PRECISION IMAGE ANALYSIS

A Small Shift from the Industry Standard Could Save Millions on Early Phase Trials.

VP OF STRATEGIC RELATIONSHIPS – CNMT, RT(N)

Christian Teague has been involved in radiology for over 20 years. It was over that period of time that he was able to gain vast experiences in diagnostic imaging as well as research. He managed imaging data throughout the world both in a HIPPA compliant, as well as Part 11 compliant manner. After graduating from Loma Linda Medical University with an emphasis in Nuclear Medicine he began his career working at large research hospitals such as UCLA Medical Center where he became accustomed to the world of research.

Using Cardiac MRI in place of Echocardiography for Proof of Concept, First in Humans, and Phase 1 trials could dramatically change the efficiency of the clinical trials lifecycle.

Christian Teague and Jason Lin of Precision Image Analysis

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Left ventricular ejection fraction (LVEF) is an important parameter that reflects how well the heart pumps blood with each contraction. LVEF determination is one of the most commonly used endpoints in cardiotoxicity studies, and has also been used to inform prognosis, regulate treatment, and determine eligibility of patients in clinical trials [1]. Thus, accurate determination of LVEF is critical not only in ensuring the well-being of patients, but also in maintaining high-quality research studies.

Currently, echocardiography is the most commonly used diagnostic imaging modality used to measure LVEF. Its major advantage comes from its widespread availability, safety, and perceived low cost [1]. Although echocardiography is the most ubiquitous tool for assessing LV size and systolic function, studies have shown that it has suboptimal reliability and reproducibility of LVEF results [1,2]. Additionally, due to echocardiography's inherently high variability, larger sample sizes are needed to reach statistical significance, thus increasing the number of patients needed to enroll and therefore escalating overall costs of clinical trials [3]. Consequently, there is a pressing need to develop a more reliable alternative to assess LVEF.

Emerging data has pointed to cardiac magnetic resonance (CMR) as the appropriate replacement for echocardiography in the determination of LVEF. CMR has proven to be the most powerful and effective diagnostic tool in the evaluation of left ventricular volumes, ejection fractions, and mass. CMR provides superior results compared to other imaging modalities, and is now considered the gold standard for LVEF assessments[4]. Compared to echocardiography, CMR's highly reproducible measurements enable a significant reduction in sample size, making it an attractive alternative for determination of LV functional endpoints in clinical trials[5].

In a study conducted by Grothues et al, the coefficient of variability for LVEF measurements from CMR was 3.7%, compared to 11.5% from echocardiography[3]. Using these variabilities and assuming typical conditions for statistical significance (power of 90% and an alpha error of 0.05), the sample sizes required to detect a clinically significant change in LVEF (3% change) was calculated to be 11 for CMR and 87 for echocardiography; an 87% reduction in sample size when using CMR. Other clinically significant changes also demonstrated similar sample size reductions when using CMR instead of echocardiography, as shown in Table 1[3].

TABLE 1 Sample Sizes Required to Detect a Clinically Significant Change in End-Diastolic Volume, End-Systolic Volume, Ejection Fraction, and LV Mass (with a 90% power and an α error of 0.05)*

	Echocardiography		CMR		Reduction in Sample Size by CMR
	SD	Sample Size	SD	Sample Size	
Total study group					
10-ml change in end-diastolic volume	13.5	39	6.7	10	74%
10-ml change in end-systolic volume	14.0	42	5.4	7	83%
10-ml change in stroke volume	13.1	37	5.2	6	84%
3% absolute change in ejection fraction	6.1	87	2.1	11	87%
10-g change in LV mass	25.0	132	7.7	13	90%

Given that the average cost per patient for cardiovascular clinical trials is $20,000[6], a switch from echocardiography to CMR would yield significant cost savings by substantially reducing the required number of participants. Specifically, sample size reductions would result in a decrease in patient recruitment numbers, as well as retention costs; hospital and health care personnel fees; trial costs from organizing and monitoring studies; and drug production and use costs. Another potential benefit of using smaller sample sizes would be allowing otherwise impractical research to be conducted, i.e. the study of rare cardiovascular diseases that have smaller numbers of eligible participants[3].

Budget conscious investors and companies are continuously looking at new and innovative ways to cut costs. In Proof of Concept, First in Humans, and Phase 1 trials, this switch to a more efficient imaging technique would yield tremendous savings. For example, a study that can reach a significant end-point with 60-patients (at $20,000/patient enrolled) using the current echocardiographic standard, requires a minimum of $1.2 million in expenses. In contrast, when using CMR, the sample size reduces to 8, thereby reducing costs to approximately $160 thousand, and allowing both easier and faster patient recruitment, which may be particularly beneficial for rare

disease studies. The money saved, in this case roughly $1 million, might then be better used in more patient centric activities. Another advantage from replacing echocardiography with CMR would be the significant amount of time and expense saved by analyzing only 8 patients instead of 60 patients.

The accuracy of LVEF measurements can directly impact patients' lives, and therefore should not be compromised with the convenience of a suboptimal imaging modality. As a powerful imaging tool, CMR not only provides reliable measurements of cardiac function, but also has the potential to significantly reduce overall costs of clinical trials. By accruing such multifaceted benefits across all stakeholders, including the FDA and investors, in such an efficient and expeditious manner would certainly be beneficial in all stages of clinical trials.

CREDITS

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