CHDR
Centre for Human Drug Research

Cardiology Services

An integrated approach using a wide range of techniques

CHDR's Cardiology Services® provides our sponsors with 'one-stop shopping' for all of their cardiology needs. Working together with clinical cardiologists at Vrije University Medical Center in Amsterdam (VUmc) and Leiden University Medical Center (LUMC), we can provide a full range of GCP-certified diagnostic procedures for analysing the effects of a test compound on cardiological function in both healthy subjects and patients. In addition to performing electrophysiology, we can also perform a wide variety of cardiac imaging techniques, including MRI and PET.

Practical answers to important research questions

Is our compound potentially arrhythmogenic?

Compounds designed to treat cardiac and/or non-cardiac conditions can interfere with cardiac rhythm, for example by interfering with one or more ion channels. Using our unique approach to analysing ECG data, we can detect subtle changes in cardiac rhythm, indicating the need for further study.

Does our compound cause a prolonged QT interval?

At CHDR, we use an innovative approach to measure the test compound's effect on the QT interval, which serves as an important indicator of the compound's safety profile. By reducing variability, this approach can provide sponsors with key safety data. For more details, see below.

Does our compound interact with the cardiac $Na_V1.5$ sodium channel?

To study the effects of putative anti-arrhythmic compounds that target the cardiac $Na_V1.5$ sodium channel, we can perform a panel of highly sensitive measurements, including the duration of the QRS complex and ventricular activation time, which provide a measure of $Na_V1.5$ channel activity.

Does our compound affect myocardial function?

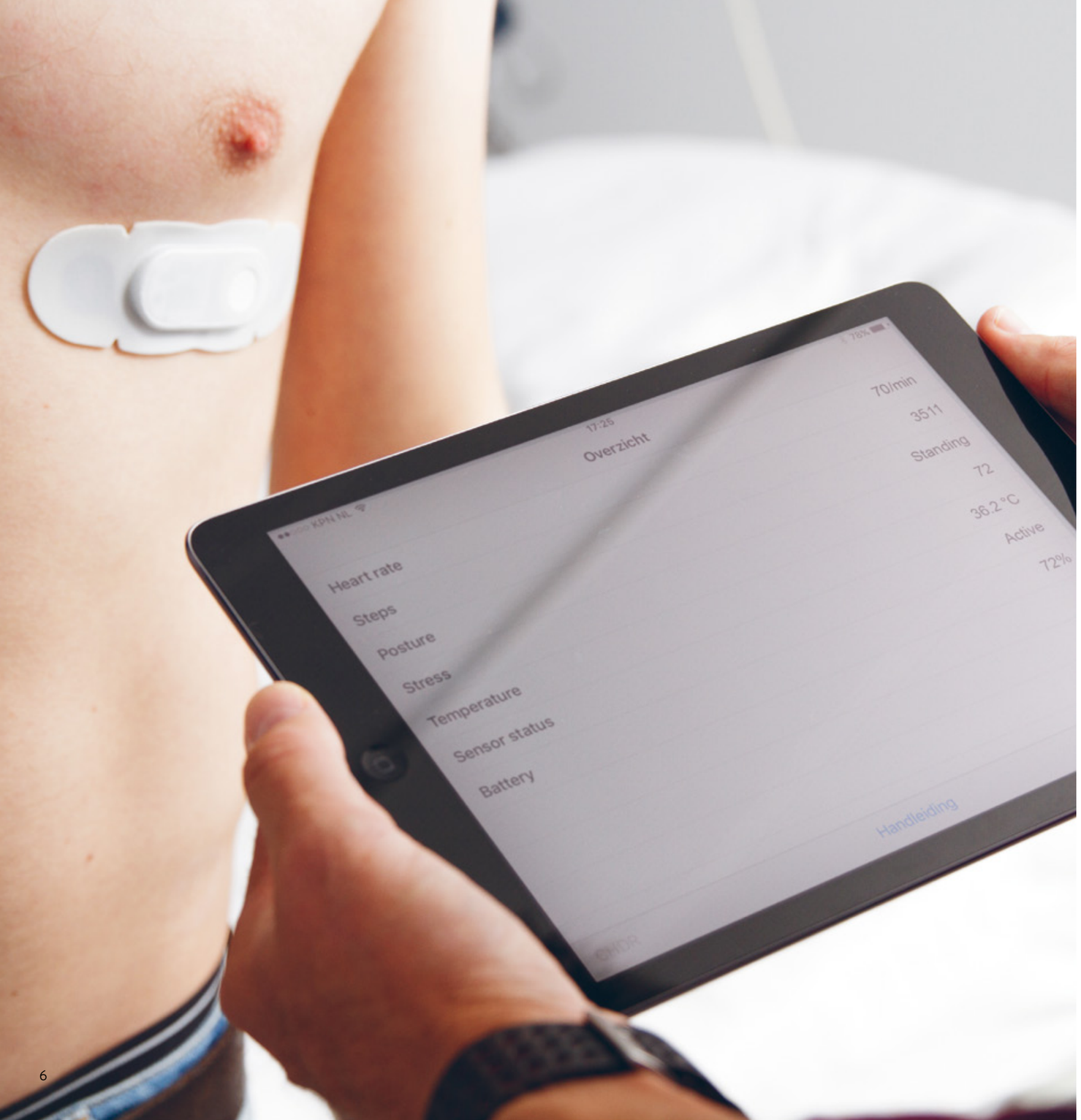
Some compounds can affect myocardial function, particularly after prolonged use. However, measuring a change in healthy subjects after just a single dose requires tools that are robust and extremely sensitive; such tools are available at CHDR's Cardiology Services.

Is our compound effective at treating atrial fibrillation?

Finding clear evidence that a paroxysmal arrhythmia has been treated successfully can be highly challenging, particularly in patients who experience asymptomatic episodes, for example in the case of atrial fibrillation. That's why CHDR uses non-invasive, highly sensitive wearable devices that can detect cardiac arrhythmia during long-term monitoring.

Cardiology Services highlights

- We offer a wide range of diagnostic procedures that can be tailored to meet the needs of the sponsor and satisfy the regulatory authorities.
- To obtain detailed ECG data, we use high-quality 12-lead ECG data. This approach is highly efficient and provides an integrated approach to clinical drug development.
- Continuous 12-lead ECG (Holter) data can be collected from subjects who stay at CHDR's clinical research unit and from subjects who participate in a Trial@home study.
- CHDR's Cardiology Services combines our in-house expertise in cardiology and internal medicine with experts at VUmc and LUMC.
- Additional diagnostic procedures such as cardiac MRI and PET scan can be used to study the compound's effects on the heart.



Cardiology Services: a closer look

Cardiovascular safety

When developing a new drug, safety is always our top priority. If the test compound is likely to cause severe adverse effects, it's important to know this as early as possible in the development process, particularly with respect to the compound's cardiovascular safety profile. Cardiovascular safety is even more important in the context of our ageing population, as the elderly are more vulnerable to adverse cardiovascular effects. At CHDR, we recognise the need to thoroughly analyse a compound's potential cardiovascular risks.

'One-stop shopping' for our sponsors

CHDR's Cardiology Services provides a wide range of cardiovascular diagnostic procedures to sponsors in the early stages of clinical drug development. The benefits are clear: because we already use high-quality ECG to ensure the safety of our subjects, it is relatively easy to perform additional analyses as needed in order to rule out possible adverse effects and/or study the compound's effects on cardiovascular function. Moreover, more reliable results are obtained when the data are interpreted in the overall context of the study and based on each subject's individual features. For example, data obtained from a 22-year-old healthy athlete should be interpreted differently from data obtained from a 65-year-old hypertensive subject. Importantly, CHDR's integrated approach also ensures that all key data are located securely in one central database for easy addition to the trial dossier.

As discussed above, CHDR's Cardiology Services was built on our long-standing collaboration with clinical cardiologists at the Vrije University Medical Center in Amsterdam and Leiden University Medical Center. In addition to high-quality 12-lead ECG and continuous Holter monitoring, we can provide specific analyses such as comprehensive QT studies (see below) and imaging procedures such as echocardiography, cardiac MRI, and PET, all of which are provided in accordance with Good Clinical Practice (GCP) guidelines.

A more reliable means of measuring the QT interval

One of the most important issues to address when developing a new drug is its potential to alter cardiac electrical activity, in particular the duration of the ventricular action potential (i.e. the QT interval, or QTI). An increase in the QTI has been associated with sudden death due to ventricular arrhythmia, particularly torsade de pointes, a severe form of ventricular tachycardia. At CHDR, we developed an innovative new

method for measuring the QTI using ECG data. Providing a comprehensive assessment of a compound's putative effect on the QTI is an essential step in clinical drug development and is now one of the core elements in our portfolio.

The conventional method for measuring a compound's effects on the QTI is to perform single 10-second ECG measurements at fixed times during the clinical experiment; the time points are usually based on the compound's concentration in the blood. Unfortunately, however, this sampling method is not particularly accurate in terms of assessing a compound's true effects on the QTI, due to its intrinsic variability. Thus, the QTI can be overestimated or underestimated, leading to an inappropriate change in – or even termination of – the compound's development.

To overcome these limitations, we developed and validated a new sampling method that is more robust than standard ECG sampling in detecting a change in the QTI. Using continuous telemetric ECG recording, we analyse 5-minute blocks of ECG data in order to accurately measure the QTI and analyse the relationship between plasma concentration and the QTI. Importantly, using this approach greatly limits the effects of variability in the QTI, enabling us to provide sponsors with more robust safety data, which they can then use to make strategic decisions with respect to further testing and/or development.

Measuring changes in the myocardium and myocardial function

Some drugs interact directly with cardiac muscle, affecting the heart's ability to pump blood. For example, many anti-cancer drugs can be highly toxic to the myocardium. Studying the effects of a single dose of a test compound requires the ability to measure extremely subtle changes in cardiac function in real-time. At CHDR's Cardiology Services, we have considerable experience using highly sensitive imaging modalities, including cardiac ultrasound and cardiac MRI. Working closely with the sponsor, we can develop a tailor-made protocol to address specific questions regarding the compound's effects on the myocardium.

Trial@home: measuring heart function in everyday life

In addition to collecting detailed measurements at CHDR's clinical research unit or in a university hospital setting, CHDR's Cardiology Services uses our Trial@home approach to study the drug's effects while subjects go about their daily business. Using non-invasive wearable devices that record a variety of parameters, including heart rhythm, movement, and body temperature, CHDR can perform studies while the subject is at home, at work, and at play. These devices can also be used to monitor subjects during the 'washout phase' of a drug trial, during which the compound is cleared from the body, thereby providing important information regarding the compound's long-term effects on heart function and other physiological properties.

To facilitate studies that combine remote sensors with smartphones (which can be linked using Bluetooth® technology), CHDR developed a unique proprietary platform called REMOS (REmote MOnitoring System). This platform has been validated and will soon be used in clinical studies.

Why choose CHDR?

The Centre for Human Drug Research specialises in early-phase clinical drug research. CHDR's overall mission is to improve the drug development process by collecting as much information as possible regarding the candidate drug in the early phases of development. This information helps sponsors make informed decisions regarding the course of clinical development for their product.

Why choose CHDR?

Research at CHDR covers a wide range of fields, including the central nervous system (CNS) and pain, the cardiovascular system, haemostasis, immunology, and dermatology. In addition, CHDR is at the forefront in developing novel biomarkers and methods for measuring drug-related effects in all of these research areas.

Pharmacology matters

Whether studying a new cognitive-enhancing drug, a next-generation painkiller, or a new monoclonal antibody designed to treat rheumatoid arthritis, the goal is to determine how the compound's effects correlate with both the dose and blood concentration at any given moment. In addition, understanding which biological systems are activated is an essential first step towards quantifying this relationship. At CHDR, our focus on pharmacology is reflected clearly in what we call question-based drug development.

Question-based drug development

CHDR actively uses question-based drug development - or QBD - as a more rational approach to drug development compared to conventional approaches. QBD can be best described as a series of questions that are addressed throughout the process. These questions often seem simple enough, but failing to answer even one question - or even addressing the questions in the wrong order - can have dire consequences. Thus, using this approach can potentially save companies millions of dollars by helping predict a catastrophic issue early in the development process, before the more expensive latter stages (for example, large-scale clinical trials or the marketing phase).

From a general perspective, the most important questions are:

1. Does the biologically active compound and/or active metabolite(s) reach the intended site of action?
2. Does the compound cause its intended pharmacological and/or functional effect(s)?
3. Does the compound cause any unintended pharmacological and/or functional effect(s)?
4. Does the compound have a beneficial effect on the disease and/or clinical pathophysiology?
5. What is the compound's therapeutic window?
6. How does any variability with respect to the drug response in the target population affect the product's development?

Contact

To learn about CHDR's full range of services, contact us today.

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