WORLDWIDE CLINICAL TRIALS

6 REASONS EARLY PHASE ONCOLOGY TRIALS FAIL

Learn the pitfalls that can cause early phase trials to fail and tips to prevent your own trial from struggling

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EARLY PHASE ONCOLOGY RESEARCH FACES UNIQUE CHALLENGES

Only 15% of oncology drugs that get started in clinical trials reach phase III studies, and the likelihood of approval (LOA) for any new anticancer drug entering clinical trials is just over 5%.[1] This is not only expensive but also frustrating and discouraging for all involved. Furthermore, it creates a deterrent to sites and patients who might be willing to participate if the odds of success were greater.

WHY IS THE SUCCESS RATE SO LOW? WHAT CAN YOU DO FROM THE START TO AVOID A FAILED EARLY PHASE STUDY?

The world of oncology clinical trials is changing. Anticancer therapies hitting the realm of clinical research increasingly include molecularly targeted agents (MTAs) – small molecule inhibitors, monoclonal antibodies, and immunotherapies – which, up until two decades ago, were largely just part of the dream of precision medicine. Unfortunately, these new classes of therapies fail prior to approval at alarmingly high rates, in part due to the fact that the entire history of early phase oncology trials has evolved around the proper study of a different class of drugs: cytotoxic agents. But there's clearly more to the story.

New therapies for cancer face an uphill battle. Unlike many studies of drugs for chronic diseases and acute illnesses, cancer drugs must typically demonstrate a substantial impact on progression-free survival in a group of patients who desperately need an effective treatment. Side effects and quality of life, together with surrogate efficacy end points, create a daunting array of data to juggle and factors to consider. This pressure can make it even more challenging to select a contract research organization (CRO) to help bring your drug from preclinical studies to post-approval success.

By proactively working to avoid the common roadblocks in early phase oncology trials – and bringing in trial planning and administration experts to lay out an optimal strategy for your drug development program – you can give your drug the best possible chance at success.

IT'S HARD TO BE A NOVEL CANCER DRUG

New cancer drugs have a LOA of just 5.1% compared to the overall average of 9.6%, and the highest success rate is in hematology (26.1%).[1]

63% of phase I oncology trials progress to phase II, but only 25% of phase II studies move on to phase III. This means only 15% of oncology studies in phase I will make it to phase 3.[1]

Solid tumor programs are only half as likely to get through to approval as hematologic cancer drug programs (4.1 vs. 8.1%).[1]

Companies with numerous drugs in the works pay > $5 billion to get a single drug to market because of the high drug failure rate.[2]

The cost of failure is high for patients and pharmaceutical companies.

Why do early phase oncology drug trials perform so poorly?

Many studies need to be rescued because of complications arising from the following problems listed on the next several pages.

1 | MISSING PARTNERSHIPS

Many promising new therapies have been abandoned on the road to approval due to late-stage surprises. Often, these surprises arise from a challenge that plagues the entire range of investigational therapeutics: the lack of scientific partnerships.[3,4]

In the early phases of clinical research, it is not uncommon to find a lack of informative preclinical data in animal models, pharmacokinetics, toxicity, mechanism of action, drug pathways, up- and down-regulation of affected pathways, probability of resistance, and more. Not only does this predispose many oncology drugs to unpredictable early phase studies but also it hinders the ability to select study parameters that can maximize the likelihood of detecting true efficacy.

Lack of sufficient scientific partnerships can snowball into uncertain decision-making in the selection of patient populations, dosing levels, laboratory markers, combination therapies and comparators, and end points.

Worldwide Clinical Trials offers support for both clinical and preclinical research that can help build a robust scientific foundation for early phase oncology trials. Services include:

BIOEQUIVALENCE TESTING

PHARMACOKINETIC/ PHARMACODYNAMIC CORRELATION

TOXICOKINETICS AND BIOAVAILABILITY

2 | STATISTICS CAN ONLY DO SO MUCH

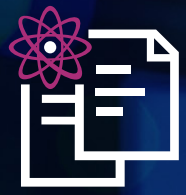
When the science is missing, statistics can do little to help. And when the science is good but the statistics are in doubt, even a potential superstar drug can be in trouble.

Statistics are not intended to make a drug look better than it is, and they should not be used to indicate an effect when there is none. However, statistics can be powerful tools that, when used properly, can give a new therapy the best possible chance of demonstrating its efficacy and safety via a trial that minimizes risk and optimizes resources.

Studies relying on bad statistics – face the likely stumbling blocks of improperly sized studies, difficulty detecting clinical significance, and confusion over appropriate stopping points.

Worldwide offers comprehensive biostatistical support solutions, including:

Methodology planning and statistical management



Study randomization assistance

Dose-finding, sample size, and power calculations

Parametric and non-parametric analysis of clinical and pharmacokinetic end points

Interim and summary analyses

3 | STUDY DESIGN NEEDS STRENGTHENING

Study design is informed by science and optimized by strategy. Floundering early phase studies often cannot be saved with novel scientific approaches without substantial timeline setbacks. But studies that carefully evaluate and consider preclinical data can significantly improve the chance of clinical success. Evaluation of that preclinical data by Worldwide's scientific experts is exactly that. We are careful, and we consider the entirety of your program before we design the study.

Key threats to a successful clinical design include:

Overtaxing participants. The more visits and procedures involved in a study, the more demanding and difficult the study schedule is to maintain.

Improperly timing dose escalations. Timing each new participant's exposure and each dose escalation properly can allow faster identification of safety risks and more efficient progression toward target toxicity levels.

Selecting the wrong parameters. Regardless of the underlying science, study designs often include the wrong number of patients in various dosing groups, poorly optimized dose levels, poorly selected end points, and checkpoints that do not provide enough data.

Neglecting the idea of combination therapies. Early phase oncology trials often do not include combination therapies that could provide protective or synergistic therapeutic effects, likely because of the rush to get a new potential therapy to trial. By overlooking opportunities to combine the new drug with approved products, trials may be poorly positioned to identify the drug's true potential in the clinic.

Worldwide was selected as a top performer in all rated categories in ISR Reports 2019 CRO Quality Benchmarking – Phase I Service Providers study.[5]

Let our early phase study design experts build your study appropriately and give your drug the greatest chance of demonstrating success. We have special expertise in clinical pharmacology, complicated and unique procedures, and special populations.

4 | SURROGATE END POINTS HAVE A DOWNSIDE

In oncology, surrogate end points can have definite advantages; the trick is using them effectively. Worldwide has teams dedicated to early phase oncology work, with experts in bioanalytical services who can help plan a study right – from the start – and keep it from derailing due to inconclusive findings or excessively extrapolated data.

After the initial thrill over the approved use of surrogate end points, such as a shrinking tumor or a reduction in biomarkers, the field of oncology has had to face a sobering reality: End points are still a point of difficulty for many early phase studies.

Surrogate end points can be great for hastening progression through early research phases, but they can be misleading. They can initially suggest that a treatment is promising when it may make no difference in disease progression and survival or quality of life, and they can also result in inappropriate decisions for future study phases.

By nature, surrogate end points rely on extrapolation. When there is insufficient information about how well the surrogates predict the true outcomes of interest, programs can find themselves in trouble as they move to each new stage in the journey toward approval. This may result from basing study sizing, dosing, and design approaches around anticipated drug efficacy that arose from misleading findings from a surrogate end point.

And the dangers do not end there. Drugs approved based on surrogate end point data need to later demonstrate impact on overall survival or quality of life or risk removal from the market. Unfortunately, by several years after approval, many (up to 86% of drugs approved based on surrogate end points) fail to conduct/report this research or fail to demonstrate increases in survival.[6]

5 | SCREENING IS A DOUBLE-EDGED SWORD

Early phase oncology trials must walk a fine line in their selection of initial participants. Strict inclusion and exclusion criteria are essential to the identification of individuals who are well enough to take part, unlikely to have confounded results, and representative of the remaining patient population intended for the drug. However, when criteria are overly restrictive or not highly customized, the trial may fail to achieve recruitment targets or the selected participants may not actually be among the patient group most likely to benefit from the drug.

In recent years, the widespread emergence of biomarkers and genomic screening during participant selection processes has somewhat lessened these risks. Yet despite their potential utility, biomarkers are not always used in inclusion criteria for Molecularly Targeted Agents trials and, in some cases, are not clinically validated or available. This can make it extremely difficult to detect a drug's true potential – even when the statistics and study design are otherwise excellent.

Worldwide offers **validated assays**, as well as customized support for bioanalytical method development, validation, and application.

Let our experts in bioanalysis and method validation guide you to a meaningful solution for your screening and study end point requirements.

6 | SITES NEED MORE SUPPORT

The sites that make early phase research a reality have a crucial role in the success of a study. Unfortunately, sites are not always selected properly or are selected without taking the time to develop a strong relationship with clinical staff on the ground.

Half or more of all study sites recruit one or no patients.[7,8] Furthermore, sites may be overwhelmed by the administrative, procedural, and staffing burden of many studies. Ineffective sites translate to bad news for study success.

Sites with inadequate support or poor relationships with the CRO or sponsor may:

- **Be insufficiently prepared for protocol procedures**
- **Lack the proper resources for contributing to the study**
- **Fail to properly engage with potentially eligible patients**

In short, failing to adequately support and court study sites can result in struggling studies at any stage of research, but the shortcoming can be particularly damaging in early phase trials, when study sites are often limited in number.

Worldwide can do the work for you, no matter where you want it done. We support trials in more than 60 countries, and we also operate more than 100 studies per year in our Clinical Research Unit (CRU) in San Antonio, TX. Our CRU has:

- **180 beds**
- **On-site cGMP phase 1 compounding pharmacy services**
- **Local Pharmacokinetic analysis**
- **Capacity to facilitate a wide range of complicated testing, selection, and special population services**

The Best Way to Save a Study from Failing Is to...

...form great scientific partnerships

Worldwide offers the expertise needed to rescue failing studies, of course. More importantly, we offer unparalleled experience in the design of new clinical trial programs with the most advanced strategic planning.

Let us help give your study program the best chance at success by working to optimize your approach, starting from the very beginning. We stand by our track record of successful trial design and satisfied customer relationships[5] for every phase of research, and we hope to have the opportunity to show you why we are the uncommon CRO.

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Sherilyn Adcock, R.Ph., Ph.D.

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Dr. Sherilyn Adcock, R.Ph., Ph.D., serves as Chief Scientific Officer, Early Phase Development, at Worldwide Clinical Trials, LLC (Worldwide). Prior to joining Worldwide in 2001, Dr. Adcock was the Senior Director of Clinical Site Operations for SCIREX Corporation in Austin, Texas.

In addition, she held posts as Vice President of the Clinical Research Center and Director of Business Development at Phoenix International Life Sciences, Director of Clinical Research and Business Development at HealthQuest Therapy and Research Institute, a Senior Project Director for the Biomedical Research Group and a Principal Investigator and Assistant Director of Project Management at Pharmaco International. She began her career as a Pharmacist and Clinical Instructor in Pharmacy and was the Pharmacy Services Supervisor at Mother Frances Hospital in Tyler, Texas. In addition to her licensure by the Texas State Board of Pharmacy, Dr. Adcock is certified in basic cardiac life support and sterile products preparation. She is a Member of the American Association of HealthCare Pharmacists, the Drug Information Association (DIA), and the American Association of Pharmaceutical Scientists (AAPS). Dr. Adcock earned her B.S. in pharmacy, a M.S. in health science, and a Ph.D. specializing in community health, all from the University of Texas at Austin.

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Dr. Cantarini brings a long history in clinical research to her role as medical and scientific affairs consultant at Worldwide. Sponsors focused on oncology appreciate her experience with the Oncology Early Clinical Development organization at AstraZeneca, where she was involved in Phase I/IIb studies across several cancer indications across global locations (including the EU, US, Southeast Asia, Japan, South America, South Africa, and China). Most recently, Dr. Cantarini was involved as Executive Medical Director in the Osimertinib (indication T790M-positive non-small cell lung cancer (NSCLC)) program, taking the clinical development from first dose-in-human to full regulatory approvals in all major territories (FDA, EMEA, Japan, and China) in four years. She has been board certified in Pharmaceutical Medicine (GMC specialist register) since 2005 and has a 30-plus-year record of publications in peer-reviewed journals.

ABOUT WORLDWIDE CLINICAL TRIALS

Worldwide Clinical Trials is a global, midsize contract research organization (CRO) that provides top-performing preclinical and Phase I-IV clinical development services to the biotechnology and pharmaceutical industries.

Founded in 1986 by physicians committed to advancing medical science, our full-service clinical experience ranges from early phase and bioanalytical sciences through late phase studies, post approval, and real-world evidence. Major therapeutic areas of focus include cardiovascular, metabolic, neuroscience, oncology, and rare diseases. Operating in 60+ countries with offices in North and South America, Russia, Eastern and Western Europe, and Asia, Worldwide is powered by its almost 3,000 employee experts.

For more information, please visit **www.worldwide.com** or connect with us on **Twitter**, **LinkedIn**, **Facebook**, and **Instagram**.