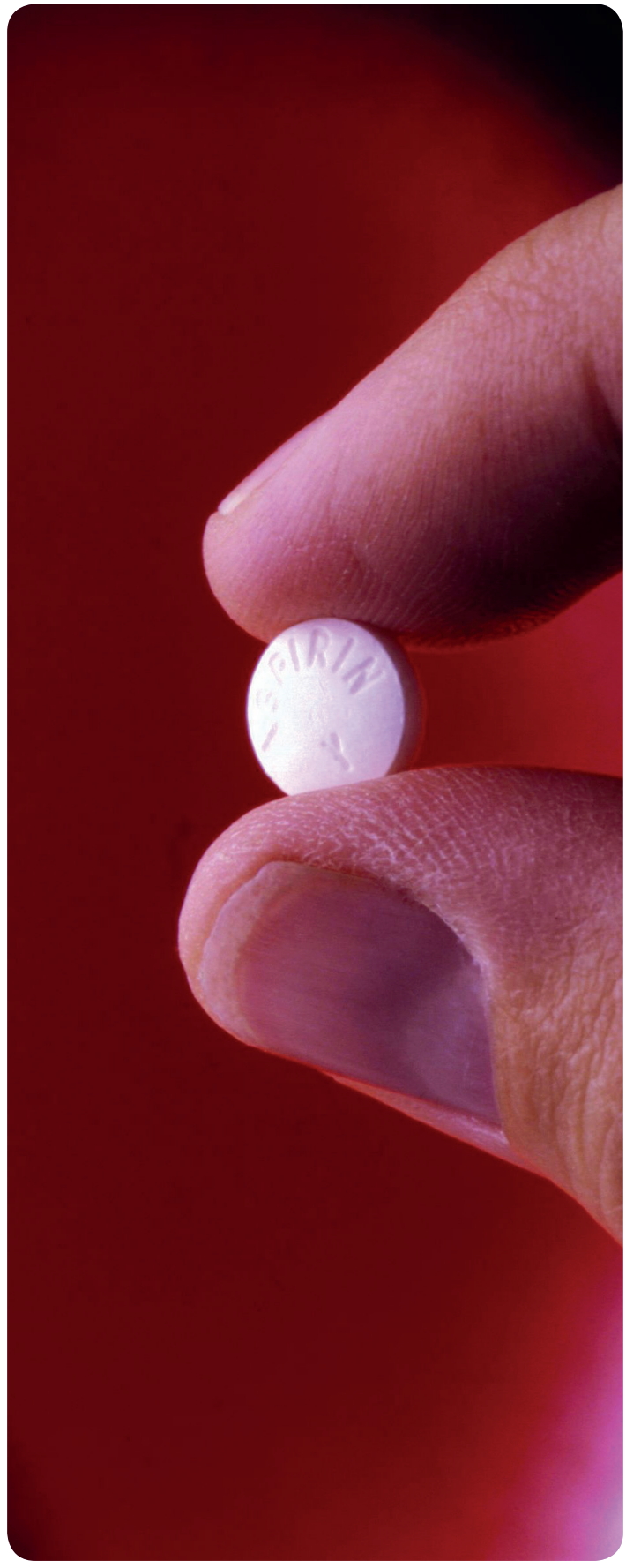
Why would Cardiovascular Outcomes Trials and Rare Disease Studies have Anything in Common?

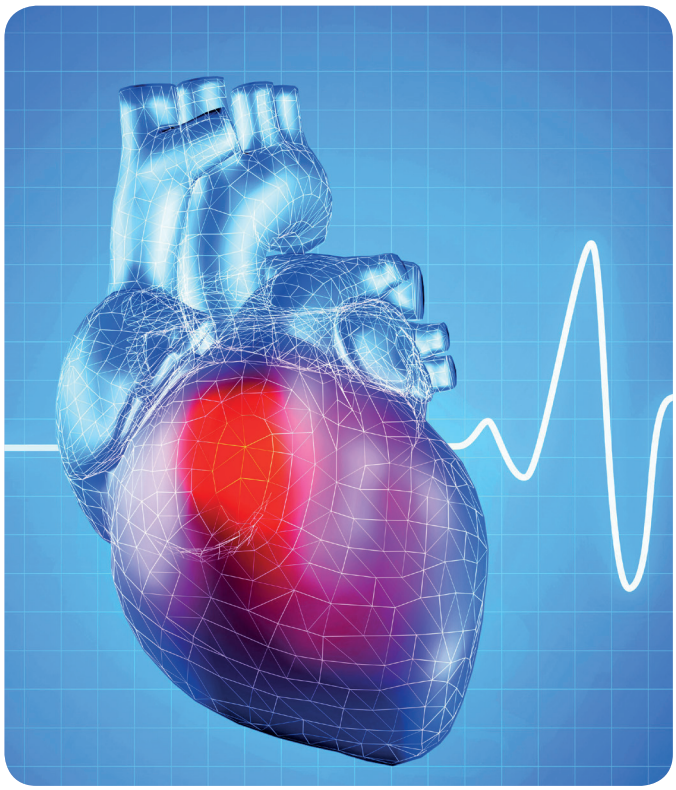
Cardiovascular outcomes trials (CVOTs) are some of the largest interventional trials being conducted, enrolling several thousand subjects, sometimes with follow-up over several years to accrue the required number of major adverse cardiovascular events. By contrast, and for obvious reasons, rare disease studies are very limited in size. Indeed, the ongoing anacetrapib CVOT (the REVEAL study) has enrolled 30,624 participants[1], which is almost four times the world total of 7713 diagnosed Fabry Disease patients[2]. However, the general design of these two widely different and extreme types of trials is surprisingly similar. Does this have implications for other types of trials?



Studies on rare diseases are inherently limited by the availability of participants. Many rare diseases are multi-organ genetic diseases which have different manifestations, depending on the specific mutation. Patients present with significant comorbidities, but such studies cannot afford to have extensive exclusion criteria. The variability of the population can lead to challenges in demonstrating efficacy. For example, the orphan drug, ixazomib, initially received negative EMA CHMP opinion because the data from the main study were insufficient to demonstrate a benefit. The company had proposed restricting the use of ixazomib to patients with refractory multiple myeloma, which relapsed after a treatment, and those whose disease had returned after at least two treatments. However, the data in these subgroups were not compelling enough and the risk-benefit-ratio was insufficiently favourable[3] (conditional approval was subsequently granted).

CVOTs, as relatively late-phase large trials (III, IIIB or IV), generally try to target a broad range of subjects in an attempt to replicate the real-world use of the drugs. The expense of performing such huge studies can only be ventured in common conditions, where the potential return on investment exists, i.e. where large and widespread sales can be achieved. But just as in rare disease studies, the enrolment of subjects is the rate-limiting issue, and the designers of such trials need to be as inclusive as possible to maximise enrolment.

It may be that the very different requirements of these two types of studies both tend to push the study designers towards the pragmatic end of the explanatory -> pragmatic continuum. This axis was first explored by Schwartz and Lellouch almost 50 years ago[4], but still generates discussion today[5]. One might expect these two types of studies to lie at opposite ends of the pragmatic explanatory axis. While CVOTs could certainly not be described as pragmatic studies, they are certainly further down the continuum than the 'average' study. The shortage of subjects for rare disease studies and the



sheer number of subjects required by CVOTs means that the same pressures on inclusivity affect both types of studies.

Retention of subjects is equally vital to both. For rare disease studies, the need to retain subjects is obvious, but identifying and enrolling patients is so difficult that having non-evaluable data is a critical waste. On CVOTs, the sample sizes for analysis are actually the endpoint events, and those numbers will be much smaller than the number of participants. An extreme example is the celecoxib PRECISION study that was reported recently in the NEJM[6]. This study involved 24,081 subjects in three arms and ran for nearly 10 years. However the actual number of events in the primary analysis was only 607, and the difference in the number of events between the "best" and "worst"' arms was only 30! This number is much smaller than the number of subjects that were lost to follow-up. Had this been an efficacy study (it was not), it is certain that the data would not have been acceptable to regulatory bodies. Similarly, in 2013, the FDA Advisory Committee recommended rejection of tolvaptan for the indication of slowing kidney disease in adults with autosomal dominant polycystic kidney disease (ADPKD), partially because of the amount of missing data, especially from the higher number of patients lost to follow-up in the tolvaptan group[7].

Does this observation about rare disease trials and CVOTs, at opposite ends of the trial spectrum, have any implications for other trials? It is clear that purely exploratory studies are necessary to early phase research, but does the more pragmatic approach used in such disparate trials suggest that the same could be true for many more trials in the middle ground? Treweek and Zwarenstein argue this would be better for patients in the long run. As for patient retention, this is just good science!

References

1. ClinicalTrilas.gov website (accessed 12 December 2016): https://clinicaltrials.gov/ct2/show/NCT01252953?term=anacetrapib&rank=9
2. Fabry Disease Foundation website (accessed 06 December 2016): http://www.fabrydisease.org/
3. EMA CHMP Website (accessed 07 December 2016): http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/003844/WC500207384.pdf
4. Schwartz D, Lellouch J: Explanatory and pragmatic attitudes in therapeutical trials. J Chronic Dis. 1967, 20: 637-648.
5. Treweek S, Zwarenstein M: Making trials matter: pragmatic and explanatory trials and the problem of applicability. Trials 2009 10:37
6. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med 2016; DOI: 10.1056/NeJMoa1611593
7. FDA Panel Vetoes New Tolvaptan Indication: Medpage Today, 05 August 2013 (accessed 13 December 2016): http://www.medpagetoday.com/nephrology/generalnephrology/40844

Philip Galtry is Vice President, Clinical Development at INC Research, where he leads the Cardiovascular and Endocrine group. Philip holds a biochemistry degree from the University of Bristol, UK, and has worked on the management of large cardiovascular trials for almost 25 years.
Email: phil.galtry@increasearch.com
Website: www.increasearch.com

Cinzia Dorigo, PharmD, is Executive Director, Clinical Development for Rare Disease and General Medicine, and leads INC Research's Rare Disease Consortium, which focuses on an effective strategic implementation for successful delivery of rare and ultra-rare disease studies. She has 17 years of experience in rare and ultra-rare clinical development, including extensive experience in early-phase, adaptive study design and paediatric rare disease studies.
Email: cinzia.dorigo@increasearch.com
Website: www.increasearch.com