CALYX™

CALYX MEDICAL IMAGING

Behind the Breakthrough

How imaging — when done right — can expedite accelerated trials.

Clinical trial sponsors who are granted Breakthrough Therapy designation understand that there is no one-size-fits-all approach to approval. The process is iterative. And it is unpredictable.

Your service providers — especially your centralized imaging providers — should have a successful track record of supporting Breakthrough Therapy approvals. Only then will you have confidence in their ability to navigate the challenges you'll face from an operational, regulatory, medical, and scientific point of view. Getting this wrong could be catastrophic.

The Value of Imaging

Earning the FDA's prized Breakthrough Therapy designation is just the beginning of the race, one that may require use of an imaging surrogate for preclinical evidence or accelerated approval (Figure 1). And that means getting medical imaging right.

Breakthrough Therapy trials are complicated, with incredibly high stakes. Patients are suffering and doctors are clamoring for a treatment. You need to move fast. And you don't want to underestimate the challenges that clinical trial imaging might present.

Get the Foundation Right

When imaging results are required for preliminary clinical evidence, they must be performed quickly. Data can be required by the agency in less than one month. Rapid delivery is everything in this trial incubation phase.

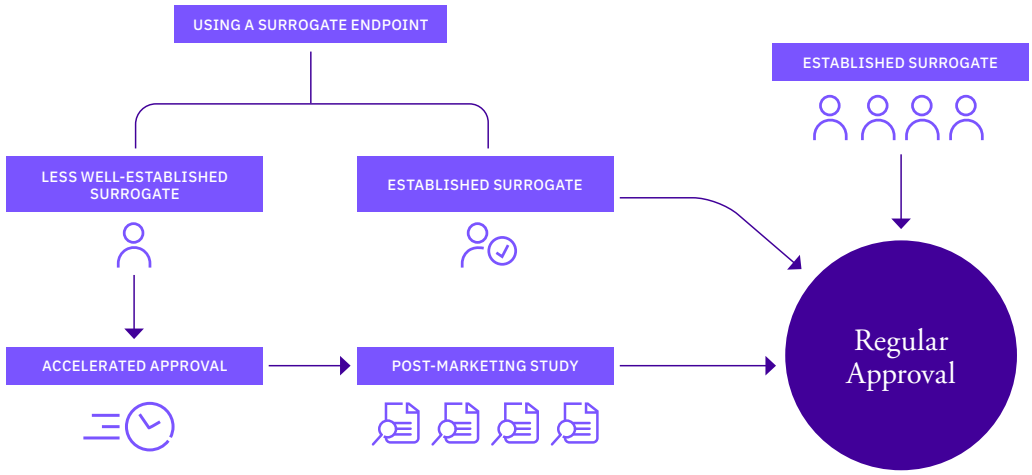
All requests for Breakthrough Therapy designation are reviewed within 60 days of receipt, and the FDA will either grant or deny the request. Once a drug is designated as a Breakthrough Therapy, the FDA will expedite the development and review of such drug.

Your imaging provider must be able to quickly:

- Collect images
- Onboard & train expert readers
- Create solid systems to ensure data meets regulatory scrutiny
- Provide clean and quality data — on time

Imaging can also be used to enrich and speed patient recruitment, ensuring that sites only enroll patients that are appropriate for the study. For example, determining if a tumor is measurable on CT scan.

Figure 1:



Expect Intensity

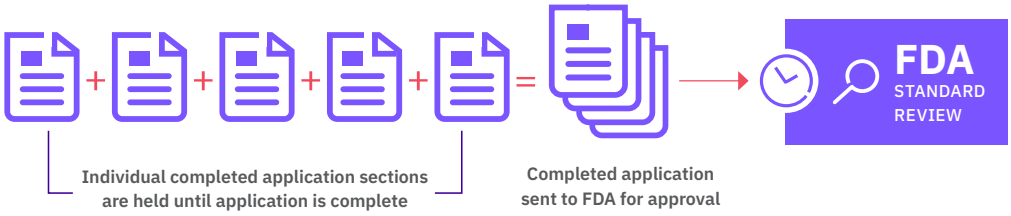
When Breakthrough Therapy designation is granted, the FDA expedites development and review by:

- Applying all the fast-track program features, including the ability to submit a portion of an application prior to the completed version—also known as rolling review (Figure 2)
- Providing more intensive guidance on an efficient drug development program
- Involving senior management in such guidance
- Conducting meetings with the sponsor and the review team throughout the development of the drug

Figure 2:

Standard Review

Clock starts once FDA receives COMPLETED application.



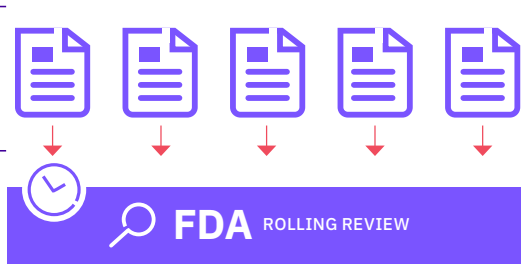
Individual completed application sections are held until application is complete

Completed application sent to FDA for approval

Rolling Review

Clock starts upon submission of first single completed section of application.

Individual application sections are sent to FDA upon completion for rolling review



In turn, imaging trials have significantly changed over the past decade. Gone are the days of an imaging vendor providing a data export at study close, taking their time to release charters and systems. Clean imaging exports are likely included at each stage of the rolling review; your imaging provider must be the engine toward meeting each data cut.

Managing a Breakthrough

When Breakthrough Therapy designation is granted, study oversight takes on new meaning.

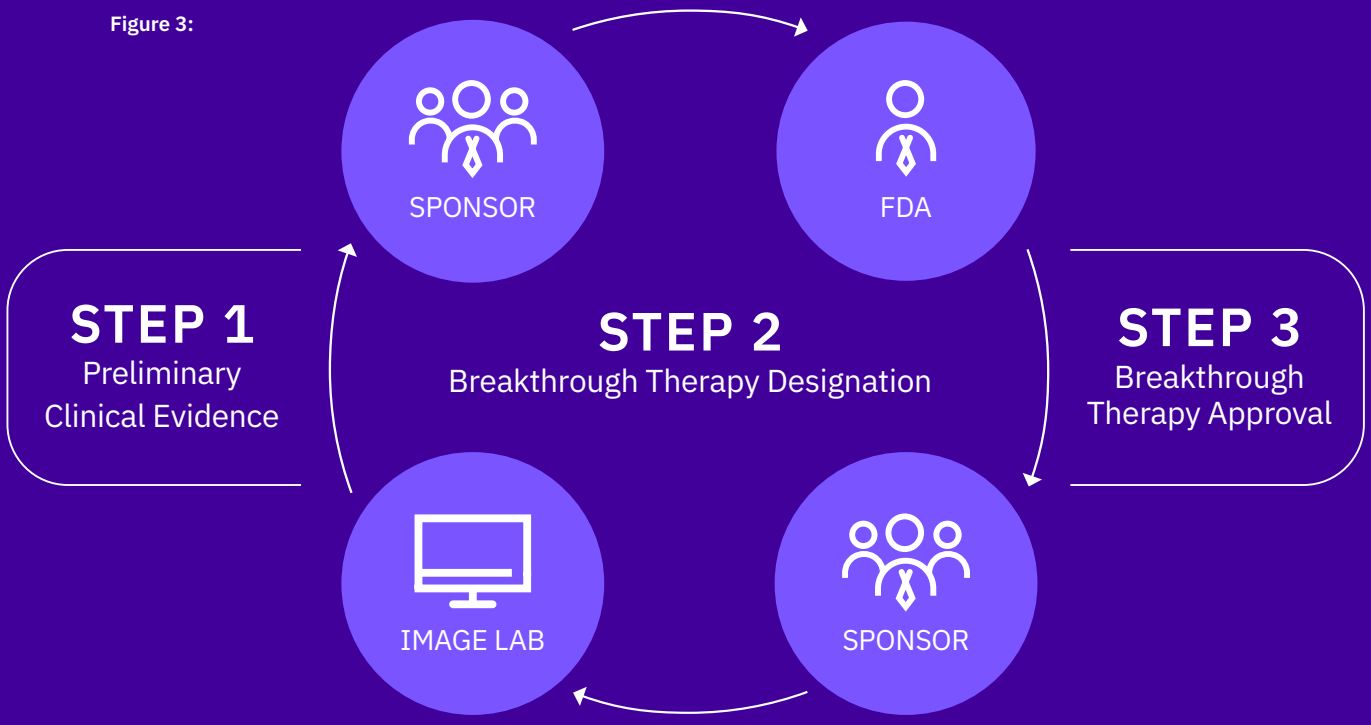
When imaging is a key component of a Breakthrough Therapy trial, project management plays a critical role. The best project managers share key characteristics:

Commitment
The FDA assigns senior staff to monitor Breakthrough Therapy trials, from initial request of the designation to submission. The FDA, in turn, expects the same level of commitment from both the sponsor and their providers. (Figure 3)

Flexibility
The project manager must be flexible and able to pivot on a dime. If data is needed quickly or the study design needs to be altered, the imaging staff must be able to adapt.

Documentation
The FDA requires that the sponsor and imaging provider have clearly documented each key decision. A project journal can capture these decisions in an auditable way to ensure inspection readiness.

Figure 3:



Scalable Imaging Review

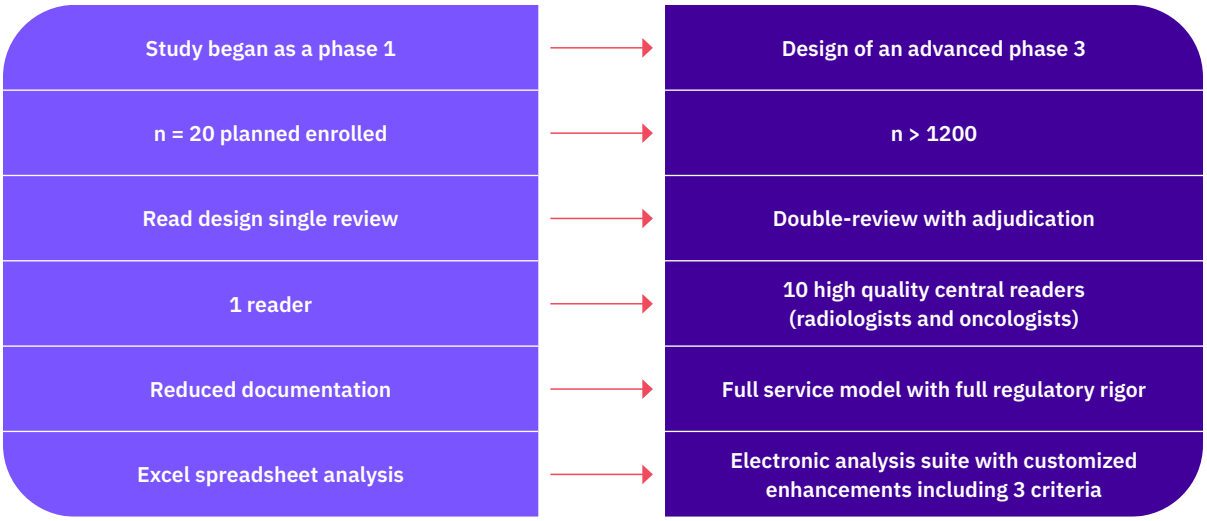
The central imaging review process plays an instrumental role.

Principal investigators care for patients. Central imaging review cares for images, providing critical quality assurance to decrease the variability of image interpretation.

Each reader needs to be specialized in the therapeutic area, trained on the trial's imaging charter, and on proper application of the analysis criteria—and most importantly, committed and available for the duration of the study. A plan for adjudicating disagreements and monitoring inter- and intra-reader variability also needs to be in place.

Even more important, however, is the ability to quickly scale the number of readers trained and able to join the image review team when a study accelerates. Breakthrough Therapies often have massive scope changes based on changes to the protocol, an FDA request, or addition of studies. A few dozen enrolled patients can quickly jump to over a thousand, and the reader team may need to grow ten-fold.

Breakthrough Medical Imaging: A Case Study



RESULTS

20 total regulatory approvals across FDA, EMA, PMDA, NMPA (formerly CFDA) across melanoma, lung, RCC, head and neck, and lymphoma; 4 are Breakthrough Therapy approvals; provision of images for preliminary clinical evidence for the designation of + 1 FDA audit; largely due to this program, Calyx was awarded "Vendor of the Year."

It was no surprise to Calyx's Medical Imaging team when this sponsor received Breakthrough Therapy designation on its novel oncology compound. Even non-scientific staff noticed tumors disappearing from CTs and MRIs, indicating this compound could change cancer treatment significantly.

Calyx's scalable infrastructure enabled us to pivot quickly in order to meet the trial's accelerated timelines. The sponsor was awarded Breakthrough Therapy approval, delivering a novel cancer treatment to patients whose lives depended on it.

The sponsor initially didn't know if they needed a comprehensive imaging solution so we proposed a simple study design and provided data that was used for preclinical evidence. The sponsor achieved the coveted Breakthrough Therapy designation and our team immediately pivoted this simple phase 1 trial to the design of an advanced phase 3 trial. In less than three months, Calyx's Medical Imaging team:

- Wrote a charter
- Coded and released an application with three criteria (RECIST 1.1, iRECIST, and volumes)
- Selected and onboarded 10 radiologists and clinical oncologists
- Began supporting the enrollment of over 1200 patients
- Supported multiple rolling reviews

Breakthrough Expertise

From design to endpoint, trials are guided to the best outcome with Calyx Imaging. Our track record supporting Breakthrough Therapy approvals speaks for itself.

We've guided over 70 Breakthrough Therapy trials. In fact, Calyx Imaging supported most of the Breakthrough Therapy approvals granted by the FDA in 2019/2020.

Our imaging experts have seen it all and can share an insider's view of what happens when the stakes, scrutiny, and demand are all sky-high.

Talk with the Experts

Ask us about our customized half-day workshops. A Calyx Medical Imaging expert will review your protocol and suggest how to set up your trial for success. With scientific integrity and regulatory compliance – to help you break through and get to market earlier.

For more information, contact hello@calyx.ai.

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Breakthrough Therapy designation is a remarkable regulatory innovation that changes the economics of drug R&D. It shortens the timeline and reduces the cost of clinical research to the point where one can wonder why any company would want to develop anything else."

Bernard Munos
Pharmaceutical Industry Consultant
and Forbes Blogger

CALYX™

Reliably solving the complex.

calyx.ai
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