Time Has Come to Raise the Bar in Oncology Clinical Trials

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In the 40+ years since the war on cancer was announced, over a $105 billion and hundreds of thousands hours by researchers, statisticians, data managers, and clinical trial offices have been spent in oncology research. There has been amazing progress made in some cancer types during these four decades, however the process is still taking too many resources for too little gain. It is time to speed up this progress by, among other things, re-envisioning the goals, or the bar of oncology research.

The accompanying article for this editorial, Ellis et al provide specific guidance on how to raise the bar for oncology clinical trials in selected patient populations. This report of four working groups, convened by American Society of Clinical Oncology, challenges current clinical trial design to stop seeking only limited gains but to strive for clinically meaningful results that are “larger incremental gains than have been achieved in the past.” While the article identifies these goals as aspirational or stretch goals currently, it is time that trial designs with such high expectations be created, executed, and prioritized by funding agencies, companies, and regulatory agencies.

Throughout history, innovations have been influenced by stretch goals, or prizes, which to be achieved required meaningful advances to their fields. We know of Thomas Edison as the inventor of the incandescent light bulb not because he was the first to invent one (there were over 22 inventors of light bulbs before Edison) but because he was the first to create a bulb that lasted a meaning amount of time. Indeed, different organizations have been set up strictly to foster material, significant innovations, including government agencies (eg, the Defense Advanced Research Projects Agency [DARPA], responsible for early global positioning system and the Internet) and commercial entities (eg, Bell Lab, responsible for transistors, lasers, and charge-coupled devices; IBM Research Lab, responsible for hard disks, the modern automatic teller machine, and universal product code barcodes; and Palo Alto Research Center, responsible for the laser printers and graphical user interface).

Returning to clinical trials with high aspirations, the problem is that such trials are by definition meaningful (ie, they upset the status quo and require a different view of what is needed in and by a clinical trial). Two views that should be included in every new trial are the inclusion of “omics” and the use of adaptive trial design. The former provides information concerning which patient populations may benefit from the intervention, and the later uses such information to help properly select which patients for which treatment arm, thus reducing the total accrual requirements for the trial. Such trials have already been successfully executed in oncology, including the BATTLE (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination), the I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response With Imagine and Molecular Analysis 2), and the CUSTOM (Molecular Profiling and Targeted Therapy for Advanced Non–Small-Cell Lung Cancer and Thymic Malignancies) trials. Like many meaningful innovations, using such knowledge can make the phase III trial faster to complete, provide more and better information, and be less expensive to complete. These designs then fulfill the old Bell Labs motto: better, cheaper, or both. However, like all radical innovations, they also come with risks.

The first risk is that of lack of knowledge. As acknowledged in the article, validated biomarkers or companion diagnostics are not always present. It is difficult to hit a target when it is not certain where it is or if it is valid. This, not insubstantial risk, should be ameliorated in the near future as all major clinical research organizations are banking specimens, some of which are highly annotated, and as technology to analyze such specimens become faster, better, and cheaper.

The second risk is that the expectations of patients and regulatory agencies out strip the technical capabilities of achieving the aspirational trial goals. There are numerous examples of technologies that could not keep up with meaningful expectations, including the personal robots, the self-cleaning kitchen, and, until recently, self-driving cars. Thus expectations need to be tempered with reality.

However, saying that, there is a complementary risk of not striving hard or fast enough. The genius of Steven Jobs was not only that he was a consummate inventor but also that he understood how to create a future that customers wanted, even if they didn’t know they wanted it. Apple computer, without Jobs’ leadership, became an organization that concentrated on incremental improvement and it nearly entered bankruptcy. Today, Apple is acknowledged to be one of the most radically innovative firms in the world. This took risk taking, an understanding of customer’s desires, and a tight knowledge of underlying technologies. It is time that oncology clinical trials become less incremental and more innovative, striving for more, faster. Basically, it is time for them to invent the future of oncology care.

The final risk with striving for aggressive goals is in not understanding the need to manage the inevitable failures in a visible and collective manner. It is important that such failures not be a focus of blame but viewed as a set of lessons learned to improve the entire clinical trial process. For example, when Corning was creating the
200-inch mirror for the Mount Palomar Observatory, their first attempt failed. Rather than hiding it away, Corning put this disk in their Corning Glass Center for all to see, as a symbol of their persistence in the face of failure. Just as there is a need to build a learning system in health care, there is a need to link such a system to the design and conduct of meaningful clinical trials.

Given these risks, is it worthwhile striving for the aspirational goals laid out by Ellis et al. The answer to that question is an emphatic “yes.” Oncology clinical trials are at a major crossroads, one that comes infrequently in science. There is a need to completely re-envision what a clinical trial looks like, including the mandatory use of “-omics,” and adaptive design enabled by high-functioning systems and processes. There is a need to prioritize trials that are more clinically meaningful, even if they come with higher risks, because that is how one creates the future.

It will be difficult to reach the meaningful goals recommended by Ellis et al so there will need to be advocates from many areas. First and foremost should be patient advocates who provide the voice of the customer to clinical trials. Do not be satisfied with the status quo and remember to push clinical trialists to strive for more. Clinical trialists must be willing to take the risks associated with such trials but these risks can be ameliorated, at least in academic research, by more understanding university tenure and promotion policies. For trialists in industry, it is an opportunity to set the future direction of the entire industry, something that will allow for better, more meaningful treatments to patients sooner. For the regulators, such trials could be considered as pilots for new process of conducting clinical trials. But the ideas that were successful in the pilots should be incorporated in future trials. Finally, funding agencies must balance their research portfolios among maintenance, incremental, and radical trials. It has been well documented that the existing government funding system can discourage support for radical innovation. What might be required is a more DARPA approach, where answering high-risk questions are fostered and supported.

Finally, let me end with a quote from Lewis Carroll: “She generally gave herself very good advice, (though she very seldom followed it).” It is time to overcome this knowledge-doing gap by not only accepting the advice by Ellis et al but using it for the betterment of patients with cancer and cancer research.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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REFERENCES

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