Medical Imaging in Rare Disease Trials
Idiopathic Pulmonary Fibrosis (IPF)

OVERVIEW

Clinical trial sponsors face many challenges when medical imaging is used to evaluate the safety and efficacy of new medical treatments. These challenges are even more significant when the treatment is being developed for rare diseases. Medical imaging plays an important role in these trials as it provides a non-invasive way to assess treatment response.

As a requirement, most rare disease clinical trials are multicentre, and often multinational for sufficient patient recruitment, even in phase I and II trials. This can challenge clinical study protocol harmonization, the selection of appropriate biomarkers, ethical review, site IRB approval, indemnity, organization of clinical services, standards of care, and cultural diversity.

And, most diagnoses classified as rare diseases affect numerous body systems. It's not unusual for a patient with a rare disorder to have symptoms and/or underlying disease that affects their cardiovascular, neurological, and respiratory systems, among others. As a result, the sponsor's selected imaging partner should possess broad expertise across all therapeutic areas and a thorough understanding of the imaging modalities typically used across each rare disease and body system.

Additionally, as there are not many people living with the diagnosis, finding patients and keeping them engaged in clinical trials is critical. Trial sponsors can't risk a patient dropping out of a study because imaging processes were not performed correctly (i.e, requiring the patient to repeat scans, etc.) or the imaging analysis were unreliable.

Significant progress has been made in our understanding of the biological basis of disease mechanism for rare diseases. This has been possible with the use of novel laboratory, analytical, and imaging techniques combined with the expertise and hard work of scientists and physicians taking care of these patients. Leveraging the expertise of these scientists and physicians is important while designing and executing rare disease clinical trials.

For these and many other reasons, trial sponsors need an imaging provider with a combination of robust, proven processes, extensive experience, and far-reaching scientific expertise for medical imaging to be used effectively and reliably during the clinical development of rare disease treatments.

CASE STUDY - IPF

BACKGROUND:

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive lung disease characterized by scarring (fibrosis) of lung tissue, resulting in reduced intake of oxygen. It is a rare disease of unknown cause that affects 13 to 20 out of every other 100,000 people, primarily adults.

In IPF clinical trials, medical imaging is one of the key diagnostic tests used to screen subjects. High-resolution CT (HRCT) is the imaging modality of choice for the diagnosis of IPF. In some cases, when HRCT diagnosis is not conclusive, a review of lung biopsy tissue by a pathologist may be required to confirm the diagnosis of IPF. This requirement makes IPF clinical trials uniquely complex. The imaging review of chest HRCT in IPF studies requires special training of radiologists and significant clinical experience in reading lung HRCT scans. The same is true for pathology.

Additionally, there are published guidelines by scientific experts and societies that are used by radiologists and pathologists for the review of images and biopsy specimens. These guidelines allow a harmonized and standardized way to confirm a diagnosis of IPF. While these guidelines are aimed at standardizing the diagnosis of IPF in clinical trials and the clinic, there still exist challenges associated with getting experts to agree on the diagnosis in some cases.

Minimizing reader discordance and central-site reader discordance is one of the challenges in imaging clinical studies. At Calyx, we have developed a comprehensive reader selection and training program to harmonize the central review process for IPF studies and other rare disease indications. This program is enhanced periodically based on lessons learned from current studies.

STUDY IMPLEMENTATION

Calyx Medical Imaging played a vital role in multiple phase 2/3 IPF studies being conducted by a clinical trial sponsor seeking regulatory approval for the first-ever treatment of IPF. The imaging data was critical to the sponsor's success as it supported the studies' key goal to enrich the IPF patient population in the study. To ensure the accuracy of the imaging reads, Calyx identified and recruited world-class radiologists and pathologists to participate as independent reviewers as part of the central read model.

Calyx Medical Imaging was responsible for supporting two data streams during these studies, i.e. radiology and pathology, which required a unique set of scientific and operational expertise. The two data streams required logistics expertise since the data came in through two different workflows and were routed to different sets of readers. While the data streams were unique, the final decision reported to the sites required a combination of assessments from both data streams.

Moreover, if there was discordance in the diagnosis of IPF between radiologists and pathologists, a hospital-style multi-disciplinary discussion (MDD) session was arranged virtually (vMDD), to facilitate discussion between the readers and an independent clinician. The goal of this session was to make a final decision based on consensus between all the parties. The latter was very well received by the investigators since it emulated clinical practice in a trial setting.

Calyx's management of multiple data streams, comprehensive IPF training program for internal stakeholders and partners, and reporting of unified results, combined with internal scientific expertise and strong collaboration with KOLs led to the delivery of reliable imaging data that demonstrated the efficacy of the compound and was key to the success of these studies and their subsequent regulatory approvals.

CALYX EXPERIENCE IN RARE DISEASE STUDIES

Calyx Medical Imaging's experience is drawn from managing over 2,600 trials to date which include more than 4.4 million images from roughly 155,000 sites globally. Within this experience is our management of over 170 rare disease trials, which have led to the approval of over 20 indications classified as rare diseases.

INDICATION	# OF TRIALS	# OF SUPPORTED APPROVALS	MODALITIES
Amyloidosis	2		Nuclear medicine
Autosomal Dominant Polycys-tic Kidney Disease (ADPKD)	14	3	MRI
Cystic Fibrosis	1		HRCT
Esophagitis	6	1	Endoscopy and Photography
Fabry Disease	3		ECHO, CT, MRI
Fibrodysplasia Ossi-ficans Pro-gressive (FOP)	7	1	DXA, X-ray, MRI, Ultrasound, WB-CT
Gaucher's Disease (Endocrine)	3		DXA, X-ray, MRI, CT
Hereditary Hemochro-matosis (HH)	1		CFP
Idiopathic Pulmonary Fibrosis (IPF)	29	4	HRCT, MDCT, Surgical Lung Biopsy/Pathology (SLB)
Mantle Cell Lymphoma	19	4	CT, MRI, PET, Bone Scan, Skin Lesions
Merkel Cell Carcinoma (MCC)	2		CT, MRI, Brain Scan, Photography, FDG-PET
Muscular dystrophy	6		DXA, MRI
Mutated Rare Cancers	1		CT, MRI, Brain
Neuroendocrine Tumors	5		CT, MRI, Bone scan
Neurofibromatosis, NF1 or NF2	10	1	MRI, Photography
Osteogenesis Imper-fecta	1		X-ray, DXA
Pancreatic Ductal Adenocarci-noma	35		CT, MRI, Brain Scan, X-ray, Bone Scan
Pediatric B-Cell Lym-phoma (NHL)	1		CT, MRI, PET-CT
Pulmonary Hyper-tension (Pulmonary Disorder) (Pediatric)	3		Cardiac MRI, ECHO, HRCT

Pulmonary Sarcoidosis (Res-piratory)	7		HRCT, PET-CT, X-ray, cMRI (cardiac MRI)
Scleroderma Lung	1		HRCT, CT
Sickle Cell	4		MRI, MRI CNS, DXA, MUGA
Systemic Sclerosis Interstitial Lung Disease (SSc-ILD)	2		HRCT
T-Cell Lymphoma	14		CT, MRI, FDG-PET, Photograph
Thalassemia (Hema-tology)	4		CT, MRI, DXA, MUGA
Transfusional Hemo-siderosis	1		ECHO
Adrenoleukodystrophy (ALD)	1		Brain MRI
Waldenstrom's	7	5	CT, MRI, FDG-PET
Smoldering Myeloma	2		MRI, FDG-PET, CT
CNS Lymphoma	39		CT, Brain MRI, DWI/PWI, X-ray, Bone Scan, PET, SPECT, ECHO
Adult-onset leukoen-cephalo-pathy with axonal spheroids and pig-mented glia (ALSP)	2		Brain MRI
Multiple system atro-phy (MSA)	1		PET/CT
Encephalitis	2		MRI

Contact hello@calyx.ai to learn how Calyx Medical Imaging and our dedicated experts can design and deliver high quality Medical Imaging to drive your trial's success.

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