

A conversation with Professor Arti Rai, January 6, 2016

Participants

- Professor Arti Rai – Elvin R. Latty Professor of Law, Duke University, and Co-Director, Duke Law Center for Innovation Policy
- Nick Beckstead – Program Officer, Scientific Research, Open Philanthropy Project

Note: These notes were compiled by the Open Philanthropy Project and give an overview of the major points made by Professor Arti Rai.

Summary

The Open Philanthropy Project spoke with Professor Arti Rai of Duke University as part of a general conversation about policy research and advocacy related to the regulation of late-stage biomedical research and development. Conversation topics included clinical trial data sharing, advocacy, organizations working in this area, and other people to talk to.

Clinical trial data sharing

A report published by the Institute of Medicine (IOM) in January 2015 details the ways in which increased clinical trial data sharing could be used to advance biomedical research and ensure that drugs on the market are performing as marketed. Supporting work to increase data sharing is a potentially high-impact, near-term funding opportunity. Barriers to progress in this area include lack of funding, lack of entrepreneurial spirit, and lack of agreement on key issues such as privacy and informed consent.

Public and private funders including the National Institutes of Health (NIH) and biopharmaceutical companies seem to have a high level of commitment to data sharing in an abstract sense, but the high costs associated with convening all relevant parties to create common data standards to address matters of privacy and consent have contributed to slow progress on this issue.

Potential interventions would include:

- Creating template language for obtaining informed consent from patients for sharing their data.
- Political advocacy to convince public funders such as NIH to pursue increased data sharing.
- Creating the necessary infrastructure to increase data sharing, such as common data standards and interoperability. There is a high need for funding in this area.
- Advocacy and research to better define intellectual property.

Informed consent

Many consent forms that have been used in past clinical trials allowed data sharing only for the trials for which consent was given. New consent forms will need to be created to increase the amount of data sharing to which people consent, and it remains to be determined whether exceptions to informed consent requirements can be applied retroactively to past consent forms. For example, if data can be de-identified, then informed consent is no longer a problem. However, barriers to de-identification include high cost and lack of agreement about how to best de-identify data.

Creating a template

Multi-Regional Clinical Trials: The MRCT Center of Brigham and Women's Hospital and Harvard (MRCT) might be a good organization to work on creating a template informed consent document.

Selection bias

There is concern that including increased data sharing in informed consent documents may cause selection bias in clinical trial participants if participants who do not agree to the template language are excluded from the trial.

Opposition to data sharing

Opponents of data sharing sometimes take advantage of logistical hurdles, such as common data standards and interoperability, and the lack of agreement on issues such as privacy, informed consent, and intellectual property in order to avoid sharing data.

Intellectual property

Intellectual property rights can be claimed when someone has information about a drug that suggests the possibility of a new use. It is legitimate to maintain confidentiality in order to patent the new use of the drug. However, this channel can also be misused to conceal information that does not fall under the "new use" category, without providing an explanation as to why the data cannot be shared. For example, the European Medicines Agency has decided that as of this year, it will make clinical trial data publicly available. This data will be only lightly redacted to remove patient data and some of the information that is considered trade secret information. Many people in industry oppose the EMA decision. Industry may claim a large amount of information as trade secrets to prevent it from being shared.

Funding for both advocacy and research will be needed to overcome this issue. More research will need to be conducted in order to create a system in which pharmaceutical companies share an adequate amount of data but are able to benefit

from keeping certain trade secrets. This could be done, for example, by employing a researcher to review a confidential form of the data that a company claims is trade secret information and determine whether this is reasonable in each case.

Defining trade secret information

Aside from the “new use” category, which has a clear function in protecting the ability to patent, it is unclear what should qualify as trade secret information. Claiming “roads not taken” as trade secrets may provide a slight competitive advantage, but creates waste in the system by causing other researchers to waste money pursuing the same unsuccessful ideas.

Defining an appropriate exemption for trade secrets is an achievable goal. But because the stakes are high, litigation may eventually be necessary in order to clearly define trade secrets.

Advocacy

21st Century Cures Act

The 21st Century Cures Act, which was passed by the US House of Representatives in 2015, would enact large-scale reforms of FDA and policy surrounding intellectual property. One of the main goals of the initiative is to shorten the timelines of FDA clinical trials. But FDA has already invested a fair amount of effort in creating accelerated pathways through which many drugs are now being approved.

There is not a major need for advocacy for the 21st Century Cures Act because the pharmaceutical lobby is advocating strongly for it. However, the initiative includes adaptive regulation, which involves putting a drug on the market before it has proven safe and effective in clinical trials and doing post-marketing surveillance to track safety and efficacy. While the pharmaceutical lobby is pushing for adaptive regulation, it does not always advocate as strongly for the post-marketing surveillance element, and additional advocacy may be necessary to ensure that drugs on the market are safe and effective.

Policy related to biologics

Advocacy will be needed to reduce high costs associated with market exclusivity and the delay in bringing biosimilars to market.

Market exclusivity

The way in which market exclusivity is allotted to different classes of drugs is not very systematic, and will need to be updated. This is a long-term advocacy goal.

In the US, small-molecule drugs get 5 years of market exclusivity while biologics get 12 years. This creates incentives for pharmaceutical companies to do more work on biologics, which tend to be more expensive to create.

Biosimilars

Biosimilars, which would reduce costs by acting as generic competition for biologics. As a long-term goal, gaining a better understanding of biologics and the manufacturing process through which they are produced would be key to reducing drug costs. Pooling information about the mechanisms for manufacturing biologics would enable biosimilars to be put on the market as soon as the patent and market exclusivity expire, but these mechanisms are typically kept as trade secrets and patent laws do not require them to be disclosed. An act of Congress would be necessary to change these patent laws, and if the laws were changed to require more information to be disclosed, developers of biologics may elect to forego patents and rely on their 12-year market exclusivity in order to skirt disclosure requirements.

Michael Tarlov, the division chief of biomolecular measurement at the National Institute for Standards and Technology (NIST), is working on understanding and standardizing mechanisms for manufacturing biologics in order to hasten the production of biosimilars after the expiration of patents and market exclusivity.

Rescue drugs

Professor Rai is interested in pursuing drugs that have failed to reach their clinical endpoints in phase II clinical trials but were proven to be safe. Failed molecules are typically abandoned, but she believes that they could be used to develop new drugs more cheaply, because the research to establish their safety has already been conducted. Increased transparency concerning the reasons a drug failed and what its mechanism of action is could enable scientists to apply the drug to a different disease that acts via the same pathway.

NIH's National Center for Advancing Translational Sciences (NCATS) is providing this transparency by acting as a trusted intermediary that receives information from pharmaceutical companies about failed molecules and makes a small amount of that information public so that scientists can consider alternative uses. So far, NCATS has provided information about 10 molecules to new investigators who will attempt to revive the drugs, and one of these drugs has been successfully taken through phase 2 trials. If a drug made from a failed molecule is effective, a new use patent would provide sufficient protection against competition because there is no generic molecule on the market.

Opposition

Two arguments against the pursuit of rescue drugs are that this work should be accomplished by market pressures and that failed molecules may have had problems apart from not reaching their clinical endpoint, and should be abandoned. Professor Rai is unpersuaded by these arguments and would be interested to see more research in these areas.

Market pressures

Some people argue that work in this area is not needed because market pressures should encourage a rational pharmaceutical company to work on relicensing failed drugs, since there is money to be made from them. However, there seems to be a breakdown of full rationality here, and pharmaceutical companies are not always independently pursuing new uses of failed molecules. Reasons for this may include high transaction costs involved in selling drug information to other pharmaceutical companies and difficulties in creating agreements and addressing trade secrecy. The work that NCATS is doing is valuable because it avoids transaction costs and solves the issue of trust between new and old researchers by being a trusted intermediary.

The question of whether this work could be accomplished by market pressures alone has not been thoroughly investigated, and would require detailed qualitative empirical research. Henry Chesbrough has written a report based on interviews with people in the pharmaceutical industry. Professor Rai would like to see additional research along these lines.

NCATS' room for more funding

NCATS has been doing good work in this area, but it is cautious and is limited by funding. Additional funding could be used to expand its mechanism for rescuing failed drugs and to incentivize pharmaceutical companies to locate old data associated with failed molecules and have that work revived by someone who has ideas about how to use it in a different way.

Before considering expanding their work, it may be productive to conduct an intensive investigation including discussions with heads of research and development at pharmaceutical companies about whether this work is scalable enough to merit a large financial investment.

Determining an ideal budget

NCATS' work on rescue drugs has a budget in the tens of millions of dollars. This is both a small amount of funding and a small fraction of NCATS' total budget. Determining an ideal budget for its work on rescue drugs would require additional research like Henry Chesbrough's. This might involve finding and interviewing the people he interviewed, as well as talking to heads of research and development at pharmaceutical companies, to gain a better understanding of why projects are abandoned when they are and whether it is true that failed molecules typically have flaws apart from not reaching their clinical endpoint.

The work of Professor Stephen Paul could also be used to find an ideal budget for NCATS. Professor Paul has made strong arguments for why a rescue drug would be cheaper to take to market than a non-rescue drug. While most of the total expenditures in drug development are in phase 2 and phase 3 trials, Professor Paul

argues that the phase 1 trials that have been conducted may provide data to reduce the cost of phase 2 and 3 trials.

Organizations working in this area

MRCT

MRCT is a neutral convening organization in Boston associated with Brigham and Women's Hospital and Harvard University. At the request of the IOM, MRCT is working on implementing the high-level ideas about how to increase data sharing that were outlined in the January 2015 IOM report.

MRCT uses its own data as well as data drawn from a clinical data sharing network with Harvard-affiliated hospitals. It is working to expand this network, but will need additional funding to do so.

Patient-Centered Outcomes Research Institute

The Patient-Centered Outcomes Research Institute (PCORI), which was created as part of the Affordable Care Act, gives grants to investigators to locate clinical trial data and identify which drugs are effective and which are not. Part of this work involves finding ways to use existing data and make it more available to investigators. PCORI receives a moderate budget from the federal government.

Other people to talk to

- Dr. Barbara Bierer – Faculty Co-Director and Co-Chair, MRCT Executive Committee
- Christine Colvis – Director, Drug Development Partnership Programs, NCATS
- Michael Tarlov – Division Chief, Biomolecular Measurement, NIST
- Henry Greely – Director, Center for Law and the Biosciences; Professor (by courtesy) of Genetics, Stanford School of Medicine; Chair, Steering Committee of the Center for Biomedical Ethics; and Director, Stanford Program in Neuroscience and Society, Stanford Law School

*All Open Philanthropy Project conversations are available at
<http://www.givewell.org/conversations>*