable to provide prepublication proofs. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal*'s various print and electronic publications and in collections, revisions, and any other form or medium.