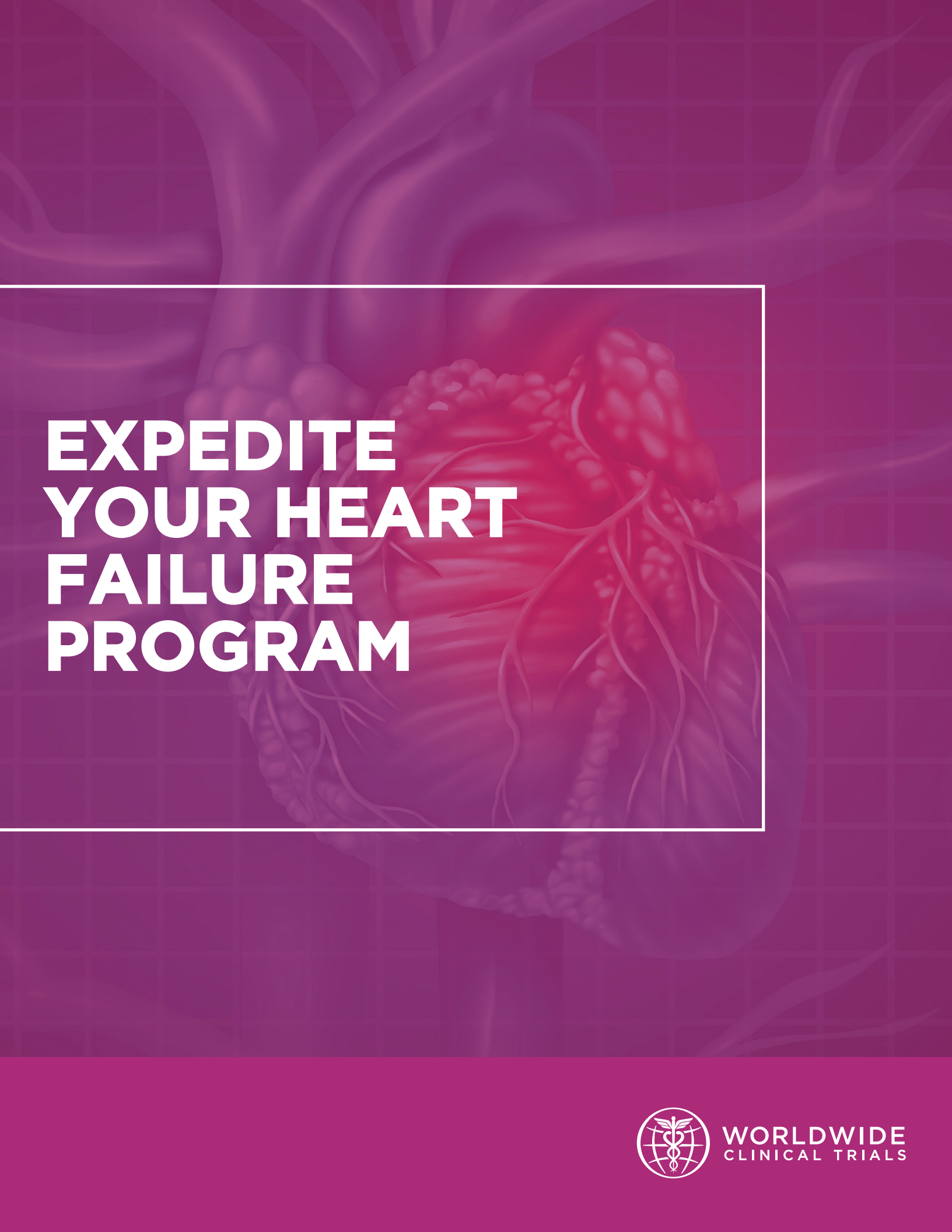

EXPEDITE YOUR HEART FAILURE PROGRAM

WORLDWIDE CLINICAL TRIALS

WORLDWIDE CLINICAL TRIALS

Heart Failure (HF) is a clinical syndrome that is characterized by typical symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.

Due to the high and increasing prevalence rates, HF constitutes an enormous economic burden for the healthcare systems in industrialized countries. For example, Europe and the US spent 1–2% of their annual healthcare budget on HF.[1]

Many heart failure trials yield results that are disappointing or difficult to interpret. Therefore, having a well-built protocol with clearly defined exclusion and inclusion criteria, well-chosen end points, carefully estimated events rate, and critical biomarkers tracked is of crucial importance for the success of your program.

EXPEDITE YOUR HEART FAILURE PROGRAM

Despite significant advances in the treatment of chronic heart failure during the past 30 years, there is a broad consensus that new treatments are needed because morbidity and mortality in this disorder remain unacceptably high. Especially in patients with preserved ejection fraction, valid therapeutic options are missing due to a lack of evidence. In the face of a very heterogeneous condition with an ongoing debate over etiology and pathophysiology, it is a challenge for clinicians to provide optimal care for these patients.

WORK WITH A CRO THAT UNDERSTANDS YOUR CARDIOVASCULAR INDICATION

The basis for treating symptomatic patients with HF is a meticulous diagnostic work-up to determine the etiology of the syndrome and an optimal treatment of the underlying condition. Although HF is first and foremost a clinical diagnosis, the use of BNP or NT-proBNP as an adjunct to the clinical diagnosis improves diagnostic accuracy above and beyond other clinical variables. Beyond their value for diagnosis, elevated BNP and NTproBNP are closely associated with high risk of adverse HF outcomes, including death and rehospitalization. The ability to predict risk is particularly useful for enriching the study population with patients who have higher event rates to minimize risk for type II error in underpowered studies.

CIRCULATING BIOMARKERS HAVE BEEN USED IN HF CLINICAL TRIALS AS:

- An inclusion criterion to enrich the study population with higher-risk subjects,
- A measure of drug toxicity,
- An outcome measure/end point,
- A means to retrospectively explain efficacy of a therapeutic, and
- A target for therapy.

Choosing an appropriate biomarker threshold to identify risk is crucial when designing studies with biomarkers as an inclusion criterion and should be done by methodically balancing identification of high-risk patients with the need to be inclusive of a wide range of patients to improve the generalizability of the results.

[1] www.ncbi.nlm.nih.gov/pmc/articles/PMC5930493/

WORLDWIDE
CLINICAL TRIALS

YOU'RE DEDICATED TO IMPROVING THE QUALITY OF LIFE FOR HEART FAILURE PATIENTS, AND WE ARE, TOO

The goal of pharmacotherapy in HF is the improvement of the survival rate and the reduction of morbidity, such as recurrent hospitalizations and symptoms, while improving functional capacity and quality of life.

Despite treatment, HF remains a chronic, progressing, and ultimately debilitating syndrome with a prevalence of over 10% among people over 70 years of age, depending on geographic region. HF proves to be challenging in light of an aging population and the limited resources of healthcare systems.

Worldwide Clinical Trials has a long history of heart failure trial experience, including enrolling patients in an acute setting. From trials with less than 20 patients globally to over 1,000+ patient studies, our team is proficient with very complex protocols, that require detailed training of sites and team members all over the globe.

OUR IN-DEPTH EXPERIENCE BUT FLEXIBLE APPROACH HAS ENABLED US TO HELP SPONSORS IMPROVE TIMELINES AND OUTCOMES BY IMPLEMENTING THE FOLLOWING METHODOLOGIES:

Ensuring the right country and site strategy for the required patient population

Overcoming the challenges and differences in identifying and treating patients in an acute setting versus an outpatient clinic

Understanding the challenges regarding the optimal end point(s) for both acute and chronic heart failure trials and how to capture these effectively

WORLDWIDE CLINICAL TRIALS: WE'RE THE CURE FOR THE COMMON CRO

Worldwide Clinical Trials employs more than 1,600 professionals around the world, with offices in North and South America, Eastern and Western Europe, Russia, and Asia. Founded by physicians committed to advancing medical science, Worldwide is out to change how the world experiences CROs – in the best possible way. From early phase and bioanalytical sciences through late phase, post-approval and real-world evidence, we provide world-class, full-service drug development services.

With infrastructure and talent spanning 60 countries, we execute predictable, successful studies with operational excellence across a range of therapeutic areas, including central nervous system, cardiovascular, metabolic, immune-mediated inflammatory disorders (IMID), oncology, and rare diseases. We never compromise on science or safety. We're never satisfied with the status quo. We're the Cure for the Common CRO.

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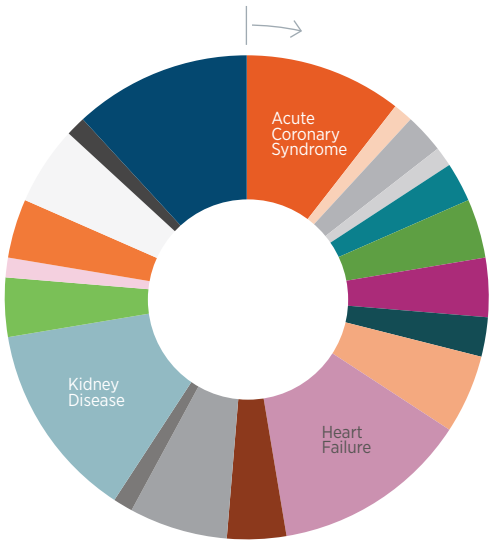
WORLDWIDE CARDIOVASCULAR AND METABOLIC EXPERIENCE

Studies by Indication

Indication	Studies	Sites	Patients
Acute Coronary Syndrome	8	321	14,407
Acute Intracranial Hemorrhage	1	100	440
Angina	2	68	985
Arrhythmias	1	71	640
Atherosclerosis	2	120	720
Congenital Adrenal Hyperplasia	3	33	382
Diabetes Type 2	3	54	646
Dyslipidemia	2	76	580
Gaucher's Disease	4	11	64
Heart Failure	10	479	3,089
Hypercholesterolemia	3	203	2,601
Hypertension	5	65	651
Hypertension, Pulmonary	1	16	29
Kidney Disease	10	428	3,055
Metabolic Conditions	3	52	145
Mucopolysaccharidoses	1	2	8
Myocardial Infarction	3	171	6,961
Myocardial Ischemia	4	441	9,796
Obesity	1	8	260
Vascular Disease	9	1,713	25,795
Total	**76**	**4,432**	**71,254**



Studies by Phase

Study Phase	Studies	Sites	Patients
Phase I	1	12	50
Phase II	27	776	5,270
Phase III	33	1,300	27,681
Phase IV-Interventional	7	2,158	36,350
Phase IV Non-Interventional	8	186	1,903
Total	**76**	**4,432**	**71,254**

76

Full-service* cardiovascular and metabolic trials conducted

Worldwide has extensive experience with the successful management and execution of clinical trials. Worldwide has conducted 76 full-service cardiovascular and metabolic trials globally, including sites in North and South America, Western Europe, Central and Eastern Europe, the Commonwealth of Independent States, and the Middle East and Northern African and Asia Pacific regions.

Q4 2018
DATA VALID THROUGH 31-JANUARY-2019

THERE'S NO SUBSTITUTE FOR UNCOMMON EXPERTISE. MEET YOUR PARTNERS.

Worldwide is committed to delivering uncommon value. We go above and beyond to deliver solutions and services that exceed your expectations.

Karen Hill

Senior Vice President, Project Management, Cardiovascular and Metabolic Diseases

Karen joined Worldwide Clinical Trials in 1993 and is responsible for Global Project Management within the Cardiovascular and Metabolic division. Karen has more than 25 years of experience in the CRO industry and has worked on numerous large cardiovascular outcome studies, including INJECT, GUSTO III, InTIME-II-TIMI 17, OPUS-TIMI 16, PROVE IT–TIMI 22, CLARITY–TIMI 28, and MERLIN-TIMI 36, where she held the position of Global Project Manager/Director. In 2003, Karen took over as head of the Project Management department, which included the management and supervision of the company's project managers, CRAs, and the IVRS development and support teams. Karen currently leads the Global Cardiovascular and Metabolic Project Management group at Worldwide and continues to supervise global teams working on both large cardiovascular and metabolic outcome studies, as well as other phase II-IV studies in other cardiovascular and metabolic indications.

Nancy Newark

Executive Director, Project Management, Cardiovascular and Metabolic Diseases

Nancy joined Worldwide in July 2010. She has provided operational oversight and leadership for the CV projects and currently serves as a Franchise Lead within the CV Therapeutic Area. Prior to joining Worldwide, Nancy worked at Duke University Medical Center for 25 years. For 11 years, she was a critical care transport nurse for the helicopter and ground ambulance program, and for 14 years, she provided senior operational leadership for global multi-center clinical trials and registries, including direct responsibility for regulatory compliance, and strategic development of Project Management, Site Management, and Clinical Monitoring services at the Duke Clinical Research Institute (DCRI). She managed multiple therapeutic business units over the years, including the development and operational oversight of the cardiovascular therapeutic area. Nancy has a BSN and is a registered nurse.

Rafal Ziecina

Executive Director, Scientific Solutions

Dr. Ziecina is a graduate of the Medical University of Warsaw, Poland, where he also earned his Ph.D. in renovascular hypertension. He completed a Diploma in Pharmaceutical Medicine training at the Université libre de Bruxelles and went for specialty training at the Royal College of Physicians in London. He is a Fellow of the Faculty of Pharmaceutical Medicine in the UK. He has designed numerous protocols and clinical development plans and has been involved in more than 70 Phase I through Phase IV clinical studies. He has extensive experience in HF trials (acute and chronic), starting from studies evaluating beneficial effects of carvedilol to the most recent program evaluating use of SGLT-2 inhibitors in HFpEF and HFrEF subjects.

Monika Iten, Ph.D., MSc

Vice President Project Management, Cardiovascular and Metabolic Diseases

Dr. Iten has over 18 years of experience in the CRO industry in Clinical Operations, Performance Management and Marketing. Dr. Iten has a proven record of successful management, oversight and conduct of large clinical trials programs in Cardiovascular and Metabolic Diseases, which lead to marketing authorizations in US and EMEA. She is highly experienced in managing complex teams and leading them to success. Dr. Iten also has been building and leading global Project Management Office and Clinical Performance groups with substantial positive impact on project delivery and team performance. Dr. Iten has an MSc from the ETH Zurich in Switzerland and a PhD in Cell Biology from the University of Basel in Switzerland.