In hunting for cures, ethics can strengthen clinical trials

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Clinical trials provide the cornerstone for evaluating the safety and efficacy of new drugs and therapies to treat disease. While trials are designed to follow established ethical and regulatory requirements, Alex John London, the Clara L. West Professor of Ethics and Philosophy at Carnegie Mellon University, said he believes there is room for improvement.

"Studies that lack social value aren't morally benign," said London, who is the first author on a study examining the ethics of clinical trial portfolios published in the August issue of The Hastings Center Report. "They harm patients, suck up resources that could be used elsewhere and [put additional] cost burdens on healthcare systems that are already strapped."

In Search of Treatments

People have the impression that drug development follows an orderly progression where the results of previous studies inform future research. According to London, this is an over simplification and is not always true. In reality, clinical trials are more complex.

The U.S. Food and Drug Administration (FDA) requires multiple studies to establish that a new treatment is safe and effective. These trials are initiated often at the same time to evaluate the safety of a drug and to look for potentially beneficial effects in multiple diseases. The different

studies that test the same drug constitute a portfolio of studies, analogous to the way that a group of investments constitutes a portfolio of investments.

Currently, individual trials are the focus of regulatory oversight and ethical scrutiny. But London and Jonathan Kimmelman argue that many of the same issues that determine the ethics of individual studies also apply to whole portfolios of studies. However, there is no mechanism in place for evaluating those portfolio-level concerns.

"This work came out of years of empirical research studying how drug developers and public sponsors actually test drugs," said Kimmelman, director of biomedical ethics unit at McGill University and co-author on the study. "I was surprised to discover that even if a drug for one disease shows promise of working in a different disease, trials are pursued simultaneously, making it impossible to economize the patient risk and burden."

Similarly, they argue that whether or not an individual trial is ethical can depend on the composition of the larger portfolio of studies in which that trial is included. In part, this is because the different studies needed to establish the safety and efficacy of a new drug play very different roles in drug development. The information produced by studies that occur early on in the development of a new drug is most useful when it feeds into subsequent trials that provide a more definitive test of the hypothesis that a new drug works.

Reducing Harm, Improving Outcomes

London said he believes that a number of organizations have a role to play, including the Institutional Review Boards (IRBs), drug regulators and data monitoring committees, which are charged with implementing the moral frameworks used to evaluate the safety and efficacy of clinical

trials. He said they could leverage their combined influence to broaden the base of information used to judge the strength of individual studies. These groups could consider whether individual trials are part of a portfolio of studies that is likely to generate socially useful information and either prohibit those trials that are not or ensure that portfolios are adjusted appropriately.

Similar to oversight bodies to promote ethics in clinical trials, London and Kimmelman also propose developing a portfolio-level data safety monitoring board. The board could facilitate planning, coordination and use of information within a portfolio. This approach could maximize the use of medical data, promote a fair and equitable distribution of cost and minimize the risk to patients.

"Bottom line, the current system of research, ethics and oversight is inadequate. The mechanisms in place for evaluating clinical trials are incapable of addressing a range of important issues unless they are changed to consider portfolios of trials," London said. "We hope now there will be increased scrutiny and attention given to what the best mechanism is to fill this gap."

London and Kimmelman published their study, titled "Clinical Trial Portfolios: A Critical Oversight in Human Research Ethics, Drug Regulation, and Policy," in the August issue of *The Hastings Center Report*.

More information: Alex John London et al. Clinical Trial Portfolios: A Critical Oversight in Human Research Ethics, Drug Regulation, and Policy, *Hastings Center Report* (2019). DOI: 10.1002/hast.1034

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