

LE Magazine September 2007

REPORT

The Abigail Alliance

Motivated by Tragic Circumstances, Families Battle an Uncaring Bureaucracy

By Sue Kovach



Founded in November 2001 after the tragic cancer death of its young namesake, Abigail Kathleen Burroughs, the Abigail Alliance is working for FDA regulatory changes that would allow patients with cancer and other life-threatening illnesses—and no other treatment options—to have access to promising investigational drugs.

The Abigail Alliance is seeking to have legislation passed that will remove the regulatory barriers currently preventing seriously ill patients from gaining early access to developmental drugs showing efficacy in clinical trials. The Alliance also aims to modernize the FDA's antiquated scientific approval process for drugs intended to treat life-threatening diseases, and seeks to place the decision to use experimental treatment options with patients and their physicians, rather than the FDA.

ABIGAIL BURROUGHS: INSPIRING CHANGE

Abigail Kathleen Burroughs was only 21 years old when she succumbed to squamous cell carcinoma that had invaded her neck and lungs. Her cancer diagnosis at age 19 was a tremendous shock, as the type of cancer she had is particularly rare in one so young. Typically, older men who smoked and drank for decades receive this devastating diagnosis. Abigail was an honor student and high school athlete, a confident yet humble person who was wise beyond her years, according to her family and friends. And she was compassionate, devoting much of her young life to charity work, making beds at homeless shelters and creating a free tutoring program for 50 families who couldn't afford tutors. Abigail had a great love of life and a deep respect for all beings.



Not long after her diagnosis, the Burroughs family learned of an investigational cancer drug, Erbitux®, that showed good response in early trials. Abigail's prominent oncologist at Johns Hopkins Hospital believed the drug had a significant chance of saving her life. But every effort on the part of her family, physician, and supporters to procure the drug for Abigail failed. She was ineligible for a clinical trial and the drug company couldn't provide her with Erbitux® for compassionate use. The FDA was unmoved by her life-and-death situation.

In November 2000, Abigail was recovering from a round of chemotherapy and radiation treatment when she said to father, Frank: "Dad, if I make it, I'd like you and I to devote our lives to helping people with cancer and other illnesses where there's an unmet need." After seven months of battling to acquire Erbitux® for Abigail, she died, her young life tragically cut short by an indifferent system that has cost an untold number of lives.

Hours after she died, through his tremendous grief, Frank Burroughs realized that the inability of seriously ill patients to obtain effective drugs still under study was a critical unmet need. His daughter had wanted to help not only herself, but others like her, and Burroughs knew then that he had to continue fighting the system.

Burroughs explained, "Hundreds of thousands of Americans die every year awaiting drug approval, a catastrophe of immense proportions. I said to myself, 'Why should I quit now? There are other people out there who are just as precious as Abigail.' She had planted the seed of an idea. She was the embodiment of the unmet need. But we certainly weren't the only ones."

THE ABIGAIL ALLIANCE: WHAT YOU NEED TO KNOW

- Under the FDA's outdated system of drug approval, it can take years before beneficial drugs become available to seriously ill people. Every year, hundreds of thousands of patients with cancer and lifethreatening illnesses die while waiting for promising investigational drugs to receive approval.
- Abigail Burroughs was a young cancer victim who perished because she was not able to access an experimental cancer drug. After Abigail's death, her father Frank Burroughs formed the Abigail Alliance.
- The mission of the Abigail Alliance is to make potentially life-saving investigational therapies readily available to patients with cancer and other life-threatening illnesses.
- One of the key objectives of the Abigail Alliance is to pass a bill that would allow seriously ill individuals to gain early access to promising investigational drugs that have not yet been approved by the FDA.
- The Alliance's other objectives include helping cancer patients to gain better access to experimental therapies such as Erbitux® and Nexavar®, promoting better awareness of clinical trials, and supporting efforts that would eliminate the use of placebos in clinical trials.

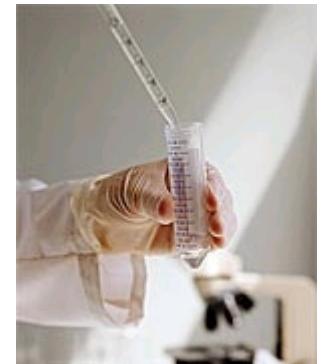


After his daughter's death, Frank Burroughs formed a non-profit advocacy group, the Abigail Alliance for Better Access to Developmental Drugs. He gathered volunteers and supporters to raise awareness on Capitol Hill and in the general public of the issues surrounding compassionate use of developmental drugs, and to push for change in the FDA system that denies seriously ill patients access to possibly life-saving therapies.

In its short six years of existence, the Alliance has gained favorable media coverage for these issues and has presented the heartbreaking stories of the patients behind them. With the help of the Washington Legal Foundation, the Alliance has shown that it won't be ignored by filing a Citizen Petition and even taking the FDA to court. Its practical solutions to fix a flawed and deadly system are contained in the proposed legislation, which could save countless lives.

DRUG APPROVAL SYSTEM FAILS PATIENTS IN NEED

The problems inherent in the FDA clinical trial and drug approval system can be fully illustrated by looking at how it failed Abigail Burroughs and others, such as Jennifer McNellie, wife of Abigail Alliance co-founder Steve Walker. Jennifer was diagnosed with colon cancer at age 45 and ran out of treatment options after her first regimen. The couple, both scientists, did their own research and learned about several drugs under study that were found to be effective in trials. But they, too, discovered that the drugs were beyond their reach and that approvals could be years away. Jennifer McNellie died at age 47, another victim of the clinical trial system.



Says Steve Walker: "I delved into the regulations, trying to figure out why the system wasn't working. As scientists, Jennifer and I both understood how the trials were being conducted. It didn't take us long to determine that the FDA is an ineffective agency. I lobbied senators and representatives, and I lobbied the FDA, which was completely non-responsive."

The FDA's drug study and approval system is meant to protect patients, certainly, but shouldn't it also reap the benefits of billions of research dollars and years of drug development and testing by bringing medical progress to those who need it most? No seriously ill person should have to die merely because the FDA stamp of approval on a drug is years away. Yet that's exactly what is happening. The reason it's happening was a shock to Burroughs, Walker, and Abigail Alliance supporters.

LEGISLATION THAT THE ABIGAIL ALLIANCE SEEKS TO PASS WILL:

- Allow seriously ill patients who have exhausted all other treatment options to receive developmental drugs outside of clinical trials. The drug company would provide the drug and control this process, and the medications could be provided as early as completion of Phase I trials, but only if there is compelling evidence for efficacy.
- Protect clinical trials by requiring patients to have exhausted approved treatment options for their disease, including clinical trials and expanded use programs, before acquiring a developmental drug under the Tier 1 Approval Program.

- Ban the use of placebo and no-treatment arms in trials involving seriously ill patients.
- Return some risk-benefit decisions to patients and their physicians, eliminating current law and policy that places risk-benefit decisions solely with the FDA.
- Remove cost disincentives that prevent small biotech firms who develop most innovative investigational drugs from participating in expanded use programs.

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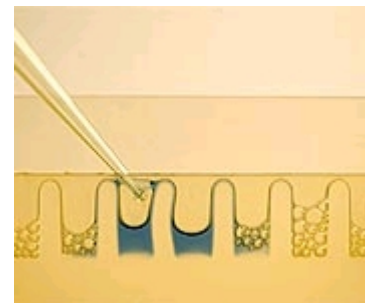
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NOVEL THERAPIES UNAVAILABLE TO MOST PATIENTS

Currently, drugs showing efficacy in clinical trials are completely unavailable to seriously ill patients who don't qualify for trials. The drugs often can't even be obtained on a compassionate use basis. But getting into clinical trials, no matter how ill you are, could be compared to winning a lottery because the odds of being selected can be almost as slim. This is due to the vast number of restrictive participant requirements imposed by the FDA, some of which demand that seriously ill patients with little time to waste first try—and fail—one or more other available treatments.



With no compassionate use program, Abigail's and Jennifer's only hope was to get into a clinical trial. In Abigail's case, Erbitux® was found to be effective in early trials against the type of cancer cell she had, one shared by both colon and head and neck cancer, among others. Cancer, however, is characterized in trials not by its cellular properties, but by the initial tumor site. So later trials were conducted according to where the cancer is located rather than the type of cancer cell—in this case, for colon cancer only. This restriction was the primary reason Abigail was kept out of the Erbitux® trials—though she had the right type of cancer cells, her cancer was in the wrong place. Economics also played a part, as the drug company would have had to spend twice as much money to put Erbitux® on two separate approval paths.

“Increasingly narrow trial participant restrictions—and more of them—leave most terminally ill people out of clinical trials, including Jennifer McNellie. Many of the restrictions are put in place purely for statistical reasons,” says Walker. Of the patients who do qualify, only a few will be given the chance for a longer life. A Phase III clinical trial for a lung cancer drug, for example, might enroll only 700 patients, yet more than 150,000 die from lung cancer every year. Even worse, only half of those in trials will actually get the potentially life-saving drug because the FDA usually requires that 50% of trial patients—for statistical reasons—receive a sugar pill placebo. Seriously ill patients don't know if they're taking a new drug that could save them, or an empty placebo equal to a death sentence.

ACCOMPLISHMENTS AND CONTINUING EFFORTS OF THE ABIGAIL ALLIANCE

- Developed the Tier 1 Initial Approval (Tier 1) initiative that would greatly increase access to developmental drugs for tens of thousands of cancer patients and others with life-threatening illnesses. This effort resulted in the introduction of bills in the House and Senate known as the ACCESS (Access, Compassion, Care, and Ethics for Seriously Ill Patients) Act (S.1956 and H.R. 6303).
- Filed a Citizen Petition with the FDA in support of Tier 1, with the help of the Washington Legal Foundation, resulting in the FDA working on proposed policy changes. (Unfortunately, this is a very slow process at the FDA.)
- Filed a lawsuit effort in support of better access to new life-saving and life-extending therapies with the pro-bono help of the Washington Legal Foundation and the law firm of Latham and Watkins, LLP. Progress continues and in May 2007, the Abigail Alliance won a legal round in the US Appellate Court.
- Efforts led to an expanded access program for the colon cancer drug Erbitux®.
- Contributed to the effort to get thousands of multiple sclerosis patients back on the efficacious drug Tysabri®.
- Successful in having placebos removed from a clinical trial for kidney cancer, eventually resulting in all patients in the trial—and many who left the trial—receiving the efficacious cancer drug Nexavar®.

- Helped acquire trial drugs for several individuals who had to leave clinical trials on minor issues, but were responding well to their therapies. Additionally, helped other patients get compassionate use of promising investigational drugs.
- Along with others in the private sector, pushes the Critical Path Initiative (CPI), a US Department of Health and Human Services/FDA modernization project that would cut the costs of drug approvals, speed up the approval process, and reduce the use of placebos.
- Promotes ways to better inform the public about clinical trials. With the Lorenzen Cancer Foundation, the Alliance continues to work on an improved clinical trial database called Cancer Patients' Alliance for Clinical Trials (CancerPACT). Due to Alliance efforts, the NIH better promotes the vital website, www.clinicaltrials.gov.
- Continues to be the rallying point for individuals and organizations who agree with the need for change in the system, adding more friends and allies each year.

CLINICAL TRIALS RULED BY STATISTICS, NOT COMPASSION

"The clinical trial system is run by statistics—a branch of applied mathematics," notes Steve Walker. "It's caused millions of people to die sooner than they should have and it's all because of the FDA's single-minded focus on statistics as the only tool to use. In any other field of science, this is sacrilege. Statisticians are a support specialty. But in clinical research, it's considered sacrilege to question statistics. And statistics in no way reflect the reality of disease."

Specifically, the statistic so desired by the FDA is the probability value, or p-value—the mathematical probability that the data are the result of random chance. (Data with a low p-value of less than or equal to 0.05 are considered to be "statistically significant." A p-value of 0.05, for example, means there is a 1 in 20 probability that the data result from random chance.)

What many people don't realize is that the current drug approval system bases the decision to approve or not approve a new drug on average results. The way this drug approval process is designed, statistical analysis evaluates the probability that a drug will have a predefined desired outcome, such as a 50% reduction in tumor size and/or number, based upon an average result.

If a new cancer drug produced a dramatic improvement in 15% of the patients with a deadly form of cancer, yet the average of all patients achieving 50% reduction in tumor size failed to achieve statistical significance, this drug would be unlikely to be approved under today's outmoded system. But if the same drug did not produce a dramatic improvement in any patient, yet achieved statistical significance based upon an average response rate, the drug would be more likely to be approved in the current system.

Although the FDA is slowly and begrudgingly moving towards using active comparators rather than placebo in many studies, many drug approval studies in serious disease states like cancer still use placebo as a comparison. This raises significant ethical issues—why should a patient with deadly life-threatening cancer participate in a study when there is a high likelihood of receiving placebo for treatment?

Says Burroughs: "Essentially, they want people to die so they can see how many die. And that's the cruelty of all this. Cancer trials aren't like trials for toenail fungus cream. People's lives are at stake here."

The formal drug approval process needs to balance compassion with statistical analysis. The FDA's continued insistence on using placebo instead of active comparators of approved drugs raises significant ethical questions, since the lives of seriously ill patients are at stake.

KIANNA KARNES: ANOTHER VICTIM OF THE FDA'S DELAY

The Alliance's face of the placebo trials issue was Kianna Karnes, a 44-year-old mother of four and grandmother of one whose kidney cancer had spread throughout her body. By early 2005, she had little hope left, except for two developmental drugs that had shown efficacy against her type of cancer for several years, but were still unapproved.

Despite desperate pleas from Karnes' family, supporters, and the Abigail Alliance, the FDA refused to hasten approval of the drugs. Astoundingly, the agency instead created new testing requirements that effectively shackled the drugs' manufacturers and prevented them from giving Karnes the drugs on a compassionate basis. The requirements demanded that a sugar pill placebo be given to dying patients, all in the name of obtaining survival data.

"The public should be totally outraged," Walker says. "Statistics has turned the FDA clinical trial system into a barbaric, almost

criminal pursuit of p-values. It has nothing to do with the responsible and ethical practice of medicine.”

Media coverage of Karnes’ plight was intense. The Wall Street Journal was blistering in its condemnation of the FDA, accusing the agency of having a “placebo fetish” and editorializing on March 24, 2005: “The problem here is the FDA’s unethical—and let us stress, unscientific—placebo-controlled trials, in which a subset of study patients are knowingly denied the new treatment and in some cases denied access to any active treatment at all. This may be moral with an antihistamine; it’s certainly not with treatments for a terminal disease. What’s more, it’s entirely unnecessary. We already know what happens to most cancer patients who don’t get treated. They die.”¹

ABIGAIL ALLIANCE DRUG SUCCESSES

THE ABIGAIL ALLIANCE LOBBIED FOR EARLY ACCESS TO THE FOLLOWING DRUGS, WHICH ARE NOW FDA-APPROVED:

DRUG	CONDITION(S)	YEAR AA STARTED LOBBYING
Abraxane®	Breast, head and neck, prostate, gastric cancers	2004
Alimta®	Lung cancers (non-small cell, malignant pleural mesothelioma)	2002
Avastin®	Many uses	2002
Bexxar™	Non-Hodgkin’s lymphoma	2002
Eloxatin®	Colon and other cancers	2002
Erbix®	Colon, head and neck, and other cancers	2001
Fragmin®	Symptomatic venous thromboembolism (VTE)	2004
Gleevec®	CML (leukemia)	2001
Nexavar®	Kidney cancer	2004
Revlimid®	MDS (blood disorder) and multiple myeloma	2002
Sutent®	Kidney cancer	2002
Tarceva®	Lung and pancreatic cancer	2002
Torisel™	Kidney cancer	2004
Tysabri®	Multiple sclerosis, Crohn’s disease	2005
Tykerb®	Breast, brain, lung cancer	2004
Velcade®	Multiple myeloma	2002

DRUGS FOR WHICH THE ABIGAIL ALLIANCE IS NOW SEEKING EARLY ACCESS:

DRUG	CONDITION	MANUFACTURER
Genasense®	CLL (leukemia)	Genta
Provenge®	Prostate cancer	Dendreon

And so did Kianna Karnes, one day after the editorial was published. But the cruelest twist of all had occurred when the FDA, red-faced from the Journal’s op-ed piece, had relented and told Karnes’ family it would approve the drugs’ use on an emergency basis—much too little, far too late. In announcing Karnes’ death days later, the Journal again took the FDA to the woodshed, calling its oncology division “incorrigible” and stating: “... it’s time for Congressional action mandating that the agency use 21st-century science and statistical methods to get these therapies to patients sooner. More specifically, drug approvals could be based on large trials open to all comers and analyzed with so-called Bayesian statistics [which incorporate prior knowledge and accumulated experience into probability calculations], as already happens in the FDA’s medical device division. (Yes, the agency at least recognizes that studies involving, say, ‘placebo’ defibrillators would be beyond the pale.)”²

It’s not that the FDA doesn’t know how to fix the broken system of cancer drug approval. The problem seems to be that it simply won’t. The FDA is a stagnant agency existing in a constant state of institutional worry, says Burroughs. While the Abigail Alliance talks about the issues, the FDA talks about the status quo. “The resistance to change is so powerful. People want to hold on to the status quo,” Burroughs says. “They say, ‘This is how we’ve always done things.’ They’re concerned about how to handle the PR if someone dies during early access use. We are not trying to dismantle the clinical trial process—all we want to do is improve it.”

PROMOTING CHANGE

The solutions proposed by the Abigail Alliance would indeed improve the process by modernizing the methods used to fit the current state of science, while relegating the use of statistics to its proper secondary role in the process. The Abigail Alliance has taken a hard stance in its fight against the FDA. Its first major effort, a 2003 white paper plan titled Tier 1 Initial Approval, became the basis for the legislative action. It described a three-tier approval process in which Tier 1 would allow early approval and provide developmental drugs to those abandoned by the current system. The Tier 1 white paper was presented to then-FDA commissioner Mark McClellan in person. The FDA's response was a letter to the Alliance that essentially said the agency would continue to do business as usual.

The Alliance then filed a Citizen Petition with the FDA in June 2003. To this day, they've received no response. Undeterred, the next step was a lawsuit filed on July 28, 2003 against McClellan and Tommy Thompson, then-Secretary of the Department of Health and Human Services (the FDA is an operational division of DHHS). The lawsuit seeks to stop the FDA from enforcing a policy that "violates the constitutional privacy and liberty rights of terminally ill patients, including numerous Abigail Alliance members, and their constitutional guarantee against deprivation of life without due process." The suit was dismissed in District Court in 2004, but the Alliance appealed and last May won the first round in Appellate Court, says Burroughs.

"The case was heard before a panel of three judges and we won in a two-to-one decision. The lawsuit was reinstated. But the FDA appealed and has requested that the US Appellate Court of DC re-hear the case en banc, meaning before all ten judges."

Legal watchers say the court is pretty evenly divided and they believe the appeal could go either way. But the Alliance is optimistic—when oral arguments were presented, observers say a third of the judges were hard on the Alliance, but a third were hard on the FDA, and the remainder were simply quiet. A decision is expected literally any day now.

Says Burroughs: "We hope and pray that the patients win. One way or another, this will likely end up in the US Supreme Court, as the FDA will probably appeal if they lose, and if we lose, we'll definitely appeal. My guess is the Supreme Court will hear the case, as this is a landmark issue, and an important issue."

The Alliance believes that at its core, this is a major civil rights issue. While the FDA trembles at the word "risk," terminally ill patients can view the risks of taking developmental drugs as the only option they have left. The FDA greatly amplifies concerns about safety, and minimizes and contests evidence of efficacy, says Walker. "It's a risk-averse stance that the FDA routinely takes on all drug development and approval programs, and they use statistics to do it."

It's also a privacy issue in that the decision to take an investigational drug and the unknown risks associated with it should be the private decision of a patient in consultation with their doctor. The FDA shouldn't make the decision for others, a fundamental reason why the Alliance's fight can be viewed as patient and doctor versus paternalistic FDA.

Says Burroughs: "One of our strengths is that we get the facts out there. We get a lot of good press, and when our issues are in the media, it resonates with the public. People understand that these are important issues. In poll after poll, we find that the public is willing to take risks, and the last time I checked this was a democracy, but that's not what we're seeing. The FDA currently decides what the risk-benefit is, and they're sorry you have a terminal illness, but they don't want you having any side effects."

HOPE FOR THE FUTURE

The best evidence of the Alliance's effectiveness is that every drug they've pushed for has been approved. "Every drug for cancer and other serious life-threatening illnesses that the Abigail Alliance has pushed for earlier access to in our six year history is now approved by the FDA," Burroughs says. "Many lives could have been saved or extended, if there had been earlier access to these drugs."

PHASES OF CLINICAL TRIALS

Phase I: An experimental drug or treatment is tested in a small group (e.g., 20 people) for the first time to evaluate preliminary short-term safety, determine a dosage range, study metabolism and pharmacologic actions in humans, and identify side effects with increasing dosages. Phase I trials may include healthy participants and/or patients.

Phase II: The experimental drug or treatment is tested in a larger group (e.g., 80 patients) to determine effectiveness for a particular indication or indications in patients with the disease or condition under study, for further safety evaluation and to continue to evaluate for side effects.

Phase III: Performed after preliminary evidence suggesting effectiveness has been obtained, the experimental drug or treatment is given to larger groups of people (e.g., 1,000 patients) for longer periods of time. The overall risk-benefit relationship of the drug is evaluated and information is gathered for physician labeling. Phase IV: Post-marketing studies on the drug or treatment gather additional information on the risks, benefits, and optimal use.³



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