May 28, 2014

Representative Fred Upton
2183 Rayburn House Office Building
Washington, DC 20515

Representative Diana DeGette
2368 Rayburn House Office Building
Washington, DC 20515

RE: 2nd White Paper -- 21st Century Cures: An Update on the President's Council of Advisors on Science and Technology 2012 Report on Propelling Innovation

Dear Chairman Upton and Representative DeGette:

Thank you for your recent endeavors to examine efforts in which Congress can provide additional direction to Federal agencies to accelerate the discovery, development, and delivery of innovative new treatments and cures, creating more jobs, and maintaining our nation's role as the innovation capital of the world. The Heart Rhythm Society looks forward to being a partner with you in developing the appropriate legislative framework in the next several months.

The Heart Rhythm Society (HRS) is a leading resource on cardiac pacing and electrophysiology. This specialty organization represents medical, allied health, and science professionals from more than 70 countries who specialize in cardiac rhythm disorders. HRS's overall mission is to improve the care of patients by advancing research, education and optimal health care policies and standards. Given that focus, HRS's agenda also includes the goals of discovery, innovation, and development with regard to scientific understanding and the technology that is so critical for our profession. HRS is uniquely situated to provide content expertise on clinical, scientific, and technology matters. In addition, HRS already has existing relationships with the Food and Drug Administration (FDA), other professional societies (such as the American College of Cardiology or ACC and the American Heart Association or AHA), the Centers for Medicare and Medicaid Services (CMS), and participates in collaborative approaches that define equitable and rational approaches to care, including in the development of multi-stakeholder scientific statements, professional society guideline documents, consensus statements, appropriate use criteria, etc.

DEVICE INNOVATION

In reviewing the information from the President's Council of Advisors on Science and Technology (PCAST) 2012 Report on Propelling Innovation, the HRS urges you to not only focus on pharmaceutical innovation but to also examine device innovation. As you know, many of our patients rely on key medical devices, such as implantable cardioverter defibrillators, or ICDs, to treat arrhythmias by shocking a dangerously racing heartbeat back into a normal rhythm. And, in our horizon scanning of key technologies for our patients, such as MRI-compatible/conditional cardiac implantable electrical devices (CIEDs), we are particularly interested in quicker, more efficient regulatory pathways for these and similar breakthrough technologies.

REGISTRIES

We agree with the PCAST report focus on post-approval studies and their ability to provide additional information. We strongly believe that professional societies, such as HRS, can be instrumental in developing and maintaining registries which can be useful post-approval tools. Thus, we hope that, as you examine these issues, you ensure that such activities can continue to flourish.

AGENCY COLLABORATION

Finally, while the PCAST report does not specifically address this, we hope that you will further consider potential collaboration between the FDA and CMS. For patients truly to have improved access to new medical technologies, the patients require both access to those products, as well as appropriate coverage or reimbursement. And, for many of the newly emerging technologies, there will need to be a system change in how technology is reviewed by FDA and reimbursed by CMS. For instance, during a recent conversation between HRS, FDA, and CMS, HRS was particularly interested in the CMS's and FDA's views of how best to develop remote monitoring technologies for those with cardiac implantable electrophysiology devices (CIEDs), such as pacemakers and implantable defibrillators. Evidence demonstrates that remote monitoring of these devices (by wireless and/or internet transmission) can enhance patient safety by allowing patients and their physicians the opportunity to closely monitor device function and medical conditions and, to intervene to provide clinical care. It also improves communication through use of real-time data. Clinical research is currently underway to further demonstrate the clinical utility of remote monitoring.[1] Both CMS and FDA acknowledged the difficult regulatory environment for remote monitoring, given that such monitoring requires a systems approach which requires interoperability among all key players (e.g., vendor, patient, and clinician), as well as a reimbursement model that has not been adapted to this new clinical activity of continuous follow up (not an office visit once every three months). Thus, for remote monitoring to be successful, many key health care components would need to come together seamlessly. For this and other reasons, we hope that you will also examine ways in which CMS and FDA can further work together to develop more of a systems approach to health care.

Again, we strongly appreciate your efforts in this area, and we look forward to continuing to work with you. If you have any questions or would like to discuss our recommendations further, please feel free to contact Laura Blum, Vice President of Health Policy at [redacted]

Sincerely,

[redacted]

Richard Fogel, MD, FHRS
President, Heart Rhythm Society

[1] Varma N, Brugada P. Automatic remote monitoring: milestones reached, paths to pave. Europace. 2013;15(suppl 1):i69-i71

AcademyHealth

June 5, 2014

The Honorable Fred Upton
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U.S. House of Representatives
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The Honorable Diana DeGette
Committee on Energy & Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
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Re: Comments on President's Council of Advisors on Science and Technology Recommendations

AcademyHealth is pleased to submit feedback to the Committee on Energy & Commerce on its 21st Century Cures initiative and specifically, the recommendations of the President's Council of Advisors on Science and Technology (PCAST) on strategies for propelling innovation in drug discovery. We represent the interests of more than 5,500 scientists and policy experts and 185 organizations that produce and use health services research to improve our nation's health and the performance of the health care and public health systems. Their work, largely funded by the federal government, is helping us understand and improve a complex and costly health care system so that we can achieve better outcomes for more people at greater value.

PCAST's recommendations for enhancing the speed of drug development, increasing drug safety and efficacy, and effectively incentivizing innovation are sound and if implemented, would contribute to the Committee's 21st Century Cures initiative. However, PCAST has neglected to address a critical component of drug development, one that arguably has the greatest impact on improving health—the health care delivery system itself. Discovery shouldn't end when a drug comes to market. Indeed, when a drug enters the health care delivery system, a different and equally critical type of research, health services research, helps us understand the drug's performance in the real world, determining for whom the drug works, in what settings, under what circumstances, and at what cost. In developing the 21st Century Cures initiative, we urge the Committee to consider the role of health services research in facilitating drug deployment and evaluating its performance across the general population. It isn't enough to ***develop*** cures. Understanding how to most effectively and efficiently ***deliver*** cures to patients has implications for health care quality, costs, access and ultimately patient outcomes.

The federal government has a longstanding role in supporting the health research continuum—from basic research to health services research (see Figure 1). In the same way the federal government built the interstate highway system from which all Americans benefit, the government supports health research and innovation that would not occur in the private marketplace alone and offers benefits to the nation as a whole. As highways are an engine for commerce, development, and expansion, health research is an engine for increased productivity, innovation, and value.

Figure 1: The Health Research Continuum

These components of the health research continuum work in concert, and each plays an essential role—any one type of research on its own cannot effectively or appreciably improve health. Take heart disease as one example…			
Basic research discovered the contributions of elevated blood pressure, elevated cholesterol, and tobacco use to heart disease.	**Clinical research** determined which treatments were safe and effective to treat hypertension, hypercholesterolemia, tobacco addiction, and to prevent and treat heart disease, in general.	**Population-based research** identified strategies to reduce the risks of heart disease in communities through non-medical interventions, such as reduction of trans fats in food and tobacco control measures to reduce smoking.	**Health services research** determined how to best deploy these discoveries to achieve the best health outcomes. This research helped identify who had the least access, what barriers existed, and innovative strategies to mitigate them. This research also led to new quality measures that are now used to report on the quality of cardiac care.

Source: *AHRQ: 15 Years of Transforming Care and Improving Health,* AcademyHealth, Jan. 2014. Available at: http://academyhealth.org/files/AHRQReport2014.pdf

The United States spent $2.8 trillion—17.2 percent of our economy—on health care in 2012. Health services research has shown we waste as much as 30 percent of what we spend on health care on unnecessary services, inefficiently delivered services, and missed opportunities for prevention.[i] Finding new ways to get the most out of every health care dollar is critical to our nation's long-term fiscal health, and health services research is our nation's research and development, or 'R&D,' enterprise for such innovations.

While medical research discovers cures for diseases, health services research discovers innovative cures for the health system. This research diagnoses problems in health care and public health delivery and identifies solutions (see Figure 2). Innovations from health services research can be used right now by patients, health care providers, public health professionals, hospitals, employers, and public and private payers to improve care today.

Figure 2: Contributions of Health Services Research to Quality Improvement

Thanks to health services research, we know that health care sometimes falls short…
An estimated 1.7 million hospital-acquired infections occur each year, leading to about 100,000 deaths.
Patients do not receive the care recommended for them by evidence. For example, patients with diabetes receive recommended preventive care only 21 percent of the time.
Health care is increasingly complex and for patients with multiple chronic conditions, poor coordination results in unnecessary tests, hospitalization, and readmissions. One study found that almost one-fifth of Medicare patients were re-hospitalized within 30 days.
Thanks to health services research, we know that falling short costs money…
In 2008, costs attributable to medical errors were estimated at $19.5 billion—more than half of the National Institutes of Health's annual budget. Medication errors alone cost as much as $2 billion each year—equivalent to the federal annual investment in health services research.
The average cost of care for a patient with a catheter-related blood stream infection is $45,000, costing up to $2.3 billion annually nationwide.
Medicare spends $12 billion a year on preventable hospital readmissions—more than double the discretionary budget of the Centers for Disease Control and Prevention.
Thanks to health services research, we have identified innovations that work…
Systematic reviews of adverse events have been instrumental in improving health care safety and the well-being of patients. For example, a report documenting the adverse events related to ephedra was instrumental in the withdrawal of the substance after a well-known baseball player died after using it. Another report documented the potential harmful side effects of atypical antipsychotics in the elderly, which led to a new FDA black box warning.
Implementation of computerized physician order entry could prevent between 570,000 and 907,000 serious medication errors each year.
Quality improvement approaches, including improved primary care, discharge planning, and follow-up care can prevent or reduce hospitalizations and rehospitalizations.

Federal investments in the Agency for Healthcare Research and Quality (AHRQ)—the federal agency with the sole purpose of supporting health services research—has created a wealth of knowledge about our health care delivery system. For example, Dr. David Penson of Vanderbilt University Medical Center used funding from AHRQ not to find the newest drug for the treatment of prostate cancer, but to maximize outcomes using the treatments already available and to get information about what works to patients and providers so they can make better decisions. His focus on innovation is to bring health services research to the frontiers of

personalized health decision-making in cancer treatment, where a patient can go to a website, type in demographic data, and see the likely outcomes for a range of treatments for their demographic. Such innovative tools will allow for patients to participate as informed parties in their health care decisions.

During his tenure as Executive Vice president and Chief of Medical Affairs for UnitedHealth Group, Dr. Reed Tuckson used health services research to make America's largest health company an industry leader in care improvement. One "extremely important" tool in Dr. Tuckson's evidence arsenal was AHRQ's *Guide to Clinical Preventive Services.* The guide summarizes evidence-based recommendations on the performance of medications, screening, and counseling developed by the U.S. Preventive Services Task Force—an independent, nongovernmental panel of primary care providers. The guide informs health care practitioners' and other stakeholders about existing evidence about what treatments work for whom, and is a critical resource for health plans such as UnitedHealth Group. "One of the unfortunate realities of science is that answers are not often black or white, but are made up of nuances and subtleties," said Dr. Tuckson. "The Guide provides a legitimate, trustworthy, and thoughtful scientific forum to evaluate evidence so that others can use it to make fundamental decisions that affect the health of millions of people."

Even with more, better, and faster drug discoveries, these innovations will fall short of their potential if we don't determine how to best deploy them to physicians and patients. Put plainly, health services research helps maximize the return on investment in basic and clinical research, ensuring that patients have access to and truly benefit from drug discoveries and medical advances. We look forward to working with the Committee to determine how to best to better integrate health services research into the 21st Century Cures initiative, and move biomedical discoveries from the bench, to the bedside, to the curbside and beyond.

If you have questions about these comments, please don't hesitate to contact Dr. Lisa Simpson, President & CEO of AcademyHealth, at [redacted].

[i] Institute of Medicine, Best Care at Lower Cost: The Path to Continuously Learning Health Care in America. September 2012. www.iom.edu/Reports/2012/Best-Care-at-Lower-Cost-The-Path-to-Continuously-Learning-Health-Care-in-America.aspx

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Comments by the American Society for Biochemistry and Molecular Biology to the Energy and Commerce Committee
Request for Comments on "21st Century Cures: An Update on the President's Council of Advisors on Science and Technology 2012 Report on Propelling Innovation"
June 10, 2014

Anyone who has ever received hospital care has benefited from the federal investment in biomedical research. The vaccines, drugs, medical devices and techniques that save the lives of millions of people on a daily basis often trace their origins to federally funded research. However, systemic flaws in the biomedical research enterprise, such as inconsistent funding and poor interactions among enterprise stakeholders, threaten the discovery, development and delivery of novel therapeutics to patients.

The American Society for Biochemistry and Molecular Biology has embarked on an initiative to move the biomedical research enterprise onto a more sustainable path. We have identified serious deficiencies in the three major enterprise stakeholders—academia, industry and government—and are committed to bringing together representatives of these stakeholder groups to find a way around the barriers that hinder the efficiency of the enterprise. We wrote a white paper on the topic and recently held a well attended panel discussion at a recent national meeting that brought together representatives from the different stakeholder groups to discuss the barriers to sustainability.[1] Our next step will be to further delve into the issues facing each stakeholder and come to an agreement on how best to break down barriers to cooperation.

A sustainable biomedical research enterprise not only benefits those working within the enterprise, but also those who depend on a functioning research system to discover, develop and deliver therapies for the variety of diseases afflicting humans today. Thus, we are delighted that the U.S. House Energy and Commerce committee is also addressing the critical issues confronting biomedical research today. Biomedical research has a long history of bipartisan support, and we are pleased that this tradition has continued in the current activities of the Energy and Commerce committee. Below are the ASBMB's responses to several of the questions posed in the "21st Century Cures: An Update on the President's Council of Advisors on Science and Technology 2012 Report on Propelling Innovation" white paper. As our expertise lies in discovery or basic research we have commented on the "Improving Drug Development and Discovery" recommendations made in the PCAST's "Propelling innovation in drug discovery, development and evaluation" report.[2]

Recommendation 1: Support Federal Initiatives to Accelerate Therapeutics
Recommendation 1A: The federal government should increase NIH funding to continue research on the underlying mechanisms of disease
The ASBMB strongly endorses the recommendation for increasing NIH funding. When taking inflation into account, the purchasing power of the NIH has been in decline since 2004. Because nearly 85 percent of the money appropriated to the NIH leaves its Bethesda campus, the decline in NIH funding is felt primarily by scientists across the country who use NIH money to create jobs and fund their research. Sequestration in 2013 magnified this loss and appears to have resulted in over 1,000 scientists losing

[1] ASBMB Public Affairs Advisory Committee. "Toward a Sustainable Biomedical Research Enterprise." 2013. http://bit.ly/1n4GOel
[2] President's Council of Advisors on Science and Technology. "Propelling innovation in drug discovery, development and evaluation." September 2012. http://1.usa.gov/1tIXn1G

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federal funding for their research and a general disillusionment with the state of the research enterprise.[3,4]

For a sustainable biomedical research enterprise to thrive, the federal government must regain its position as the enduring foundational investor in basic research. The first step toward this goal is to fund the NIH at $32 billion fiscal 2015 and then to make significant, predictable increases in NIH funding each year after that. To improve funding predictability, the ASBMB recommends instituting a cross-agency multiyear financial plan similar to the Department of Defense's Future Years Development Plan as suggested in the PCAST's "Transformation and Opportunity" report.[5]

However, increasing funding is not the only mechanism to improve the efficiency and output of the research enterprise. Significant barriers to efficiency and sustainability exist in how the biomedical workforce is trained and in the interactions among government, industry, and academia.[6] The ASBMB continues to address these problems through our work to establish a sustainable biomedical research enterprise, and we encourage the Energy and Commerce committee to examine the barriers put in place by the federal government that deter the movement of people, products and knowledge among research enterprise stakeholders as a means to improve efficiency and speed of the drug development process. For example, changes to laws and regulations that ease technology transfer and improve clinical-trial data sharing would allow industry, academia and the government to form closer ties and accelerate development of therapies.

Recommendation 1B: The federal government should vigorously support and fund the National Center for Advancing Translational Sciences at the NIH.

Translational research, research that bridges the divide between basic science and development, requires much time and money. The National Center for Advancing Translational Sciences was formed to specifically fund and promote research in this crucial aspect of the drug development pipeline.[7] The ASBMB supports efforts, such as those by NCATS, to ensure that groundbreaking discoveries are rapidly evaluated and translated to the pharmaceutical industry for development.

However, there is a delicate balance between funding for basic versus translational research. Basic research is a high-risk/high-reward endeavor that has the potential to make significant advances for improving human health. Translational research, on the other hand, takes the discoveries made by basic researchers to determine whether these discoveries can be developed into therapies and drugs. Thus, basic research provides the foundation that translational research is built on. Therefore, to maintain a robust engine of scientific discovery and development, the federal government should invest heavily in basic research to encourage foundational discoveries and ensure that any investment in translational research through NCATS does not come at the expense of basic scientists and their discoveries.

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[3] Berg, J. "The impact of the sequester: 1,000 fewer funded investigators." *ASBMB Today*. March 2014. http://bit.ly/TdeWvF

[4] American Society for Biochemistry and Molecular Biology. "Unlimited Potential, Vanishing Opportunity." 2013. http://bit.ly/1nXxAlH

[5] President's Council of Advisors on Science and Technology. "Transformation and opportunity: The future of the U.S. research enterprise." November 2012. http://1.usa.gov/1nBkviF

[6] Alberts B, Kirschner MW, Tilghman S, Varmus H. "Rescuing US biomedical research from its systemic flaws." *Proceedings of the National Academy of Sciences*. April 2014. http://bit.ly/1t5kDcx

[7] National Center for Advancing Translational Sciences. "Transforming Translational Research." 2014. http://1.usa.gov/1nLDae8

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Recommendation 2: Catalyze the Creation of a Broad-Based Partnership to Accelerate Therapeutics
The ASBMB agrees that improving partnerships among research enterprise stakeholders is critical to accelerating the discovery and development of therapeutics. To this end, the ASBMB has reached out to those in government, industry and academia to come together to discuss the barriers to enterprise sustainability and find a path forward. These partnerships are critical for fixing the systemic flaws in the biomedical research enterprise and improving the pipeline from discovery to delivery.

The PCAST report on propelling innovation suggests a high-level partnership should (1) identify key needs and opportunities to accelerate therapeutics; (2) prioritize these needs and opportunities; (3) formulate specific solutions and develop detailed plans to achieve those solutions and (4) ensure projects are launched by building coalitions of the right partners. A functioning partnership such as this would be invaluable to the biomedical research enterprise and would surely improve the efficiency and speed with which the system works.

However, this partnership cannot exist with today's enterprise. Due to a decade of flat federal funding, talented and highly trained investigators are turning away from careers in research, restricting both discovery and development of therapeutics. Graduate training at our universities does not adequately prepare Ph.D. graduates for the variety of careers available to them. Intellectual property, technology licensing and conflicts of interest keep academia and industry at arm's length. Government regulation of academic and industrial research creates increasing layers of complexity that limit an investigator's time that could be used for productive experimentation. These and many other issues threaten the stability of the research enterprise to the point where the partnerships recommended in the PCAST "Propelling Innovation" report would not function.

We suggest any broad-based partnership should also work to (1) identify barriers to interactions among all of the stakeholder groups that slow innovation and create inefficiencies and (2) make specific recommendations for each stakeholder to undertake in order to overcome these barriers. Once these barriers to sustainability are removed, discovery, development and delivery will occur at a much more rapid pace than they do today benefitting everyone from basic researchers to patients.

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The ASBMB is a nonprofit scientific and educational organization that was established in 1906 by 28 biochemists and has since grown to an organization with more than 12,000 members worldwide. Most members conduct research and teach at colleges and universities, government laboratories, nonprofit research institutions and industry. We are proud to include 102 Nobel Prize winners among our members.

We are pleased that the Energy & Commerce committee is examining so many critical issues confronting the biomedical research enterprise today. We believe the entire enterprise must move in a direction of sustainability with regard to workforce, funding, and interactions among stakeholders. Ultimately, this will accelerate the rate of discovery and reduce the costs of the technology and drug development, all in a safe and effective manner that improves the health and economic well-being of Americans. The ASBMB and the Public Affairs Advisory Committee stand ready to help the Energy & Commerce committee with this crucial endeavor.

American Society of Clinical Oncology

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June 10, 2014

Chairman Fred Upton
Energy and Commerce Committee
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Representative Diana DeGette
2368 Rayburn House Office Building
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Dear Chairman Upton and Representative DeGette,

I am pleased to provide input on behalf of the American Society of Clinical Oncology (ASCO) on your second white paper, 21st Century Cures: An Update on the President's Council of Advisors on Science and Technology (PCAST) 2012 Report on Propelling Innovation.

ASCO is the world's leading professional society representing physicians who specialize in the treatment of patients with cancer. With nearly 35,000 members, our core mission is to ensure that cancer patients have meaningful access to high quality cancer care.

As noted in ASCO's response to your first white paper, today more than two-thirds of patients with cancer are alive five years after their diagnosis, compared with less than one-half in the 1960s. There are now more than 13 million cancer survivors alive in the United States (US) and this number is growing. Despite this progress, many unmet medical needs remain for cancer patients, and we must accelerate the pace of treatment development. In 2013, about 580,000 American lives were lost to cancer. An estimated 1.6 million Americans will be diagnosed with cancer this year. The population is growing, aging, and more overweight, making it likely that cancer will take over heart disease as the leading cause of death by 2030.

The PCAST report is a timely analysis of steps that can be taken to speed the discovery, development and delivery of new treatments. I discuss progress and potential for oncology related to the PCAST report recommendations below. As a guiding principle to implementation of the recommendations, FDA should take a more coordinated approach to change. For example, Recommendation 5 calls for an adaptive approval process that allows for limited access of a new drug through an initial provisional approval that restricts access to the drug to narrowly defined patient groups and that systematically collects data on efficacy and safety. Recommendation 6 calls for an expansion of the Sentinel Program. Combining the two ideas could lead to a model whereby accelerated approval results in access limited to participants in a Sentinel program. Data would be carefully collected on this limited population and make any decisions to withdraw approval more transparent.

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Recommendation 1: Support Federal Initiatives to Accelerate Therapeutics

Both the National Center for Advancing Translational Sciences (NCATS) and Reagan-Udall Foundation are relatively new organizations, but their current projects hold much promise for accelerating research and clinical trials. NCATS projects that focus on tools for translational research, such as developing tissue chips for drug screening and Illuminating the Druggable Genome, hold much promise for accelerating the development of new treatments. A project investigating the role of Extracellular RNA in disease can lead to significant new discoveries. While these efforts do not focus specifically on cancer, they will provide a strong foundation for the development of new cancer therapies. NCATS should be fully supported, but not to the detriment of other National Institutes of Health (NIH) activities.

Two projects underway at the Reagan-Udall will potentially have significant impacts on oncology. The systems toxicology project is an attempt to understand the effect of a drug on the body's systems in order to better predict side effects and adverse events. The initial project will focus on developing predictors of cardiac toxicity of cancer treatments. If successful, these predictive models will improve safety, decrease the cost and burden of data collection by investigators, and reduce the size of clinical trials. A second project, Innovation in Medical Evidence Development (IMEDS), develops methods for safety evaluation and tools for post-market surveillance using population-based "big data" sets. These efforts support the FDA's Sentinel project, which is on a path to bring the practice of safety monitoring into the 21st century.

Recommendation 2: Catalyze the Creation of a Broad-Based Partnership to Accelerate Therapeutics

ASCO has collaborated with the Food and Drug Administration (FDA) and other professional societies on workshops to foster public discussion among biopharmaceutical companies and academic researchers to develop new therapeutic approaches and research strategies. A series of workshops in 2012 and 2013 discussed key technologies and endpoints to speed clinical trials. Workshops focused on minimal residual disease in the blood cancers, acute myeloid leukemia (AML, http://www.fda.gov/Drugs/NewsEvents/ucm341421.htm), acute lymphoblastic leukemia (ALL, http://www.fda.gov/Drugs/NewsEvents/ucm294931.htm), and chronic lymphoblastic leukemia (CLL, http://www.fda.gov/Drugs/NewsEvents/ucm340707.htm) brought together key stakeholders to discuss the use of different technologies to measure the presence of disease in clinical trials. This work will result in FDA guidance that should provide drug manufacturers with new trial endpoints that will speed the development of novel treatments.

Another workshop focused on pathologic complete response (pCR) in neoadjuvant treatment of breast cancer patients (http://www.fda.gov/Drugs/NewsEvents/ucm339396.htm). This effort is notable as an example of FDA doing its part to lead and encourage innovation. Few breast cancer trials are done in the neoadjuvant setting, but there is a need for therapies in this area. According to the FDA, "There are several potential rationales for neoadjuvant treatment for early-stage breast cancer. Giving chemotherapy preoperatively permits breast conservation in some patients who would otherwise require mastectomy and may improve cosmesis in existing candidates for breast conservation. Preoperative therapy also enables the oncologist to evaluate tumor response and discontinue ineffective therapy or substitute an alternative systemic therapy. Further, a patient's response to neoadjuvant chemotherapy may provide prognostic information that can supplement conventional prognostic data, such as initial staging, tumor grade, and receptor status." FDA

provided draft guidance and then collaborated on a public workshop to discuss how disease response would be measured in this setting and provide a pathway for sponsors to conduct clinical trials.

Recommendation 3: Expand the Use in Practice of FDA's Existing Authorities for Accelerated Approval and Confirmatory Evidence

The FDA Office of Hematology and Oncology Products (OHOP), led by Dr. Richard Pazdur, oversees development, approval, and regulation of drug treatments for cancer, therapeutic biologic treatments for cancer, therapies for prevention of cancer, and products for treatment of nonmalignant hematologic conditions. OHOP has been a leader in the use of accelerated approval. In 2012, FDASIA and subsequent FDA guidance made accelerated approval more flexible and reinforced the ability of FDA to require confirmatory trials. OHOP has made a practice of asking sponsors who are slow to complete confirmatory trials to appear before the Oncologic Drugs Advisory Committee (ODAC) to explain the challenges they face, a practice that precedes and often alleviates regulatory measures. In 2013, 3 of the 15 oncology drug approvals were accelerated approvals. In 2014, we have already reached that number with 3 of the 7 oncology drug approvals being accelerated approvals.

Expanding the use of accelerated approval requires three problems to be addressed, one oncology-specific and two more general. These issues were identified in a panel including representatives of patient advocates, industry, FDA, and academic researchers at the 2012 Conference on Clinical Cancer Research co-convened by Friends of Cancer Research and the Engelberg Center for Health Care Reform at the Brookings Institution. First, there are an increasing number of approved therapies in oncology and the current concept of "unmet need" is pushing developers to pursue accelerated approval in heavily pretreated populations. To alleviate this, FDA must recognize that unmet need exists in all cancer settings that lack a cure thereby extending the potential application of the accelerated approval pathway. Second, there is a dearth of qualified endpoints considered "reasonably likely to predict clinical benefit." The federal government must increase investment in research to analytically and clinically validate novel endpoints. Finally, there is a lack of clarity early in drug development about circumstances in which a new product will qualify for accelerated approval. FDA and industry should discuss the development plan early and agree on the appropriateness of an accelerated approval pathway, acceptable endpoints, and the magnitude of change in the endpoint that must be demonstrated for the treatment to be deemed successful. For a detailed discussion of these issues, please see the attached paper that summarizes the conference recommendations entitled, "Reevaluating the Accelerated Approval Process for Oncology Drugs."

Recommendation 4: Create a New Pathway for Initial Approval of Drugs Shown to be Safe and Effective in a Specific Subgroup of Patients

Cancer treatments are increasingly developed to target molecularly-defined groups of patients. Unfortunately, many cancers quickly develop resistance to specific treatments. Patients who have resistant cancers or who are unable to tolerate the standard treatment need additional options. FDA currently has tools to grant approvals of new treatments that may pose a high or unknown risk to the general patient population based on limited data sets. OHOP has used the accelerated approval pathway to limit indications while confirmatory trials are conducted. In addition, the REMS program provides FDA with a number of options for post-marketing regulation of high-risk treatments. A designation of "Special Medical Use" would help alert patients, physicians, payors and malpractice insurers that the drug should be reserved for use in a specific subgroup of patients, but it is not clear that a new approval pathway is required.

Recommendation 5: Explore Approaches for Adaptive Approval Via Pilot Projects Under Existing Pathways, but Do Not Create New Adaptive Approval Pathways Through Legislation

In the area of oncology, FDA has been a key stakeholder in the creation of a new approach to clinical trials: master protocols. A master protocol is a method of streamlining and coordinating clinical trials and providing a non-competitive space for trial sponsors to collaborate. A master protocol uses multiple arms, each with a different treatment that may benefit only a subset of the patients screened. Patients are accepted into the trial and a set of pathologic and molecular tests are used to group them into subpopulations who are given the treatment that is expected to provide the most benefit. As the trial progresses, more is learned about how best to assign patients to different treatment regimens and if/when to move someone from one arm to another. Arms and treatments can be added or removed as the trial progresses, as new drugs are developed and existing drugs progress toward approval or are removed from consideration. A master protocol for lung cancer has been developed (the Lung Cancer Master Protocol, http://www.focr.org/master-protocol) and is showing widespread acceptance. ASCO and other professional societies are currently working with FDA to host a workshop to explore development of a master protocol that uses a genomic approach to assign patients to metastatic breast cancer treatments.

The oncology community has also benefited from an adaptive approach to trials under the Breakthrough Therapies Program. As of the beginning of this year, OHOP has awarded more Breakthrough Therapy Designations than any other office within FDA. While the designation does not allow for the approach envisioned in the PCAST report, it allows for a great deal of interaction between the sponsor and FDA throughout the development and approval process so that trials can be designed efficiently to provide the required data and address regulatory concerns without generating a great deal of superfluous data.

Oncology drug development also typically uses an adaptive approach within existing statutory authority by continuing to learn about use of therapeutics in the post-market setting. This includes exploring different doses and combinations of approved agents, as well as testing of agents in different disease settings. Many oncology products have supplemental indications across multiple cancer types. FDA OHOP has been very innovative and flexible in use of the existing pathways to enable approval in small patient populations where the knowledge of safety and efficacy are sufficient. The existing approval pathways allow for this continued learning about the agent that is vital to how we develop new treatments, especially for smaller subpopulations and extremely rare diseases in which conducting a trial for initial approval may be difficult. However, changes to a label to add indications or modify dose can be difficult or time-consuming. While we learn about a drug with use, that information most often results in off-label indications by compendium and not by changes in the label. For example, FDA has not lowered the dose of capcitabine despite widespread recognition by the medical community that the FDA dose is excessively toxic. Because of this, clinical trial designs have continued to use the full FDA dose. FDA is finalizing guidance about how to optimize data collection in these supplemental applications to enable efficient clinical trials. ASCO has worked with FDA, NCI and investigators to articulate recommendations on this process and conducted a study to pilot test the concepts (see attached article “Optimizing Collection of Adverse Event Data in Cancer Clinical Trials Supporting Supplemental Indications”). We hope the final FDA guidance incorporates recommendations from the ASCO study to enable efficient and timely collection of data for supplemental indications – especially when we learn of changes to use that protect patient safety.

In the long-term, ASCO is developing a rapid learning system (CancerLinQ™) that will interact with providers through electronic medical records to provide point-of-care clinical decision support tools. CancerLinQ will also enable ASCO to analyze safety issues as they arise by examining data across the entire population of participating real-world oncology practices. This will dramatically increase the amount of post-marketing information collected which, when analyzed, could be used to expand the drug label. CancerLinQ could greatly facilitate an adaptive approval approach by FDA.

Recommendation 6: Improve FDA's Tools for Monitoring and Communication of Clinical Benefits and Risks

FDA should partner with professional societies and patient advocacy organizations to improve communication of the benefits and risks of marketed drug products. These organizations have the ability to reach targeted audiences quickly and are trusted sources of information. A straightforward example is that ASCO partners with FDA to alert the clinical community of new oncology drug approvals. We are also exploring a more dynamic partnership with OHOP to communicate benefits and risks through educational activities and materials. These can be beneficial in providing immediately available and practical information to prescribers and patients as new drugs become available. Working with FDA and the manufacturer to provide the information will help address any safety concerns that the FDA may have and also reduce potentially burdensome regulation. Risk Evaluation and Mitigation Strategy (REMS) programs were initially created to allow approval of medications with major safety risks that clinicians may be unfamiliar with and for which unique patient monitoring and/or management is required. The goal of the programs is to mitigate those specific risks without compromising provider-patient counseling (that balances risk and benefit), patient access, or increasing administrative burden. Unfortunately, some REMS programs do not achieve these goals and are challenging to implement.

As the FDA has done with the REMS for long-acting and extended-release opioids, an alternative approach is to use Continuing Medical Education (CME), developed by a professional society, to educate providers and reduce risk to patients. ASCO has submitted a proposal to the ER/LA Opioid Analgesics REMS Grant Review Committee to develop an innovative gaming application to address needs related to the safe prescription and management of opioid therapy. The concept is a learning game for oncology professionals that will address the full content of the FDA blueprint in the context of increasingly complex patient scenarios. The concept would employ what we know about how adult health professionals learn and place the safety information within the clinic setting in response to real-time clinical care questions.

A rapid learning system, such as CancerLinQ™, could provide rapid two-way communication; providing physicians with patient-specific risk/benefit information and relaying safety issues to the system and FDA as they arise. ASCO plans to work closely with FDA as new treatments are approved to immediately deliver clinical decision support information and collect data on specific safety and efficacy indicators. This relationship is extremely important and will enable us to monitor in real-time use of approved medications across all types of oncology patients, not just the carefully selected participants in the clinical trials.

Recommendation 7: Reform Management Practices at FDA

In 2011 the Office of Oncology Drug Products within the Center for Drug Evaluation and Research (CDER) was reorganized into the Office of Hematology and Oncology Products (OHOP). This was a positive step, grouping reviewers by disease area to focus the work of divisions within the office on

specific types of cancer rather than treatment approaches. This change reflects movement in the broader cancer community towards development of treatments that molecularly target the biological drivers of cancers.

FDA would benefit from increased communication and collaboration between offices within CDER and the Center for Devices and Radiological Health (CDRH) – in the context of specific applications as well as on overall policy approaches. As the discovery and development of molecularly targeted treatment increases, there is a growing need for diagnostic tests that can identify subpopulations of patients that would benefit from these treatments. Currently, FDA lacks clear and structured mechanisms for the evaluation of devices used in combination with treatment. The Investigational Device Exemption (IDE), which allows a non-approved test or device to be used in a clinical trial can be difficult or time consuming to acquire as there is confusion within the oncology community as to when the IDE requirements apply.

Recommendation 8: Study Current and Potential Economic Incentives to Promote Innovation in Drug Development

As we commented in our initial letter, we have concerns about the drug development process in pediatric cancers. Trials of promising new agents for pediatric cancers need to begin sooner and incentives need to be realigned. Currently, most pediatric cancer trials start only after completion of the adult pivotal trial. In order to speed drugs to children, trials should begin while the adult trials are ongoing. In addition, the pediatric patent extension program needs to be revisited. Currently, the program extends the patent of a drug if it can be used for the same disease in children. Children often do not suffer from the same diseases as adults, but we are discovering that some of the molecular targets of adult and pediatric cancers are the same. The patent extension should apply to drugs that can treat effectively pediatric cancers, even if it is not the same cancer as the adult indication.

In closing, ASCO is pleased to provide input and offers itself as a resource to you as you continue the 21st Century Cures Initiative to examine how to accelerate the discovery, development, and delivery of promising new treatments to patients. Given the nature of cancer and the nation's longstanding investment in cancer research, we believe your initiative would benefit from a roundtable discussion focused on oncology. The field of oncology has already dealt with many of the issues that have now begun to arise in other disease areas and ASCO can offer you its expertise on what has worked and what has not and how to best address remaining challenges.

Sincerely,

Peter P. Yu, MD, FASCO
ASCO President

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Clinical Cancer Research

Reevaluating the Accelerated Approval Process for Oncology Drugs

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CCR Perspectives in Drug Approval

Clinical Cancer Research

Reevaluating the Accelerated Approval Process for Oncology Drugs

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Abstract

For a new therapy to qualify for the accelerated approval pathway, it must treat a serious disease for which there is "unmet medical need"—defined as providing a therapy where none exists or providing a therapy that may be potentially superior to existing therapy. The increasing number of available therapies, coupled with the lack of accepted endpoints considered "reasonably likely to predict clinical benefit" and the lack of clarity early in development about circumstances in which a new product will qualify for accelerated approval, is pushing developers to pursue accelerated approval in heavily pretreated patients to fulfill an unmet need. To optimize the accelerated approval pathway, we propose here a reevaluation of what constitutes "unmet medical need" and "available therapy" in oncology. We also discuss ways for new endpoints to become qualified for use in supporting accelerated approval, and propose a structured process for pursuing accelerated approval. *Clin Cancer Res; 19(11); 1–6. ©2013 AACR.*

Introduction

Accelerated approval is an expedited regulatory pathway that allows a drug to be approved by the U.S. Food and Drug Administration (FDA) based on an endpoint (such as tumor shrinkage) that is considered "reasonably likely to predict a clinical benefit" [such as increased overall survival (OS)]. Drugs granted accelerated approval must be further tested in postmarketing studies to verify the expected clinical benefit and may be converted to "regular" approval if clinical benefit is confirmed or withdrawn from the market if it is not. Drugs or biologics eligible for accelerated approval must be intended to treat a serious or life-threatening disease and should show the potential to address an unmet medical need—either by providing a therapy where none exists or by providing a meaningful therapeutic benefit over an existing therapy.

This pathway was designed as a response to the AIDS crisis in the 1980s and the resulting demand from patients with HIV/AIDS for faster drug development. These patients, faced with a poor prognosis and no treatment options, were willing to accept the risk inherent with expediting the approval of a drug based on clinical activity but before confirmation of clinical benefit. Since its implementation in January 1993, the accelerated approval pathway has mainly been used for the development of HIV/AIDS and oncology drugs and, more recently, for new influenza vaccines. According to a recent analysis, 35 oncology products had obtained accelerated approval for 47 indications as of July 1, 2010 (1). Of these 47 indications, 26 were converted to regular approval, with an average time to conversion from accelerated approval of 4.7 years. Such conversion represents significant time-savings in making potentially life-saving or life-prolonging medicines available for seriously ill patients.

Although accelerated approval has been considered a success in oncology, it has come under increased scrutiny in recent years. Some have criticized the FDA as being lax in their oversight of postmarketing commitments; others have voiced concern that the FDA is making accelerated approval increasingly difficult to obtain (2–5). Two events in particular intensified this concern. The first occurred in 2010, when the FDA refused to file the application for ado-trastuzumab emtansine (T-DM1), a novel drug–antibody conjugate for treating HER2-overexpressing metastatic breast cancer. The T-DM1 application was based on a single-arm phase II study that showed a 34% response rate in women with advanced HER2-overexpressing breast cancer who had received, on average, 7 prior medicines including 2 HER2-targeted drugs (6). According to a Genentech press release, the FDA determined that the T-DM1 trial did not meet the standard for accelerated approval because all available treatment choices approved for metastatic breast cancer, regardless of HER2 status, had not been exhausted in the study population (7). Three years later, in February 2013, TDM-1 received full approval after showing a significant improvement in progression-free survival (PFS) and OS against another HER2-directed therapy, lapatinib, in a randomized trial of patients who had received a taxane and the HER2-directed therapy trastuzumab (8). The second event

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to raise concern occurred in February 2011, when the Oncologic Drugs Advisory Committee (ODAC) was convened by the FDA to discuss whether single-arm trials should continue to be used to support accelerated approval, as well as the requirements for confirmatory trials (9). The consensus was that single-arm trials should be reserved for exceptional circumstances where there are few patients and a significant treatment effect can be observed. Furthermore, the majority agreed that, ideally, 2 controlled confirmatory trials should be conducted, and that these should be at least written and ideally under way at the time accelerated approval is granted. This meeting raised concern among many that the FDA would no longer accept single-arm trials for accelerated approval.

Despite these concerns, the FDA has continued to grant accelerated approval to promising new therapies tested in single-arm trials. In 2011, brentuximab vedotin obtained accelerated approval for Hodgkin lymphoma and anaplastic large cell lymphoma, and crizotinib received accelerated approval for ALK-translocated non–small cell lung carcinoma (10, 11). In 2012, the FDA granted accelerated approval to carfilzomib for multiple myeloma (12). Each of these new agents was approved on the basis of data from single-arm trials. Furthermore, although the proteasome inhibitor carfilzomib was studied in patients who had received at least 2 prior lines of therapy including bortezomib, which is also a proteasome inhibitor, some other available therapies for multiple myeloma were not exhausted in this patient population. Nonetheless, the availability of an increasing number of approved therapies in many cancer types has raised the bar that a new drug must meet to potentially fill an "unmet need" and pushed drug developers to test new products in last-line disease settings, even though heavily pretreated patients may be less likely to respond to or benefit from a new therapy. Furthermore, restricting a study to those patients who have failed all FDA-approved therapies significantly reduces the pool of eligible patients, especially when some approved therapies are no longer used in standard practice. Other major barriers to using the accelerated approval pathway include the lack of qualified endpoints considered suitable for regulatory use and the lack of confidence sponsors have early in development as to whether a product is best suited for accelerated approval or the standard development pathway. Possible solutions to these challenges were proposed at the 2012 Conference on Clinical Cancer Research co-convened by Friends of Cancer Research and the Engelberg Center for Health Care Reform at the Brookings Institution (Washington, DC). These solutions are discussed here and summarized in Fig. 1.

Eligibility for the Accelerated Approval Pathway: What Is "Unmet Need"?

At the time the accelerated approval pathway was designed, treatment options in oncology consisted primarily of surgery, radiotherapy, and cytotoxic chemotherapy. As the treatment paradigm in oncology has shifted to therapies targeted against specific oncogenic proteins or pathways, patients' lives have been improved and extended. Nonetheless, most of these newer treatments still are not curative, some improve survival by only weeks to months, and most cause significant toxicities. Therefore, despite the availability of new anticancer therapies, significant unmet need remains, especially in the setting of metastatic cancer.

Current problem	Proposed solution
Increasing number of approved therapies and current concept of "unmet need" pushing developers to pursue accelerated approval in heavily pretreated populations	Recognize that unmet need exists in all cancer settings lacking a cure Define disease setting and "available therapy" in terms of molecular pathways where appropriate
Lack of qualified endpoints considered reasonably likely to predict clinical benefit	Increase investment in prospective studies to analytically and clinically validate novel endpoints
Lack of clarity early in development about circumstances in which a new product will qualify for accelerated approval	Develop a structured process that allows sponsors to discuss the development plan early with the agency and agree on appropriateness of accelerated approval pathway, acceptable endpoint, and magnitude of change in the endpoint that must be demonstrated

CCR Perspectives in Drug Approval AACR

Figure 1. Barriers to accelerated approval and proposed solutions.

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In oncology, sponsors usually choose to pursue accelerated approval in 1 of 2 ways: single-arm trials using historical controls in settings with no approved treatment options (such as in refractory disease) or comparator trials when approved therapies are available (such as in earlier disease settings). In the second situation, the investigational agent must show that it is potentially superior to the comparator in efficacy, tolerability, or practical benefit. This need to show superiority when other approved therapies are available is a major barrier to companies pursuing accelerated approval with an investigational agent. This paradigm is overly restrictive in oncology because there is not only a need for better drugs but also a need for mechanistic diversity to address the variety of pathways involved in tumor growth (13). A new drug may have efficacy comparable with that of available agents but, by acting through a previously untargeted pathway, may provide physicians with an additional therapeutic option from which to choose, depending on the patients' needs and the molecular features of their cancer. Postapproval studies will often identify unique benefits or safety issues that may change the consensus on which drug is superior or on how treatments should be optimally sequenced. Having an array of mechanistically diverse therapies available also fosters development of combination regimens that may overcome drug resistance and improve patient outcomes. A classic example of this is combination chemotherapy, in which the use of multiple agents targeting different pathways involved in cell division and replication has resulted in cures for some cancers, including acute lymphoblastic leukemia in children (14). More recent examples are the development of combinations of Her2-directed therapies, such as pertuzumab plus trastuzumab or lapatinib plus trastuzumab, which are more effective than trastuzumab alone (15, 16). The following proposal lays out a pathway for accelerated approval of new cancer drugs that recognizes this reality.

Unless a cancer is curable, it should be regarded as having an unmet medical need with any line of therapy. Novel investigational agents could be considered for accelerated approval if they have acceptable safety and show clear evidence of activity on an endpoint that the sponsor and agency agree is reasonably likely to predict clinical benefit. Whether this should be assessed through single-arm trials using historical controls or through prospective randomized trials will depend on the endpoint being assessed, the clinical setting, the level of activity that would be clinically meaningful in that setting, and the appropriateness of historical controls. The current trend to pursue accelerated approval in more and more refractory populations could be curbed by better defining "available therapy" and the indication being sought, and by accepting that "unmet medical need" exists in any noncurative setting. If an investigational agent targets a specific mutation or pathway, and that information would be part of the labeled indication for patient selection, then the only drugs that should be considered "available therapy" for the purposes of accelerated approval are those that also target that same pathway. If a new drug targets a previously untargeted pathway, there is no "available therapy" in that setting. Regardless of the setting, new therapies should be shown to have at least comparable activity with existing treatments for the particular stage of disease. This pathway-based distinction recognizes our increasing understanding of cancer as a genetic disease: Driver mutations not only represent druggable targets but also define unique diseases with unique biology, natural history, and treatment requirements. Sponsors seeking accelerated approval need to engage in early discussions with the FDA to define the appropriate context for initial efficacy studies.

Novel Endpoints to Support Accelerated Approval

Endpoints accepted for use in accelerated approval are often referred to as surrogate endpoints. However, true surrogate endpoints capture the full treatment effect of a drug, and the FDA requires only that endpoints for accelerated approval be "reasonably likely to predict clinical benefit." The endpoints most commonly used for accelerated approval include objective response rate (ORR) and PFS (1, 17). In solid tumors, measurement of both ORR and PFS relies on anatomic imaging using radiographs, computed tomography (CT) scans, or MRIs, and is based on widely accepted standardized criteria [for example, RECIST: Response Evaluation Criteria in Solid Tumors (18)]. PFS is generally defined as the time from randomization or treatment initiation until tumor progression or death. It usually allows a shorter follow-up period and smaller sample size than studies measuring OS, and is not confounded by the impact of subsequent therapies. In diseases such as renal cell carcinoma, PFS is accepted as an established surrogate for OS and can be used as the basis for full approval (1). ORR is defined as the proportion of patients who experience tumor regression of a certain magnitude and has the advantage over PFS that the treatment effect is directly attributable to drug activity, and therefore can be assessed in single-arm trials. ORR has the disadvantage that it does not measure stable disease or minor regressions and does not measure the durability of a response. Both endpoints are limited by the subjectivity of radiologic measurements of tumor size, and neither endpoint is appropriate in every disease setting.

Since the implementation of accelerated approval 20 years ago, the endpoints considered suitable for this pathway have changed little. Many have called for the FDA to accept new endpoints for accelerated approval, such as novel imaging endpoints or biomarkers that can be measured earlier than ORR or PFS, or can be used in settings where conventional ORR and PFS cannot be readily or reproducibly assessed. To be accepted as an endpoint for drug approval, a novel biomarker must first be "qualified." The regulatory definition of qualification is provided in the FDA draft guidance, *Qualification Process for Drug Development Tools*, which provides a framework for interactions between the agency and those wishing to develop tools such

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as endpoints that can support regulatory decisions (19). A biomarker that is accepted by the FDA for accelerated approval is considered "qualified"; that is, within a given context of use, analytically valid measurements of that biomarker can be expected to be "reasonably likely to predict clinical benefit." Qualification of a biomarker as an endpoint to support accelerated approval requires robust scientific and clinical evidence, and often requires a shared investment by many stakeholders.

An example of a recently qualified endpoint is pathologic complete response (pCR) in locally advanced breast cancer. In May 2012, the FDA announced its acceptance of pCR as an endpoint to support accelerated approval in certain breast cancer settings (e.g., neoadjuvant) and published a draft guidance, *Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval*, to describe this endpoint and the basis for its qualification (20). In this guidance, the FDA provided a formal regulatory definition of the proposed endpoint, pCR; explained the rationale for using this endpoint in the setting of neoadjuvant breast cancer therapy; summarized the evidence that supports the use of pCR; and described the types of trials that would be appropriate for use of pCR to support accelerated approval. Importantly, the guidance noted that the analyses supporting use of pCR are currently limited to analyses of treatment response and stressed that future prospective studies are needed to fully understand the relationship of pCR to ultimate clinical benefit. Given the lack of alternative endpoints considered suitable for regulatory use in early-stage breast cancer, pCR is acceptable despite this uncertainty in situations with significant unmet medical need (e.g., high-grade, triple-negative breast cancer).

The pCR guidance highlights several important criteria that contribute to the qualification of a novel endpoint for accelerated approval, many of which have been reviewed elsewhere (21–23). First, the endpoint must have an accepted, standardized definition. Second, data from multiple clinical studies should show a strong correlation of the endpoint with clinical outcomes. Third, well-powered prospective studies are needed to validate that the endpoint is truly predictive of clinical benefit and to what extent (i.e., what degree of improvement in the endpoint is needed to predict a clinically meaningful improvement in patient outcome). Fourth, prospective studies are needed to determine if the endpoint can be generalized to other patient populations, other target organs, or drugs with other mechanisms (e.g., some measures are useful only with cytotoxic drugs). The strength of evidence for the last 3 criteria will vary, depending on whether the endpoint is intended for use in "regular" approval or accelerated approval. For the latter, the evidence needs to support that the endpoint is "reasonably likely to predict clinical benefit." Evidentiary standards for meeting this threshold have not been established.

Using the above 4 criteria, we will briefly examine the use of 2[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) imaging for early evaluation of drug activity in clinical trials. We have chosen to focus on FDG-PET in this article because there is a substantial body of literature about its use in the clinic that could soon lead to a consensus opinion on its appropriateness for use as an endpoint to support accelerated approval. FDG-PET is a functional imaging technique that has been used in routine clinical practice for assessment of many different types of cancer for more than 20 years (23, 24). FDG-PET technology relies on the fact that cancers use glycolysis rather than aerobic respiration to adapt to low-oxygen environments (the Warburg effect), and it measures one consequence of this, a major increase in the influx of labeled glucose into cancer cells. Thus, it provides a measure of tumor metabolism that can be used to assess drug activity and can be evaluated earlier than tumor regression when assessed using standard response criteria.

A semiquantitative measurement of FDG uptake (standard uptake value, SUV) has been proposed as a biomarker of efficacy. SUV measurement could potentially be used to meet the first criterion described earlier by providing a standardized definition of what constitutes a response to therapy when assessed by FDG-PET. To meet the second criterion, multiple studies are needed to determine the analytic robustness of the measurement and whether a decrease in SUV following therapy correlates with improved patient outcome. To meet the third criterion, large prospective trials comparing a predefined change in SUV with clinical outcomes should be conducted to assess the degree of correlation. There are 2 ongoing multicenter trials prospectively designed to validate the ability of FDG-PET to predict clinical outcomes (lymphoma, CALGB-50303; non–small cell lung carcinoma, RTOG-0235/ACRIN6668). The CALGB (Cancer and Leukemia Group B) trial is a large, randomized phase III study in non-Hodgkin lymphoma designed prospectively to collect FDG-PET imaging as well as event-free survival data. The RTOG (Radiation Therapy Oncology Group) trial is a phase III trial in locally advanced non–small cell lung carcinoma in which the objective is to evaluate a change in the standard FDG uptake value after treatment to predict OS. Results of these trials could contribute to qualification of FDG-PET for use in supporting accelerated approval in these diseases, if not in all cancer types. However, to meet the fourth criterion described earlier, prospective trials would be needed to determine the context-dependent use of FDG-PET measurements.

Besides pCR and FDG-PET measurements, a number of other novel endpoints are being studied in a variety of disease settings. For example, the change in the number of circulating tumor cells (CTC) following treatment has been proposed as a measurement that may predict clinical outcome in multiple tumor types. At present, however, no standard definition for CTC has been established, and the many existing technologies for assaying CTCs may measure different markers or different cells. The only FDA-cleared CTC enumeration methodology at this time is the Veridex CellSearch CTC Kit, which has shown prognostic significance in breast and prostate cancer and is currently being

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studied in 2 randomized phase III trials (Cougar AA 301; NCT00638690 and AFFIRM; NCT00974311) to determine if CTC reduction is predictive of OS (25). Other novel endpoints being studied include the measurement of gene rearrangements in acute lymphoblastic leukemia to assess minimal residual disease (26) and the measurement of correlates of immunity in studies of idiotypic vaccine candidates for lymphoma (27). In the future, the availability of additional qualified endpoints will enable more efficient and expedited drug development.

Proposal for a Structured Accelerated Approval Process

Unlike fast-track designation and the recently described "breakthrough therapy" designation, there is no formal process for designating a product for development through the accelerated approval pathway. Establishing a dialogue very early in the process (phase I or earlier) between the sponsor and the FDA would help sponsors devise an efficient development plan and may incentivize sponsors to establish novel surrogate markers more likely to predict clinical benefit and that would be of potential use for multiple therapeutic products. We propose a structured process whereby sponsors and FDA meet early and formally agree either that the drug will be developed using an "adaptive clinical development plan" with the possibility for accelerated approval if certain results are generated or that the full approval process is necessary based on either existing data or new information that emerges during the drug development process. A decision by the sponsor to pursue accelerated approval should include the following: (i) an agreement between the FDA and sponsor that unmet need exists in the patient population being studied; (ii) agreement on what endpoint will be assessed; (iii) upfront agreement on what magnitude of benefit must be observed using the agreed-upon endpoint for accelerated approval to be granted; and (iv) an agreement on postmarketing commitments. Whether a single-arm trial using historical data as a control or a randomized trial with an active or placebo control is appropriate will depend on the situation as described earlier. In the case of a controlled randomized trial, the FDA and sponsor could agree on a prespecified analysis plan in which an interim analysis is conducted using an endpoint such as PFS; if sufficient efficacy is observed at this point, accelerated approval could be granted and the original trial could then be completed using a traditional clinical endpoint for conversion to full approval. The challenge in this situation is further enrollment after accelerated approval is granted. The decision of whether a drug should be developed using this adaptive clinical development plan should be made within a short time after review of relevant clinical and preclinical data (e.g., 60 days after submission by the sponsor of the data and protocol). This process and agreement documentation would be a key step in providing the predictability that is currently lacking. A more predictable path to approval would allow for better portfolio decisions within large sponsor organizations and facilitate critical funding for smaller organizations.

Conclusion

The accelerated approval pathway has played a vital role in expediting access for cancer patients to promising new therapies. Many oncology drugs initially granted accelerated approval, such as imatinib, have proven to be major therapeutic advances and are now included in first- or second-line treatment regimens. However, in recent years, accelerated approval has primarily been pursued in heavily pretreated or refractory populations. This trend is detrimental to progress in the treatment of cancer. In this article, we have proposed that "unmet need" be defined as encompassing any noncurative setting, and that "available therapy" be defined in a biologic context for targeted agents. We have also discussed the need for additional qualified endpoints and proposed a structured process for pursuing accelerated approval. Although limited agency resources may restrict full adoption of some of these proposals, we believe that their implementation would improve predictability in the accelerated approval process and facilitate its use in earlier disease settings. This proposal would also promote the development of novel cancer drugs rather than drugs that are clinically indistinguishable from those already available.

Accelerated approval inherently implies a level of uncertainty that full approval does not. Drugs approved via this pathway have a limited safety database at the time of approval and ultimately may not provide a true clinical benefit. Indeed, 3 cancer drugs have been withdrawn or relabeled because of either unexpected safety issues or apparent lack of efficacy: gemtuzumab ozogamicin for acute myeloid leukemia, gefitinib for non–small cell lung carcinoma, and bevacizumab for breast cancer (28–30). However, the majority of accelerated approvals have confirmed clinical benefit on further study and even the recent withdrawals of those 3 drugs were not straightforward. Indeed, recent data have led to calls for the reinstatement of gemtuzumab ozogamicin (31). To be sure, slow completion of required postmarketing trials exposes patients to products for which the full risk–benefit assessment is not understood for excessive periods. A more liberal approach to granting accelerated approval should also be accompanied by mechanisms to ensure timely completion of confirmatory trials and efficient withdrawal of products that fail to confirm clinical benefit. The development of such mechanisms is in the interest of all stakeholders, as it may encourage regulators to be more flexible in granting accelerated approval to novel oncology therapies, thereby improving sponsor confidence in the process, and ultimately providing patients with greater access to potentially lifesaving drugs.

Disclosure of Potential Conflicts of Interest

D.P. Schenkein is the CEO of Agios Pharmaceuticals, is Director of Foundation Medicine and Blueprint Medicine, and has ownership interest (including patents) in Agios Pharmaceuticals, Foundation Medicine, and Blueprint Medicine. No potential conflicts of interest were disclosed by the other authors.

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Disclaimer

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ORIGINAL REPORT

Optimizing Collection of Adverse Event Data in Cancer Clinical Trials Supporting Supplemental Indications

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ABSTRACT

Purpose

Although much is known about the safety of an anticancer agent at the time of initial marketing approval, sponsors customarily collect comprehensive safety data for studies that support supplemental indications. This adds significant cost and complexity to the study but may not provide useful new information. The main purpose of this analysis was to assess the amount of safety and concomitant medication data collected to determine a more optimal approach in the collection of these data when used in support of supplemental applications.

Methods

Following a prospectively developed statistical analysis plan, we reanalyzed safety data from eight previously completed prospective randomized trials.

Results

A total of 107,884 adverse events and 136,608 concomitant medication records were reviewed for the analysis. Of these, four grade 1 to 2 and nine grade 3 and higher events were identified as drug effects that were not included in the previously established safety profiles and could potentially have been missed using subsampling. These events were frequently detected in subsamples of 400 patients or larger. Furthermore, none of the concomitant medication records contributed to labeling changes for the supplemental indications.

Conclusion

Our study found that applying the optimized methodologic approach, described herein, has a high probability of detecting new drug safety signals. Focusing data collection on signals that cause physicians to modify or discontinue treatment ensures that safety issues of the highest concern for patients and regulators are captured and has significant potential to relieve strain on the clinical trials system.

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INTRODUCTION

For marketing approval, the US Food and Drug Administration (FDA) requires commercial firms to submit data from adequate, well-controlled studies that demonstrate the safety and effectiveness of investigational agents in their intended use populations.[1,2] The initial approval of an oncologic agent from a New Drug Application (NDA) or a Biologic License Application (BLA) is based on the results from trials that include approximately 1,000 patients in the aggregate. Approval in a supplemental indication often occurs years after the initial approval, usually after extensive postmarketing evaluations have been conducted in a larger, more general population.

Though considerably more is known about the safety profile of a drug at the time of a supplemental application, sponsors collect extensive safety data, similar to that collected for initial marketing approval. Recent studies indicate that documenting and validating extensive adverse event (AE) data places a substantial burden on the clinical trials infrastructure, especially at the site level.[3,4] Similar considerations apply to the collection of data on concomitant medications, where large quantities of data continue to be collected in support of supplemental applications, but are seldom used to change drug labeling. Therefore, it is important to understand the type and extent of clinical data necessary to inform regulatory decisions that lead to changes in drug labeling and to clinical decisions regarding dose modification or discontinuation of treatment.

These considerations have prompted calls for development of specific data collection standards,

particularly for supplemental NDAs/BLAs.[5-7] Collecting targeted data necessary to inform regulatory and clinical decisions may enhance physician participation in clinical trials and enable more rapid completion of studies. This may result in allowing faster delivery of new drugs to patients, reducing the cost of clinical trials and enhancing data quality.

To address these issues, a working group was formed to provide a forum for the FDA, the National Cancer Institute, academic investigators, and industry to develop AE data collection standards for supplemental NDAs/BLAs in oncology indications. Representatives from the Cancer and Leukemia Group B, Eli Lilly, Genentech, GlaxoSmithKline, and Novartis Pharma AG volunteered to re-evaluate safety data from previously completed clinical trials. The main purpose of this analysis was to determine whether subsets of an AE database used for a supplemental application could adequately identify the new safety signals that would be learned from complete AE collection.

METHODS

A statistical analysis plan (SAP) was prospectively developed and approved by the project stakeholders. The analyses evaluated subsampling methods and their likelihood of missing clinically important AEs or over-representing events, relative to the information known from the established safety profile of the agent. Further, the SAP assessed the extent of data collection and cleaning effort saved through subsampling.

In all subsampling methods evaluated, serious AEs and events leading to drug discontinuation or dose modification, referred to here as "serious+" AEs, were collected in all patients. The SAP focused on the subsampling of grade 3 and higher events, referred to as grade 3+ AEs, and of grade 1 to 2 AEs, both groups distinct from the category of serious+ events.

Eight completed phase III clinical trials were selected for individual reanalysis (Table 1).[8-15] These industry-sponsored and publicly funded trials investigated chemotherapy, biologic, and hormonal treatments in the metastatic and adjuvant treatment settings across multiple tumor types. In each case, the investigational agent had been studied in other phase III clinical trials and an established safety profile existed that served as the standard for the reanalysis. Treatment regimens differed substantially between the initial registration trial and the reanalyzed studies in four of the eight trials.

In each candidate trial, cutoffs for AE signal detection were set to capture the smallest changes in AE frequency that oncologists might consider clinically relevant; therefore, drug effects were defined as those grade 3+ events with a $\geq$ 2% difference in incidence between the treatment and control arms and as those grade 1 to 2 events with a $\geq$ 5% difference.

We identified AE signals from previous trials that lead to the initial NDA/BLA approval and other studies conducted before the conduct of the candidate trial (ie, AEs from labeling, safety databases, and published literature).[16-23] To this list, we added serious+ events that occurred in $\geq$ 2% excess from the candidate trial to establish the base known safety profile for the grade 3+ event subsampling analysis. For the assessment of the grade 1 to 2 subsamples, the base known safety profile was defined as above with the addition of grade 3+ events in $\geq$ 2% excess in the candidate trial.

AEs identified as drug effects in the candidate trial that were not listed as part of the base known safety profile were defined as events that could potentially be missed under the subsampling analysis. Noise events were defined as drug effects identified in subsamples that were not identified as drug effects in the candidate trial's full safety database.

Random and systematic sampling methods were applied to each candidate trial. Subsampling simulations on candidate trial data used 1,000 independent replications targeting 200, 300, 400, 500, and 600 patients, equally divided between the treatment arms, selected randomly by patient and randomly by treatment center. For each sample size and random subsampling method, we tabulated both the rate of event detection of potentially missed events and the mean number of noise events across the replications.

The systematic subsampling methods selected the target numbers of patients from the biggest centers and the first patients enrolled. From each subsample, we calculated the incidence differences of those AEs identified as drug effects, thus determining the missed signals and the noise AEs.

For each of the candidate studies, we determined the number of distinct AEs in the database for serious+ events, grade 1 to 2 events not serious+, and grade 3+ events not serious+. The mean number of AEs per patient was reported for each category.

We also determined the number of database records and fields needed to store concomitant medication data and whether the results were noted in subsequent FDA-approved labels.

RESULTS

Toxicity records from the candidate trials included 17,184 patients. The metastatic disease trials ranged in patient safety population size from 580 to 1,669 patients, whereas the adjuvant disease trials ranged from 1,264 to 7,963 patients (Table 1).

In the eight studies, 43 grade 3+ events were detected as drug effects (Table 2); however, 34 of these events were previously identified as part of their corresponding base known safety profile. The subsampling analysis focused on detection of the remaining nine events that could potentially be missed. Because so few AEs could be missed, known events from several trials representing varying full trial incidence differences were selected for subsampling analysis. This allowed us to observe AE detection trends as the incidence differences increased beyond the 2% cutoff rate.

Likewise, there were 24 grade 1 to 2 AEs identified as drug effects in the four relevant studies, with 20 of them represented in the corresponding base known safety profile (Table 2). The subsampling analysis focused on detection of the remaining four events that could potentially be missed, along with known grade 1 to 2 events illustrating trends across varying incidence rates.

Subsampling examples are presented and discussed in detail to illustrate overarching trends in the data across the metastatic and adjuvant studies. Reanalysis results of the adjuvant trials are reported in the Appendix (online only).

Rates of detection of grade 3+ events for the metastatic trials ranged from 62% to 94% for the 200-patient subsamples and from 61% to 100% for the 600-patient subsamples when using the random-by-patient selection method (Table 3). For the grade 1 to 2 events, rates of detection ranged from 76% to 99.5% for the 200-patient subsamples and from 99.5% to 100% for the 600-patient subsamples (Table 3). The chance of detecting these events increased with increasing subsample size. The rates of detection for the centers-at-random subsamples were consistent with, although slightly lower than, those using the random-by-patient method.

Further, the chance of event detection was larger the greater the AE rate excess in the full study. For example, "leukopenia," with a 6.7% excess in the full AVF2107g trial, was detected in 92% of the 400 random-by-patient subsets, whereas "weight decreased," with a 2.1% excess in the full AVAiL (Avastin in Lung) study, was detected in 66% of the corresponding 400-patient subsets. Across the metastatic studies, all grade 3+ AEs analyzed that had at least 3% excess in the full study were detected in at least 75% of the

Table 1. Study Characteristics

Candidate Study Profile				Source of Known Safety Profile			
Study	Patient Population	Study Treatment	Safety Analysis Population	Precursor Studies	Primary Precursor Study Population	Precursor Study Treatment	Safety Analysis Population
AVAiL[8]	First-line nonsquamous NSCLC	Arm 1: cisplatin/gemcitabine Arm 2: cisplatin/gemcitabine + bevacizumab	656	AVF2107g[9]	First-line mCRC	Arm 1: irinotecan/FU/LV (bolus-IFL) + placebo Arm 2: bolus IFL + bevacizumab	813
				ECOG 3200[16]	Second-line mCRC	FOLFOX4; FOLFOX4 + bevacizumab	585
AVF2107g[9*]	First-line mCRC	Arm 1: irinotecan/FU/LV (bolus IFL) + placebo Arm 2: bolus IFL + bevacizumab	788	AVF2119g[17]	mBC	Arm 1: capecitabine Arm 2: capecitabine + bevacizumab	462
ECOG 4599[10]	First-line nonsquamous NSCLC	Arm 1: paclitaxel/carboplatin Arm 2: paclitaxel/carboplatin + bevacizumab	878	AVF2107g[4]	First-line mCRC	Arm 1: irinotecan/FU/LV (bolus IFL) + placebo Arm 2: bolus IFL + bevacizumab	813
				ECOG 3200[16]	Second-line mCRC	FOLFOX4; FOLFOX4 + bevacizumab	585
EGF30001[11]	First-line mBC	Arm 1: paclitaxel + placebo Arm 2: paclitaxel + lapatinib	580	EGF100151[18]	Refractory advanced or mBC	Arm 1: capecitabine Arm 2: capecitabine + lapatinib	408
JMDB[12]	First-line NSCLC	Arm 1: cisplatin plus pemetrexed Arm 2: cisplatin plus gemcitabine	1,669	JMCH[19]	MPM	Arm 1: cisplatin plus pemetrexed Arm 2: cisplatin	331
IBCSG BIG 1-98[13]	PMP women with HR+ EBC	Arm 1: letrozole Arm 2: tamoxifen; double-blind using double-dummy technique	7,963	NCIC MA-17 (PI 11/2004)[20]	Extended Adjuvant	Letrozole 2.5 mg orally daily for 5 years Placebo orally daily for 5 years; double-blind using double-dummy technique	5,136
CALGB 89803[14]	Patients with resected adenocarcinoma of the colon	Arm 1: LV + FU Arm 2: irinotecan + LV + FU	1,264	Cunningham et al,[21] 1998	mCRC	Irinotecan *v* best supportive care (FU failures)	279
				Rougier et al,[22] 1998	mCRC	Irinotecan *v* FU	267
HERA[15]	HER2+ adj breast cancer	Arm 1: observation Arm 2: trastuzumab	3,386	H0648g[23]	First-line mBC	Trastuzumab + CT *v* CT alone; CT was either (1) anthracycline + cyclophosphamide or (2) paclitaxel + cyclophosphamide	469

Abbreviations: AVAiL, Avastin in Lung; NSCLC, non–small-cell lung cancer; ECOG, Eastern Cooperative Oncology Group; mCRC, metastatic colorectal cancer; FU, fluorouracil; LV, leucovorin; IFL, irinotecan plus fluorouracil and leucovorin; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; mBC, metastatic breast cancer; MPM, malignant pleural mesothelioma; IBCSG, International Breast Cancer Study Group; BIG, Breast International Group; PMP, postmenopausal; HR, hormone receptor; EBC, early breast cancer; NCIC, National Cancer Institute of Canada; PI, package insert (US); CALGB, Cancer and Leukemia Group B; HERA, HERceptin Adjuvant; adj, adjuvant; CT, chemotherapy.

*AVF2107g was a three-arm trial. A third arm with treatment of FU/LVplus recombinant humanized monoclonal antibody vascular endothelial growth factor was omitted from this analysis.

simulations with subsamples of 400 patients, regardless of the random selection method used. The two grade 1 to 2 events from the AVAiL trial had full-trial incidence rate differences of 6.4% and 15.4%. Both events were likely to be detected with random subsampling of 400 patients (Table 3).

With the systematic subsampling methods for the metastatic trials, the observed AE rate difference varied around the full study value and generally converged to the full study value with larger subsample size (Table 4). Similar to the trend observed with random sampling methods, the grade 3+ events with full trial rate differences close to the cutoff rate of 2% were sometimes missed with subsampling. However, the chance of detecting events increased as the full study event rate difference increased above 2%. Events with full-study incidence excess of 3% or greater were detected in 88% of the subsamples. As with the random subsampling methods, AE detection was more likely in the larger subsamples and as full-study event rate differences increased beyond the 2% cutoff rate. For both grade 3+ and grade 1 to 2 events using the systematic subsampling methods, AE rate differences were similar to the full study rates with subsamples of 400 patients or more.

Regarding noise event detection among subsamples of the metastatic disease trials, fewer were detected for simulations with larger subsample sizes. For example, an average of 13.2 noise events were detected in the random-by-patient subsamples of 200 patients for AVF2107g (Table 5). For simulations of the 400 random-by-patient subsamples in that trial, the average number of noise events decreased to 4.9. This trend was observed across metastatic studies in grade 3+ AE subsets selected by either random method. The number of grade

Table 2. AEs Detected as Drug Effects in the Analysis of All Patients in the Candidate Studies

Trial	Grade 3+ Events Detected in ≥ 2% Incidence Difference
AVAiL	*Weight decreased* Proteinuria* Nausea* Vomiting* Asthenia* Peripheral sensory neuropathy* Neutropenia*† Epistaxis† Hypertension*†
AVF2107g	*Abdominal pain* *Leukopenia* Hypertension* Pain† Deep thrombophlebitis*† Constipation† Diarrhea†
ECOG 4599	*Febrile neutropenia* *Infection without neutropenia* *Hyponatremia* Proteinuria* Neutrophils* Fatigue* Headache* Hypertension*
EGF30001	*Leukopenia* *Nausea* Febrile neutropenia† Neutropenia† Diarrhea*† Hypokalemia* Rash†
JMDB	Anorexia* Nausea*
BIG 1-98	No events identified in excess of 2%
CALGB 89803	*Thrombosis/embolism* Hemoglobin*† Leukocytes*† Neutrophils/granulocytes*† Platelets*† Fatigue*† Alopecia* Febrile neutropenia* Infection*
HERA	Ejection fraction decreased†

Trial	Grade 1 to 2 Events Detected in ≥ 5% Incidence Difference
AVAiL	Epistaxis*† Fatigue* Headache* Hypertension*† Neutropenia*† Stomatitis*
BIG 1-98	*Hypercholesterolemia*
CALGB 89803	*Sweating (diaphoresis)* *Constipation* Hemoglobin*† Leukocytes (total WBC)*† Neutrophils/granulocytes*† Fatigue (lethargy/malaise/asthenia)*† Alopecia* Diarrhea (without colostomy)*† Nausea*† Vomiting*†
HERA	*Fatigue* Headache* Nasopharyngitis* Nausea* Chills* Diarrhea* Pyrexia*

NOTE. Adverse events in *italics* could be missed under AE subsampling. Trial JMDB was a head-to-head study. Drug signals were determined where the pemetrexed arm had a 2% excess of incidence over the gemcitabine arm. For trial CALGB 89803, serious AEs and AEs leading to dose modifications were not identified as such in the case report forms. The determination of known events from this study was based only on a 2% excess of AEs leading to drug discontinuation or death. For study ECOG 4599, serious AEs and AEs leading to drug discontinuation or dose modifications were not identified as such in the case report forms. Therefore, there was no separate determination of known events from this study.

Abbreviations: AE, adverse event; AVAiL, Avastin in Lung; ECOG, Eastern Cooperative Oncology Group; BIG, Breast International Group; CALGB, Cancer and Leukemia Group B; HERA, HERceptin Adjuvant.

*Known from previous trials.

†Identified as known in candidate trial from analysis of AEs to be collected in all patients (see Methods).

3+ noise events fluctuated across trials for the systematic subsets of size 200, but was consistently low with subsets of 400 patients, ranging between zero to three noise events. Similar trends were observed for the grade 1 to 2 events.

Adjuvant studies Cancer and Leukemia Group B 89803 and HERA (HERceptin Adjuvant) were subsampled for grade 3+ and 1 to 2 AEs, whereas trial Breast International Group 1-98 was subsampled only for grade 1 to 2 events because no missable grade 3+ events were identified (Table 2). Under the random sampling methods, the rates of AE detection increased as subset size increased (Appendix Table A3, online only). Events with high incidence rate differences in the full trial analyses were detected in higher frequencies than those close to their associated cutoff (2% for grade 3+ and 5% for grade 1 to 2). These trends were also observed in the systematic patient subsets selected from largest centers and by enrollment order, regardless of the adjuvant trial analyzed (Appendix Table A4, online only). Noise event detection patterns for grade 3+ and 1 to 2 AE subsamples from the adjuvant disease trials mirrored those from the metastatic trials (Appendix Table A5, online only).

The overall number of AEs contained in the safety databases for seven of the trials was 107,884 (Table 6). Of these AEs, 19,621 were serious+. There were 72,801 grade 1 to 2 events not classified as serious+, ranging from an average of 2.3 to 12.0 per patient. Further, grade 1 to 2 events were from 4.2 to 9.6 times as numerous as the serious+ events in the metastatic trials and from 2.2 to 14.4 times as numerous in the adjuvant trials.

The average number of concomitant medications reported per patient ranged from 14 to 27 in the metastatic trials and from four to seven in the adjuvant trials (Appendix Table A6, online only). Of the 136,608 concomitant medication records included in the summary tabulations for these studies, none contributed to labeling changes for the supplemental indications.

DISCUSSION

The collection of all AEs in all patients in a study designed to support a supplemental NDA/BLA has the potential to identify new drug safety

Table 3. Probability of Detecting AEs Under Random Subsampling Methods for Metastatic Disease Studies

Study, AE, Active Arm Rate Excess in Full Study	Sampling Method	Subsample Size (total No. of patients)				
		200 (%)	300 (%)	400 (%)	500 (%)	600 (%)
Grade 3+ events						
JMDB, anorexia*†, 2.1%	Random by patient	62.4	61	63.3	60.4	61
	Random by center‡	50.6	49.9	52.7	56.7	56.4
AVAiL, *weight decreased,* 2.1%	Random by patient	63	65	66	68	**79**
	Random by center‡	51	54	52	59	65
ECOG 4599, *infection without neutropenia,* 2.4%	Random by patient	63	67	68	72	**75**
	Random by center‡	57	60	63	68	70
EGF30001, *leukopenia,* 2.4%	Random by patient	68	70	**79**	**86**	NA
	Random by center‡	58	61	66	**79**	NA
EGF30001, *nausea,* 2.4%	Random by patient	66	68	73	**84**	NA
	Random by center‡	54	57	64	71	NA
ECOG 4599, proteinuria,* 3.0%	Random by patient	**87**	**91**	**94**	**96**	**98**
	Random by center‡	**78**	**85**	**90**	**93**	**98**
AVF2107g, *abdominal pain,* 3.4%	Random by patient	72	**77**	**80**	**85**	**92**
	Random by center‡	65	72	**75**	**80**	**90**
JMDB, nausea,*† 3.5%	Random by patient	72.9	74.5	**78.1**	**79.7**	**82**
	Random by center‡	68.7	69.6	**75.5**	**77.2**	**80.5**
AVAiL, epistaxis,† 4.3%	Random by patient	**94**	**98**	**99.4**	**100**	**100**
	Random by center‡	**91**	**97**	**99.6**	**100**	**100**
AVF2107g, *leukopenia,* 6.7%	Random by patient	**79**	**88**	**92**	**97**	**99.4**
	Random by center‡	**77**	**85**	**90**	**96**	**98**
Grade 1 to 2 events						
AVAiL, stomatitis,* 6.4%	Random by patient	**76**	**76**	**88**	**92**	**99.5**
	Random by center‡	67	70	**78**	**87**	**97**
AVAiL, headache,* 15.4%	Random by patient	**99.5**	**100**	**100**	**100**	**100**
	Random by center‡	**98**	**99.9**	**100**	**100**	**100**

NOTE. AEs in *italics* could be missed under patient subsampling. The other events are known events but are included here because the magnitude of the active arm rate excess versus the control arm illustrates the properties of AE subsampling. Results from the two missable events from ECOG 4599—hyponatremia with 2.4% excess and febrile neutropenia with 2.6% excess—were omitted because the subsampling results were similar to those for infection without neutropenia, which had a rate excess of 2.4%. Grade 3+ events are detected in a simulation when they appear in 2% excess over the control arm; grade 1 to 2 events are detected when they appear in 5% excess over the control arm. Rates of detection in **bold** are ≥ 75%.

Abbreviations: AE, adverse event; AVAiL, Avastin in Lung; ECOG, Eastern Cooperative Oncology Group; NA, not applicable.

*Known from previous trials.

†Identified as known in candidate trial from analysis of AEs to be collected in all patients (see Methods).

‡Sample sizes are approximate. The number of centers selected at random was determined to achieve an average number of patients at or above the target level.

signals (Table 2). Weighing the number and clinical significance of these signals against the effort required to collect them leads us to recommend that, although AEs should be collected comprehensively for the initial NDA/BLA to establish the drug's basic safety profile, toxicity data collection for subsequent supplemental trials should be limited to serious+ AEs in all patients and grade 3+ AEs in a subset of patients. The asymmetric collection of AEs (ie, only in patients on the investigational arm) should be avoided, as there is then no concurrent control for the accurate assessment of safety signals.

For the collection of grade 3+ events in the metastatic trials, a 400-patient subsample selected at random provided adequate probability, averaging 85%, of detecting events that would be notable in the full study (ie, those with an active to control rate excess of ≥ 3%). For AEs with 2% to 3% excess in the full study, there is an approximate 30% chance of missing the signal with a subset of 400 patients. Importantly, AEs close to the data cutoff are hard to detect, regardless of sample size. For example, even in a trial of 3,000 patients, there is a 50% chance of missing an event that has a true 2% excess frequency at a cutoff of 2%. Also, with a 400-patient subsample, the number of noise events is acceptably low, generally in the range of three events or fewer.

For larger metastatic trials and for adjuvant trials, the subsample size should be larger than 400, but it need not be proportionately so; our analysis suggests that subsample sizes from 400 to 800 patients should be sufficient. Based on our results, two approaches were formulated to allow the prospective determination of subsample sizes (Appendix: Sample Size Rationale, online only).[24] Subsampling may not be worthwhile in studies that have fewer than 600 patients total, given the effort required to set up the process.

In the adjuvant setting, the benefit/risk profile of a drug is different than in the metastatic setting. Patients and physicians are less willing to tolerate risk. Grade 1 to 2 events may play a larger role in establishing the safety profile of the drug, causing one to question whether it is wise to omit collection of grade 1 to 2 events in this setting. It is important to note that all events meeting the serious+ criteria would still be collected. Therefore, clinically important grade 1 to 2 events—ones that cause a physician to modify or discontinue dosing—would be collected. Using this data collection strategy would have saved the collection of 72,801 grade 1 to 2 AEs across six of our trials, averaging 4.7 AEs per patient, while still not missing any clinically significant events (Table 6).

A notable feature of our reanalysis is that the indication and control-arm medications used in the candidate study differed from the studies used to define the drug's known safety profile. Despite

Table 4. AE Incidence Differences Under Systematic Subsampling Methods for Metastatic Disease Studies

Study, AE, Active Arm Rate Excess in Full Study	Sampling Method	Subsample Size (total No. of patients) 200 (%)	300 (%)	400 (%)	500 (%)	600 (%)
Grade 3+ events						
JMDB, anorexia,*† 2.1%	Biggest centers‡	0.7	1.0	1.1	**2.5**	**2.3**
	First patients enrolled	1.6	1.6	**2.1**	**2.4**	**2.0**
AVAiL, *weight decreased,* 2.1%	Biggest center‡	**2.2**	**3.2**	**2.9**	**2.3**	**2.4**
	First patients enrolled	0.1	0.7	1.6	**2.3**	**2.3**
ECOG 4599 *infection without neutropenia,* 2.4%	Biggest centers‡	**3.5**	**3.1**	**2.3**	**3.4**	**3.0**
	First patients enrolled	**2.9**	1.4	1.5	**2.4**	**2.4**
EGF30001, *leukopenia,* 2.4%	Biggest centers‡	**4.7**	**4.2**	**4.5**	**3.6**	NA
	First patients enrolled	**3.9**	**3.3**	**3.0**	**2.8**	NA
EGF30001, *nausea,* 2.4%	Biggest centers‡	**2.1**	1.0	1.0	1.2	NA
	First patients enrolled	**3.0**	**2.6**	1.4	**2.0**	NA
ECOG 4599, proteinuria,* 3.0%	Biggest centers‡	**2.8**	**3.9**	**4.4**	**3.9**	**3.7**
	First patients enrolled	**2.0**	**2.0**	**4.0**	**3.6**	**3.4**
AVF2107g, *abdominal pain,* 3.4%	Biggest centers‡	**2.3**	**3.3**	**3.5**	**2.7**	1.5
	First patients enrolled	**4.6**	**3.2**	**3.9**	**4.3**	**4.9**
JMDB, nausea,*† 3.5%	Biggest centers‡	1.9	1.9	**2.0**	1.2	1.1
	First patients enrolled	0.8	**2.4**	**2.8**	**2.1**	**2.4**
AVAiL, epistaxis,† 4.3%	Biggest centers‡	**4.2**	**3.9**	**2.9**	**4.7**	**4.7**
	First patients enrolled	**5.1**	**5.4**	**5.6**	**4.7**	**4.7**
AVF2107g, *leukopenia,* 6.7%	Biggest centers‡	**7.9**	**10.6**	**9.6**	**7.3**	**6.4**
	First patients enrolled	**2.4**	**4.8**	**7.1**	**7.3**	**6.2**
Grade 1 to 2 events						
AVAiL, stomatitis,* 6.4%	Biggest centers‡	**4.3**	**7**	**7.2**	**7.1**	**6.7**
	First patients enrolled	**10.3**	**6.8**	**6.1**	**6.2**	**7.0**
AVAiL, headache,* 15.4%	Biggest centers‡	**8.5**	**9.7**	**12.6**	**13.5**	**14.9**
	First patients enrolled	**18.9**	**19.3**	**18.9**	**17.7**	**16.0**

NOTE. AEs in *italics* could be missed under patient subsampling. The other events are known events but are included here because the magnitude of the active arm rate excess versus the control arm illustrates the properties of the subsampling. Results from the two missable events from ECOG 4599—hyponatremia with 2.4% excess and febrile neutropenia with 2.6% excess—were omitted because the subsampling results were similar to those for infection without neutropenia, which had a rate excess of 2.4%. Incidence differences in **bold** are ≥ 2 for grade 3+ AEs and ≥ 5 for grade 1 to 2 AEs.

Abbreviations: AE, adverse event; AVAiL, Avastin in Lung; ECOG, Eastern Cooperative Oncology Group; NA, not applicable.

*Known from previous trials.

†Identified as known in candidate trial from analysis of AEs to be collected in all patients (see Methods).

‡Sample sizes are approximate. Enough centers were selected to meet or exceed the target subsample size.

these differences, there were few AEs that would be missed by subsampling. Therefore, our recommendations should apply broadly across supplemental applications except for the first submission after an accelerated approval (or full approval in smaller disease populations) or where the patient population to be studied in the supplemental indication is substantially different in clinical characteristics as to be at substantially higher risk of AEs than were seen in the trials we reanalyzed.

The systematic subsampling methods revealed no consistent bias in the estimates of full-trial AE rate differences in the trials we analyzed. However, random subsampling methods would ensure the absence of bias in general. Sampling centers at random provides the best balance of statistical legitimacy and operational feasibility, for both the site and the sponsor. Limiting sites to one data collection system reduces confusion and potential impact on data quality. A random selection of sites, although unbiased, may not adequately represent the study population. Therefore, we recommend stratification of the sample based on relevant site characteristics. In order to ensure enough patients are included in the subsample, the number of sites selected should be overestimated and ongoing enrollment should be monitored.

The comprehensive collection of concomitant medications is resource intensive and within a supplemental application contributes little to defining the safety profile of a drug. Therefore, although full data collection should continue for clinical trials supporting an initial indication, we recommend that for trials designed to support supplemental applications, collection of concomitant medications should be limited to specific targeted collections based on the known safety and pharmacologic profile of the investigational agent, medications that exhibit anticancer properties, and ones that meet a specific objective of the trial (eg, health economics or costing). Concomitant medications should continue to be reported in the narrative section of serious AE forms.

In conclusion, doctors want to recognize drug safety issues that lead them to change or discontinue a patient's treatment. Collection of large quantities of data that do not inform regulatory or clinical practice decisions taxes resources that could be used to improve the collection of more relevant data and thus risks obfuscating important safety signals. For phase III trials supporting supplemental applications, an optimized AE and concomitant medication collection strategy can identify clinically significant safety information and preserve resources otherwise spent collecting uninformative information. Once

Table 5. Number of Noise Events Detected Under Subsampling for Metastatic Disease Studies

Study and Sampling Method	No. of Noise Events				
	200 Patients	300 Patients	400 Patients	500 Patients	600 Patients
Grade 3+ events					
AVAiL					
Random by patient*	9	4.3	**2.4**	**1.2**	**0.3**
Random by center*†	5.4	**2.8**	**1.5**	**0.7**	**0.2**
Biggest centers†	5	**0**	**0**	**0**	**0**
First patients enrolled	16	9	**2**	**0**	**0**
AVF2107g					
Random by patient*	13.2	7.6	4.9	3.3	2.3
Random by center*†	8.8	5.1	3.6	**2.5**	**1.6**
Biggest centers†	13	5	**1**	**1**	**1**
First patients enrolled	8	**3**	**2**	**2**	**0**
ECOG 4599					
Random by patient*	9.9	5.8	3.9	**2.6**	**1.6**
Random by center*†	6.7	4.3	**2.8**	**2**	**1.2**
Biggest centers†	**3**	**2**	**1**	**2**	**2**
First patients enrolled	5	4	**1**	**2**	**1**
EGF30001					
Random by patient*	12	7	4	**2**	NA
Random by center*†	8	5	**3**	**1**	NA
Biggest centers†	6	4	**1**	**1**	NA
First patients enrolled	4	4	**3**	**0**	NA
JMDB					
Random by patient*	**0.448**	**0.39**	**0.422**	**0.528**	**0.139**
Random by center*†	**0.534**	**0.387**	**0.449**	**0.373**	**0.17**
Biggest centers†	**1**	**2**	**1**	**1**	**1**
First patients enrolled	**1**	**2**	**3**	**3**	**2**
Grade 1 to 2 events					
AVAiL					
Random by patient*	5	**1.8**	**1**	**0.2**	**0**
Random by center*†	3.9	**1.9**	**0.8**	**0.3**	**0**
Biggest centers†	**1**	**0**	**1**	**0**	**0**
First patients enrolled	7	**1**	**1**	**0**	**0**

NOTE. Noise event quantities in **bold** are ≤ 3.
Abbreviations: AVAiL, Avastin in Lung; ECOG, Eastern Cooperative Oncology Group; NA, not applicable.
*Noise events for random sampling methods are reported as mean numbers determined from 1,000 simulations.
†Sample sizes are approximate due to analysis structure for sampling by center methods.

Table 6. Number of AEs

Study (safety population analyzed)	Distinct No. of AEs (average No. of AEs per patient)					
	Grade 1 to 2 AEs Not Serious+		Grade 3+ AEs Not Serious+		SAEs and AEs Leading to Dose Discontinuation/ Change Serious+	
	No.	Avg	No.	Avg	No.	Avg
Metastatic studies						
AVF2107g (n = 788)	NA		1,297	1.6	1,187	1.5
AVAiL (n = 656)	6,245	9.5	1,030	1.6	849	1.3
EGF30001 (n = 580)	6,943	12.0	377	0.6	725	1.2
JMDB (n = 1,669)	10,514	6.3	835	0.5	2,504	1.5
Adjuvant studies						
BIG 1-98 (n = 7,963)	28,098	3.5	9,612	1.2	12,845	1.6
CALGB 89803 (n = 1,264)	13,300	10.5	2,150	1.7	976	0.8
HERA (n = 3,386)	7,701	2.3	161	0.05	535	0.2
Total	72,801	4.7	15,462	0.9	19,621	1.2

NOTE. SAEs were not identified in study Eastern Cooperative Oncology Group 4599.
Abbreviations: AEs, adverse events; SAEs, serious adverse events; NA, grade 1 to 2 adverse events were not analyzed for trial; AVAiL, Avastin in Lung; BIG, Breast International Group; CALGB, Cancer and Leukemia Group B; HERA, HERceptin Adjuvant; Avg, average.

several applications that use this methodology have been reviewed by the FDA, it will be important to determine the benefit of subsampling itself and assess whether collection of only serious+ events may be sufficient.

Although this project focused on collection of AE and concomitant medication data, steps could be taken in other areas to further simplify study conduct. For example, significant resources were expended to perform an independent radiologic review of progression events in the Eastern Cooperative Oncology Group 2100 trial that only served to validate the original trial results.[25]

For clinical trials intended to support supplemental NDAs/BLAs, symmetric collection of events, regardless of grade, that are serious or lead to dose modification/discontinuation or death should occur in all patients. Grade 1 to 2 events and complete concomitant medication records need not be collected. Grade 3+ events should be collected in a subsample of the full trial. This optimized data collection strategy leads to a high probability of capturing events that matter most to patients and their physicians.

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