CHDR
Centre for Human Drug Research

Annual Report 2017

Foreword

It is with a sense of reluctance that we, the new Executive Board at CHDR, write this foreword to the 2017 Annual Report. After all, nearly all of last year was under the guidance of our former CEO, Prof Adam Cohen, and it would be somewhat inappropriate for us to claim credit for CHDR's outstanding performance in 2017.

On the other hand, CHDR has always been run by a team of colleagues who work together. And this may well be one of our strengths at CHDR: maintaining continuity even during times of major change. We are therefore honoured to be able to write this year's foreword.

'At CHDR, we are extremely proud that our position is healthy, allowing us to create our own R&D budget'

For those of you who are accustomed to reading CHDR's Annual Report, this year's format will be familiar, including highlights of some of our recent advances such as the use of wearable devices, the development of advanced 'wet' biomarkers, and new approaches designed to measure the effect of test compounds on driving performance. In addition, we've also introduced several new features in this year's Annual Report, including examples of the social obligations about which our staff and management feel quite strongly. We also introduce more of the people behind the scenes as an illustration that CHDR is a rather unique collection of dedicated professionals who are committed to developing better treatments.

In many ways, this year's Annual Report is a testament to our highly successful approach of performing clinical pharmacology projects that are centred around collecting valuable information regarding the investigational compounds. In this report, we highlight some of the activities that CHDR embarked upon in 2017, and you will find information regarding our three key themes: developing drugs, developing methods, and developing people. Together with our continued commitment to research, our investment in operations, and our active role in helping develop new guidelines, this approach has contributed to yet another successful year in CHDR's history. It also sets the stage for the future, in which we hope to continue to serve our clients, our research subjects, and our staff.

We hope you enjoy reading this year's Annual Report, and we look forward to serving your needs for years to come.

On behalf of all of us at CHDR,

Koos Burggraaf, CEO
Geert Jan Groeneveld, CMO/CSO
Pierre Peeters, COO

Contents

Meet CHDR's new Executive Board

From left to right: Dr Pierre Peeters, Prof Koos Burggraaf, Dr Geert Jan Groeneveld

Staying focused on people, methods, and products

Last year, after 30 years at the helm, Prof Adam Cohen stepped down as CHDR's CEO in order to turn his attention to InnoS, CHDR's new consultancy service. Cohen was succeeded by a newly established Executive Board consisting of Prof Koos Burggraaf, Dr Geert Jan Groeneveld, and Dr Pierre Peeters. This new Board will continue to use the strategy that has been so successful over the past three decades, investing in the development of new methods and new products and educating both students and staff.

During the past decade, CHDR has grown rapidly in both size and complexity. In keeping with this growth, the relatively informal management style at CHDR has changed as well. 'We've been increasingly involved in both the day-to-day management and strategic planning at CHDR,' says Burggraaf, the new CEO at CHDR. 'So for the Board, as well as our colleagues and collaborators, there have been no major changes, and we'll be able to continue our winning strategy of pursuing innovation.'

'My successors were ready to take over,' says Cohen, 'and I think a smooth transition at the top is in line with our core values. For the past 30 years, CHDR has been a highly stable organisation in a world dominated by change. While nearly everyone else was experiencing mergers, takeovers, and changes in management, we remained relatively stable. So, I think this transition is in the best interests of CHDR and our sponsors.'

Increasing complexity

The developments discussed in this annual report illustrate the fact that CHDR is still growing. 'In addition to performing more studies and employing more people than ever before,' says Peeters, CHDR's new COO, 'the complexity of our operations and our data flow have also increased.' This complexity is partly due to the growing number of studies involving both patients and healthy volunteers. Increasingly, CHDR is actively involved in a large part of the drug development process, including performing preclinical studies if needed in order to prepare for studies in volunteers and/or patients. New methods and

biomarkers are being developed every year, providing us with a growing array of tools for studying the pharmacology of new and innovative drugs.

'We expect this trend of increasing complexity to continue,' says Groeneveld, CHDR's Chief Medical Officer and Chief Scientific Officer, 'particularly with respect to the development of new technologies and methods such as wearable devices and other data-rich applications. That's why we chose to reorganise our management structure. With this new Executive Board, we can work together to make the best decisions for our organisation, our sponsors, and other stakeholders.'

'We've known each other for years,' adds Burggraaf, 'and I think our individual skills and personalities are highly complementary. Together, we'll continue to foster the culture of openness and mutual trust that has been a hallmark at CHDR since the beginning.'

Innovation

Continuity and stability are important to CHDR, but at the same time, innovation remains one of our core values. Some might see this as a paradox, but at CHDR stability and innovation go hand-in-hand.

'It's actually our focus on science and our commitment to research that provide the stability,' says Cohen. 'Our NeuroCart® test battery is a good example. I used many of the tests that are now included in NeuroCart in my PhD thesis, and although it's been repeatedly adapted and upgraded over the years since then, its core features and functions have remained the same. Meanwhile, we've also developed several new tools to study the central nervous system, including resting-state fMRI, positron emission tomography, a driving simulator, and a full-feature test car. All of these methods complement each other and have added to our understanding of CNS pharmacology. Similar developments drive the research in our other areas as well.'

An additional driving force behind innovation at CHDR is our continuous interactions with sponsors, their scientific staff, and our global network of collaborators in academia. 'We are tuned in to the needs of our sponsors and the changing field of drug development,' says Burggraaf. 'We like to innovate, but we also listen closely to our sponsors and our collaborators. What questions drive them, and what problems keep them up at night? Then we come up with our own solutions, often in collaboration with academic researchers and clinicians in our network. We're always looking for new opportunities to collaborate with leading researchers and to develop new methods and new approaches to answer our sponsors' questions. These collaborations have contributed greatly to our success, and we will of course continue to increase our academic networks as we look to the future.'

Education

In addition to developing new methods and products, CHDR will continue to focus on what we call 'people development'. Groeneveld explains: 'We have always been highly active in education at every level. For example, we help educate students in a wide range of disciplines at Leiden University, Leiden University Medical Centre, and the Leiden University of Applied Sciences. In addition, we train clinical pharmacologists, and we recently received approval to establish a research internship in clinical psychopharmacology here at CHDR for psychiatry residents. And our commitment to education does not end there. We encourage all of our staff members to push themselves, participate in research, write a PhD thesis, and actively work on advancing their career. We consider this to be a core value in itself, and of course it is also a great way to build an extensive network. We like to stay in touch with our former employees and PhD students, many of whom are now medical specialists or researchers in either academia or the pharmaceutical industry.'

'For an ambitious young scientist, CHDR is a good place to be,' adds Peeters. 'Our sponsored studies – as well as the additional opportunities made possible by our R&D Fund – provide an environment in which our researchers can immerse themselves in innovative science while contributing to the advancement medicine.'

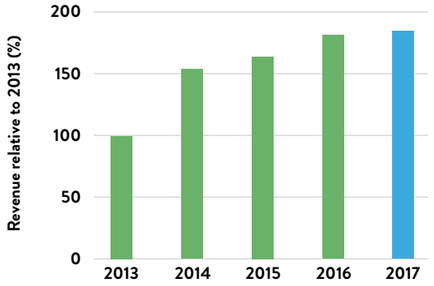
The future

So, what are the plans of the new Board? 'CHDR will continue to operate in the unique niche – innovative, data-rich early clinical drug development – that we've occupied for more than three decades,' says Burggraaf. 'Thanks to Adam's leadership, we are now in a very strong position. As an independent, not-for-profit foundation, we have no shareholders, no debt, and the means to finance independent research alongside projects sponsored by pharmaceutical companies. At CHDR, everything we do is dedicated to developing cutting-edge products and methods for use in a range of disciplines, including pharmacology, image-guided surgery, biomarkers, and more. Our goal is to continue to develop novel, innovative methods for studying how compounds affect physiology in healthy subjects and pathophysiology in patients. In a nutshell, at CHDR we'll continue doing what we love – serving the medical community and helping improve quality of life for patients everywhere.'

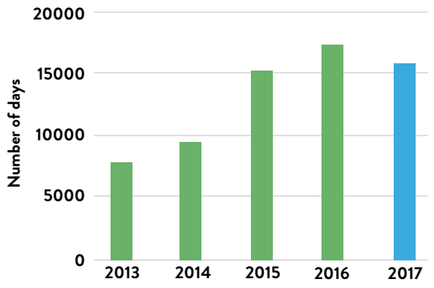
Cohen, meanwhile, will continue to serve CHDR. In the coming years, he plans to expand CHDR's consulting service, InnoS. 'It's an exciting time for consultants in the drug development field,' says Cohen. 'There's a great deal of diversity, ranging from extremely large corporations to small biotech companies. In addition, we can offer our services to government agencies and regulatory bodies, who have to keep up with – or even ahead of – the rapidly changing field of drug development. I have several new ideas for improving the process of drug development, and these can be useful in a variety of situations; one example is the concept of concurrent engineering as an alternative to the current step-by-step process, which has an inherently high risk of failure. InnoS will be a part of CHDR, and my colleagues' expertise will be a major asset. Together, we will ensure that we're always up to date, so that we can continue to contribute to the development of new drugs in order to meet the needs of patients worldwide.'

2017
at a glance

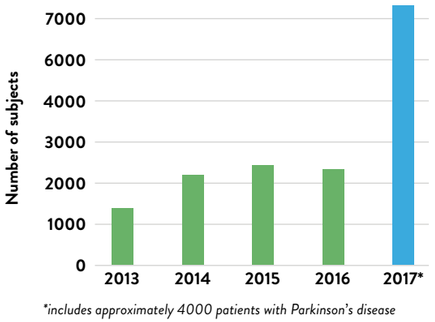
Contract revenue



Accomodation days



Subjects screened



*includes approximately 4000 patients with Parkinson's disease

2017 at a glance

65 studies

41 contracts signed

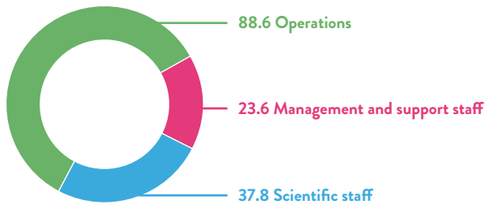
35 articles published

> 47,000 volunteers available

> 17,000 patients available

6 PhDs graduated

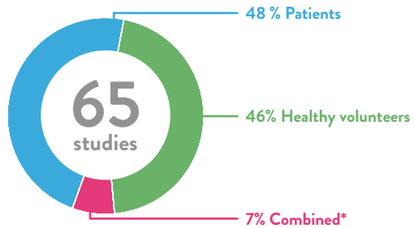
FTE by department



Overall client satisfaction

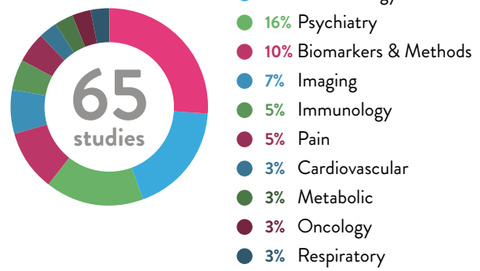
8.8

Studies with subjects

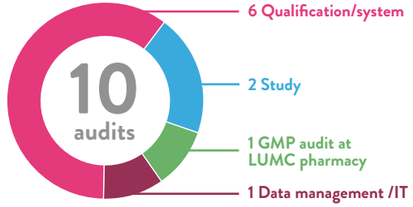


*both healthy volunteers and patients

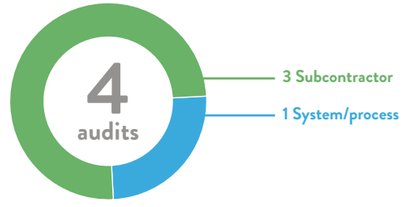
Studies per research area



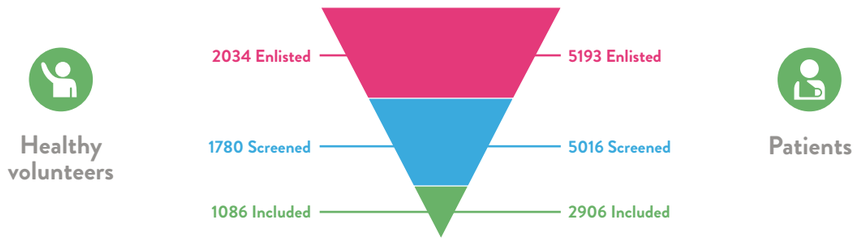
External audits



Internal audits



Subjects recruited



Where we come from

Afghanistan
Aruba
Argentina
Belgium
Curacao
Germany
Egypt
Greece
India
Iraq
Iran
Italy
Kurdistan
Morocco
Mexico
Moldavia
Netherlands
Oman
Pakistan
Poland
Portugal
Russia
Scotland
South Africa
South Korea
Sri Lanka
Suriname
Syria
Thailand
UK
USA

Celebrating 30 years

CHDR celebrates 30 years with their third Dino Meeting at Naturalis

On May 12, 2017, CHDR hosted their third Dino Meeting to celebrate their 30th anniversary. The symposium entitled 'Evolving in an Ever-changing World' was held at Naturalis (the National Museum of Natural History) in Leiden, the Netherlands, where three plenary speakers talked about emerging trends in the pharmaceutical industry.

Starting in 2002, CHDR has organised a so-called 'Dino Meeting' every five years. At their inaugural Dino Meeting, a panel of distinguished speakers, including Dr Paul Janssen and Nobel laureate Jim Black, discussed the future of the pharmaceutical industry. The connection between these meetings and the dinosaur theme serves as a reminder that in our ever-changing world, even the largest and most successful among us must continually adapt in order to thrive or even survive.

The human factor

The first speaker at our 30th anniversary meeting was Dr Jean-Jacques Garaud, a world-renowned researcher known for his role in helping develop several successful immunological products. Previously at Roche, he is now a venture capital partner at Sofinnova Partners in Paris, and he serves on the board of three biotech companies.

Standing under the watchful eye of Trix, Naturalis' T. Rex skeleton, Dr Garaud took us back in time to an era even before the time of the dinosaurs, back to the primordial soup in which life began, serving as a metaphor to describe the developments in the pharmaceutical and biotech industries over the past few decades. According to Dr Garaud, a new 'primordial soup' has emerged, potentially giving rise to new 'life forms' in the form of new biotech companies with promising new products to meet the needs of patients. During his talk, Dr Garaud shared several inspiring examples of new scientific developments. For instance, one company compiled a dataset of the molecular interactions between viruses in human cells, revealing many promising new targets for antiviral therapies. Another company in which he is more directly involved has developed a promising new treatment for septic shock. In both of these cases, however, the underlying science itself was not sufficient; to successfully obtain funding and begin the process of developing a new product for the market, researchers need a clear focus, the right connections, and solid leadership. In short, Dr Garaud showed us how the human factor is essential for these new 'life forms' to both survive and thrive in the fragile biotechnology ecosystem of the 21st Century.

The future

Next, Prof Sander van Deventer, a professor of translational gastroenterology at Leiden University, told us how he was previously involved in the development of several innovative drugs, including infliximab (Remicade®), a monoclonal anti-TNF antibody, and Glybera®, the first gene therapy product approved for use in Europe. Prof Van Deventer is the founder and managing partner of Forbion Capital Partners, and he serves on the board of several companies. In his talk, Prof Van Deventer stressed the large, currently unmet need for new medical treatments, as only 10% of all diseases can be treated effectively. He also reminded the audience of the significant benefits associated with recently developed drugs in terms of improving the quality of life and long-term survival of patients with a wide range of conditions, including rheumatoid arthritis, Crohn's disease, HIV/AIDS, and haemophilia. He showed us how these new drugs were initially quite expensive, but that the price decreased rapidly once the initial patents had expired. He also emphasised that expensive drugs are not the major factor driving the high cost of healthcare.

These days, however, the drug development pipeline seems to be leaking, with only a trickle of new treatments ultimately reaching the market. According to Prof Van Deventer, the underlying causes include the high costs associated with drug development, the company's decline in income as the price of a blockbuster drugs goes down, and the relatively long development time in the pharmaceutical industry (12 years) compared to other industries (for example, just 6 years in the aviation industry). To make matters worse, public opinion in many countries – including the Netherlands – seems to be turning against the pharmaceutical industry, causing what Prof Van Deventer calls an 'irrational war on expensive drugs', placing an additional hurdle in the drug development path.

Near the end of his talk, however, Prof Van Deventer offered a glimmer of hope. Biotech companies backed by venture capital are currently developing new treatments using a patient-centred approach and working in close collaboration with academia. Citing several examples, he showed how a successful company may in fact have only two people on the payroll, with many 'employees' working in an international network with other companies and academic researchers. These innovative approaches may help seal the 'leak' in the pipeline and stimulate the development of new drugs.

CHDR: 30 years of innovation

Back in 1987, Prof Douwe Breimer, a professor of Pharmacology at Leiden University, helped establish a small clinical pharmacology unit in a small building that used to belong to the Leiden University Hospital Pharmacy. Dr Adam Cohen, a former PhD student of Prof Breimer's, was hired to run this new organisation called the Centre for Human Drug Research. Over the following years, the CHDR grew steadily. They soon outgrew the first location, and after several moves to progressively larger facilities, they finally moved to their current location on Zernikedreef in Leiden.

Throughout the years, much has changed at CHDR, but their original spirit has remained, including their dedication to science, innovation, and providing the best service in an environment that stimulates both young professionals and experienced staff while providing a friendly setting for our study subjects.

After three decades, Prof Adam Cohen, now a professor of Clinical Pharmacology, has handed over the reins to his long-standing colleagues, Prof Koos Burggraaf, Dr Pierre Peeters, and Dr Geert Jan Groeneveld, who serve as CHDR's new Executive Board (see page 7).

Streamlining the drug development process

'Evolve or Die' was the title of the final talk by Sir Rory Collins, a professor of medicine and epidemiology at Oxford University. Prof Collins coordinated the landmark International Studies of Infarct Survival 'mega-trials' and other seminal trials that revolutionised our approach to preventing and treating myocardial infarction and stroke. Currently, he is the principal investigator of the UK Biobank study, the largest comprehensive prospective epidemiological cohort in the world, containing biological samples and the medical records of half a million individuals in the UK.

According to Prof Collins, clinical trials have become far too expensive because of 'over-regulation and a lack of thinking.' As a result, there is now a call for 'Big Data' and 'real-life data', which do not have the rigorous reliability of a randomised controlled trial. In his typical tongue-in-cheek style, he explained the causes of the problem and then proposed some solutions. As a major cause of the costs and bureaucracy surrounding clinical trials, Prof Collins pointed to the guidelines issued by the ICH[1], which he criticised for its lack of transparency and refusal to ask for input from patients and academic researchers. He showed quite clearly the underlying flaws in the ICH-GCP guidelines and what he calls a 'box-ticking mentality'.

[1] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, an organisation comprised of pharmaceutical companies and regulatory authorities.

Unfortunately, despite these major shortcomings, the ICH-GCP guidelines are now the standard, not only in clinical drug development but also in other guidelines in Europe and even developing countries, making many clinical trials much too expensive. Prof Collins then suggested several clever solutions such as using the data to monitor quality rather than performing routine site visits, which can be expensive and are often ineffective. He also mentioned the Clinical Trials Transformation Initiative by the FDA, which has sparked hope that future regulations will help facilitate clinical trials and make drug development more affordable.

Watch the lectures

Click below to watch the lectures given at our 30-year symposium:

Dr Jean-Jacques Garaud

Prof Sander van Deventer

Prof Rory Collins

‘I value CHDR’s unconventional approach’

‘I don’t know of any other organisation quite like CHDR. Most CROs lack CHDR’s academic know-how, or they are simply consultants who operate alone, rather than as part of a complete team, only trading advice for money without being involved in the implementation whatsoever. On the other hand, most academic institutions are too ‘academic’, lacking practicality and unable to make the translation to industry. In a sense, CHDR seems to have the market cornered with respect to this type of collaboration, which makes them unique.’

VP Clinical Research and Operations,
Biotech company*

**The views expressed here are the sole opinion of CHDR’s sponsors.*

Research Budget

Enjoying the fruits of our investments

As a not-for-profit organisation, CHDR has the freedom to invest a portion of our revenue in new developments. This has always been part of our strategy; but in 2016, a formal R&D Fund was established based on 10% of our annual revenues. Last year was the first full calendar year with this fund, and many funded projects have already yielded valuable results. Here, we present a few notable examples.

The R&D Fund was created to serve as an incentive for driving innovation and the realisation of new ideas. Each staff member at CHDR is eligible to apply for an R&D Fund grant through his/her Research Director. The application should discuss how the project is relevant to drug development projects at CHDR and how it will serve our core strategic priorities. In their review of each application, our Scientific Advisory Board determines whether the project is likely to contribute to the following strategic priorities:

- Biomarker development in a broad sense, including 'wet' biomarkers in the laboratory and other measurements to quantify pharmacological activity such as electrophysiology, challenge models, and/or behavioural measures;
- Trial@home, CHDR's innovative programme for conducting entire studies on an outpatient basis by monitoring study subjects through the use of wearable devices, smartphone apps, and other tools;
- CHDR's monocentre approach, in which all study participants are brought to one central study site, where all of the tests and measurements are performed; and
- Ready-for-Research, our extensive database of well-characterised patients who have indicated their willingness to participate in research studies and have been clinically evaluated and pre-screened.

Biomarkers

Our R&D Fund has already helped initiate several projects aimed at developing and/or improving measurements of specific physiological parameters relevant to drug development. In many of the cases

mentioned below, additional funding was provided by one or more of our sponsors.

For psychiatric research, we acquired and calibrated a CO_2 tolerance tester, which delivers a mixture of breathable air containing high CO_2 levels and can measure a wide range of physiological parameters. CO_2 inhalation can induce a panic attack in healthy volunteers and in patients with certain mood and/or anxiety disorders. CHDR uses this so-called 'CO_2 inhalation challenge' model to measure the anxiolytic/panicolytic effects of new test compounds (see **page 72**).

In neurology, neuronal hyperexcitability is a clinically important factor in various disorders, including epilepsy and amyotrophic lateral sclerosis (ALS). In addition to measuring peripheral excitability by stimulating motor neurons, CHDR and researchers at Twente University are using transcranial magnetic stimulation (TMS) together with EEG and EMG to directly study the effects of test drugs on CNS excitability (see **page 53**).

The effect of a drug on driving performance is extremely important from a safety perspective. Driving also presents the CNS with an interesting challenge, as it requires the integrated efforts of various parts of the brain. In addition to our driving simulator from Green Dino, CHDR has obtained and is now validating a test car that can be used to measure driving performance in real-life traffic conditions. More information about this robust new tool can be found on **page 32**.

In addition, we significantly expanded our capabilities for bioanalysis and advanced sample handling. We've acquired an additional flow cytometer, our flow hoods and incubators were expanded, and new equipment was obtained, including a fluorescence microscope, stereo microscope, and both ELISA and ELISPOT readers. Combined with our magnetic cell sorter, we are now well equipped to measure a drug's effects on its molecular target. For example, researchers have initiated cutting-edge clinical and preclinical studies to measure drug-induced effects at the cellular level (see **page 93**).

CHDR's Cardiology Services has also invested in developing a new method for measuring the QT interval in an ECG, which serves a major indicator of a drug's safety. This novel approach is more sensitive and specific than other methods, providing a better understanding of the drug's safety profile and decreasing the risk of wrongly terminating the development of a compound that is actually safe (see **page 90**).

In addition to initiatives financed by our R&D Fund, in 2017 we introduced several new sponsor-funded methodologies. For example, we expanded our cellular laboratory to allow us to study fresh biological samples (see **page 93**).

Using funds from both the R&D Fund and our sponsors, we also added several new tools to our DermaToolbox, including cutaneous microbiome measurements, multispectral imaging, 3D photography, high-resolution thermography, and optical coherence tomography (OCT). OCT is a non-invasive optical imaging technique used to study the upper layers of the skin in real-time, including epidermal thickness and vascularisation. We also developed several new dermatology-specific interfaces for the mobile apps used in our Trial@home program, including a 'selfie app' with real-time feedback for monitoring treatment effects in acne trials. For a full overview of the DermaToolbox, see **page 78**.

Other strategic goals

A main project that contributed to our Trial@home strategy was the development of REMOS, our remote monitoring system. This proprietary platform supports our outpatient studies involving wearable devices, smartphones apps, and other sources of data. REMOS is used to collect data at specified time points, allowing researchers to monitor hundreds of subjects as they go about their daily business. For more information about REMOS, see **page 36**.

Using a test car to measure driving performance

To complement our driving simulator from Green Dino, CHDR recently acquired a sophisticated test car that can be used to measure a wide range of driving behaviours in real-life traffic conditions. Researchers at CHDR have already used this new car to study the baseline driving patterns of both beginning and experienced drivers. They are now using this advanced tool to study the effects of sleep deprivation and pharmacological compounds on driving performance.

CHDR has had a long-standing interest in tests that measure driving performance, as they can help determine whether a particular drug affects a person's driving skills or ability to operate dangerous, complex machinery. This information is of course essential for safety warnings, but it can also provide important insight into the drug's pharmacology and pharmacokinetics. For example, benzodiazepines – which are commonly prescribed for insomnia – can impair driving performance, even the following morning. Thus, researchers can use these tests to determine whether a new sleep aid affects next-day driving performance, possibly giving the new compound added value. Tests that measure driving performance may even be used to determine whether new candidate drugs for treating neurological disorders can restore the patient's ability to drive safely.

A drug's effects on driving performance are also interesting in themselves. The ability to operate a car safely requires tight coordination between several components in both the central and peripheral nervous systems. When driving, we must integrate a continuous series of visual and auditory signals, apply a set of highly context-dependent rules, and simultaneously coordinate the movements of our extremities. Most experienced drivers are not even aware of these complexities, as driving has become almost second nature. But even a seemingly minor disruption – for example, texting or talking on the phone, shoulder pain, a bad night's sleep, or just being in a foul mood – can significantly affect our ability to safely operate a car. Unfortunately, most drugs affecting CNS function can also impair driving performance.

Big data

The ability to measure precisely how a given drug affects driving performance requires the collection and analysis of massive amounts of data. Thanks to modern computers and data science, it is now possible to study many specific aspects of driving at the same time. CHDR is interested in going beyond the classic SDLP (standard deviation of lateral position) test (see text box), which – although well-established and widely used – is not a very sophisticated test. Thus, CHDR's test car is equipped with an array of sensors that continuously measure a wide range of factors, including vehicle speed, distance from other cars, whether the driver signals a change in direction, and much more. In this respect, our test car is similar to the driving simulator we use in clinical studies (see text box).

Of course, when SDLP was first established as the standard test for measuring a drug's effects on driving performance, computer power was just a fraction of what it is today. Back in those days, it made sense to use a relatively simple, highly reproducible test. Today, however, CHDR believes it is time to expand our studies regarding the effects of pharmacology on driving. Using a big data–style approach, we can search for relevant patterns among the many variables that we measure. In a way, our new test car will be like taking our NeuroCart on the road.

A classic measurement: SDLP

Before any new drug receives market authorisation, its effects on driving performance must be evaluated. Regulatory authorities such as the FDA in the US and the EMA require that the drug's effects are measured using the SDLP (standard deviation of lateral position) test, either in an actual motor vehicle or in a driving simulator. To measure SDLP, the driver is instructed to drive down a 100-km stretch of road at a constant speed of 95 km/h (60 mph) while keeping the car centred in the right lane. During this time, the position of the vehicle is continuously monitored. If the driver changes speed or changes lanes (for example, to pass another vehicle), the data collected during this time are excluded from the overall analysis. At the end of the test, the car's lateral deviation is then calculated. SDLP is a well validated test that has been used for decades to reliably measure the diminished driving skills of someone who's under the influence of alcohol.

Sleep deprivation

Before using the new test car in pharmacological studies, CHDR needs to validate the measurements by studying the effects of a non-pharmacological intervention on driving performance. We will therefore use the test car to measure the effects of sleep deprivation in healthy subjects who have been kept awake for 24 straight hours. They will drive a specific route before and after sleep deprivation. As a follow-up study, we can measure the effects of sleep deprivation on someone while driving a familiar route that he/she drives every day (for example, a healthcare worker working the night shift). These studies will hopefully allow us to demonstrate the specific effects that sleep deprivation has on specific features of driving performance. These data can then be compared with the effects of increased blood alcohol levels and/or other neurotropic compounds.

Safety first

Of course, with any tests that involve real-life traffic, safety concerns must be the top priority. CHDR's test car contains sensors to monitor the subject's vital signs, and emergency equipment is on board. During a pharmacological test, a nurse or assistant is also present in the car. Importantly, just like a car used for giving driving lessons, the test car is equipped with a second set of controls on the passenger side; during a pharmacological study, an experienced driving instructor will sit next to the driver, ready to take over if needed.

Of course, even with these precautions, the subject must still feel that he/she is able to drive the car; If not, then the subject is not permitted to perform the test.

In a pharmacological study, CHDR will use the test car mainly to confirm that a given blood concentration of a compound does not affect driving performance. In the early stages of the clinical drug development process, we can use the NeuroCart test battery to measure the compound's effects on CNS function. In addition, we can use the driving simulator to measure the compound's effects on driving performance in our closed research unit (see text box). Together, these tests can provide important early information regarding the drug's safety margin with respect to blood concentration and safe driving performance. Once we've established that a given blood level is safe for driving, we can then turn to using the test car on the road. By combining NeuroCart, the driving simulator, and the test car, CHDR now has a wide array of tools for studying the neurophysiological changes caused by drugs, CNS conditions, and other factors. This approach will improve the safety of both our subjects and future patients who will use the drugs we're developing, and it will provide valuable pharmacodynamics and pharmacokinetics data.

The Green Dino driving simulator

CHDR has used **the Green Dino driving simulator** in numerous studies involving healthy subjects and patients, both with and without drugs. This driving simulator has provided valuable information regarding the effects of CNS compounds, serving as an important complement to our NeuroCart test battery.

Compared to an actual test car, a driving simulator has both advantages and disadvantages. Naturally, the simulator is much safer for the subject, allowing researchers to test a much wider range of blood concentrations. In addition, the driver's response to unexpected situations (for example, a pedestrian suddenly crossing the street) can be studied safely under controlled conditions. On the other hand, the subject is aware that the test is just a simulation; thus, the subject may take additional risks or behave differently than when driving a real car. Another disadvantage is the wide variability among subjects with respect to their reactions to the simulator itself. For example, younger subjects who regularly play video games may take considerably more risks in the simulator than they would take in real life. Nevertheless, the driving simulator has been extremely valuable in studying the neurophysiological effects of new compounds.

REMOS: CHDR's new platform for managing data collected using wearable devices and apps

Wearable sensors are revolutionising medical research. These portable devices can be used to continuously monitor movement and several key physiological parameters in both patients and healthy subjects as they go about their daily business. In addition, apps and mobile devices can be used to communicate with study participants. CHDR is pioneering the use of these new technologies as part of our Trial@home approach to clinical drug development. To integrate the flow of information, and to provide our researchers with direct access to the data, CHDR developed a powerful new platform called REMOS.

In recent years, CHDR has pioneered the use of smartphone apps in clinical studies. Our unique Trial@home approach uses data received via these apps, which can be used to remind subjects to take their study medication and/or ask them specific questions regarding their symptoms, and quality of life. A good example is our use of apps in dermatological studies, in which subjects can use their phone to send a picture of the lesion with the medication applied. The app can also be used to prompt the subject at regular intervals to report symptoms such as itching or pain.

CHDR is now expanding the use of these apps by combining them with wearable sensors in order to obtain a wealth of both objective and subjective data from subjects as they go about their daily lives. This technology is highly promising for use in the medical field in general and in drug development in particular. In the past, researchers had to rely on the subject's memory and their willingness to provide subjective information. But with these new technologies, we now have direct access to a full range of data regarding the subject's physical activity, heart rate and blood pressure, temperature, and virtually any other parameter we wish to measure.

The REMOS app

Smartphone apps can be linked to wearable devices to measure physical, physiological, and social activity. Many of these platforms also offer additional features such as data analysis. Rather than using a third-party, commercially available system, CHDR developed a unique platform called **REMOS** (REmote MOnitoring System). The participants in the Trial@home studies can download the REMOS app to their smartphone. When the study starts, they use this app to scan a personal QR code. From that moment on, the app runs continuously in the background, providing a steady flow of data.

The subject's QR code is used to activate the study protocol, determining the measurements and sampling frequencies that the REMOS app will use, sending the data directly back to the Promasys database at CHDR. Via the app, subjects can be prompted to use the study medication, take a picture the medication and/or the lesion, answer questions, or use a peripheral device to measure blood pressure, body weight, etc.

The app can also be used to monitor social interactions, including social media. For example, it can track the subject's use – but of course not the content – of social media apps, providing a basic timeline of the subject's activity. Using the phone's built-in microphone, REMOS can also track when the subject converses with others. A wide variety of functions are currently being tested and validated in a range of settings. For example, we used the app to track the use of social media by our interns. Using self-reported data, we are now developing algorithms to measure when a subject is walking, riding a bicycle, or riding in a car, bus, or train. When we introduce REMOS into our clinical studies, new features will undoubtedly need to be developed and validated.

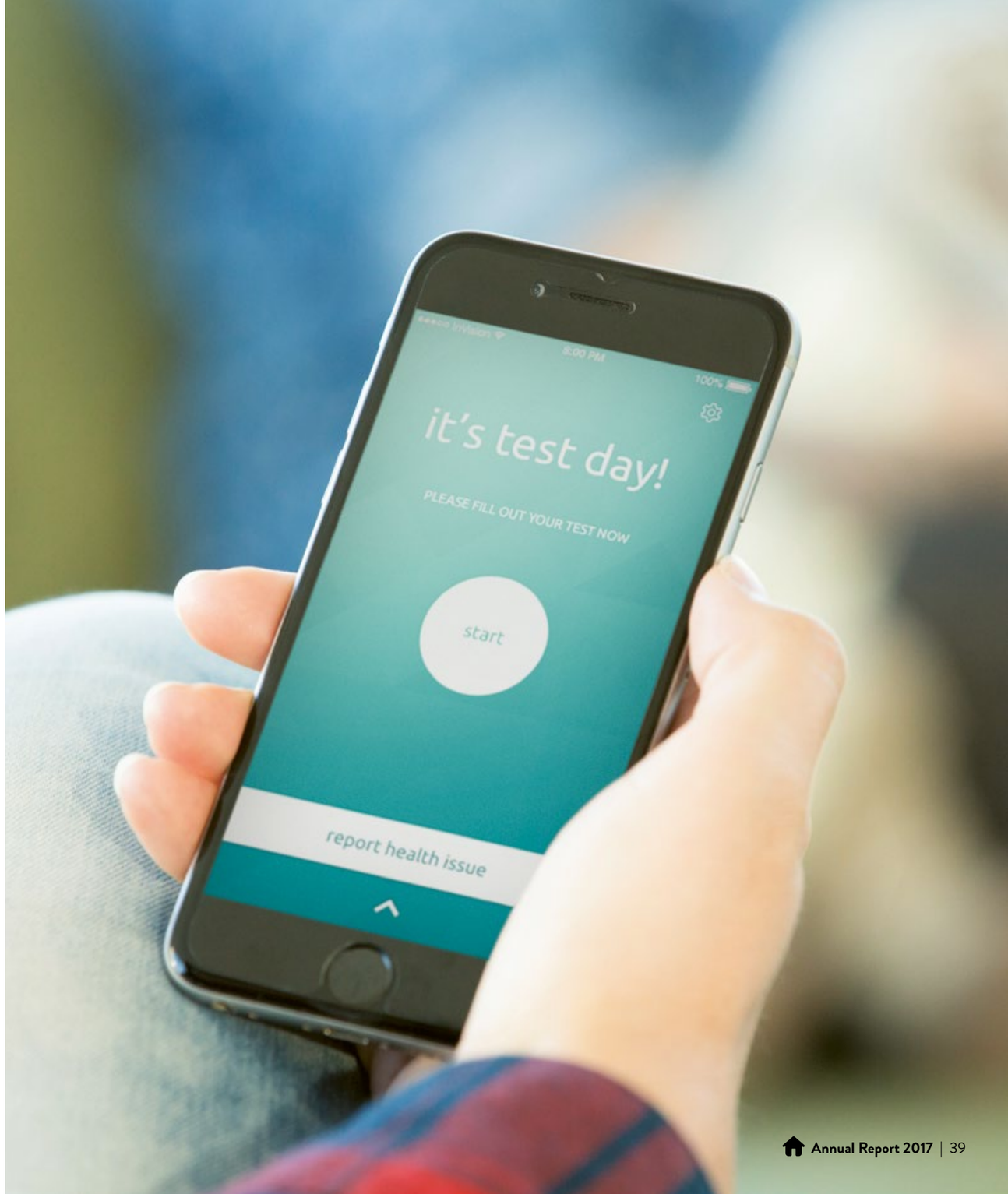
Paediatric research

Pharmacological research involving children is one of the more promising applications of these new mobile technologies. In paediatric clinical research, it is essential to minimise the burden placed on the participants; that's why many drugs are not routinely tested in children. However, if the child can participate in a study while remaining in the safe, familiar environment of their home, the study can be relatively

stress-free for both the child and his/her parents. Thanks to wearable devices, the child can stay at home and we can still collect a wealth of high-quality data. In collaboration with Basel University Hospital in Switzerland, CHDR used a special smartwatch to measure the physical activity of children before and after undergoing a tonsillectomy. The data clearly show how the children's activity steadily returns to previous levels following surgery; thus, this approach may also have added value in pharmacological studies involving children.

Psychiatry

REMOS can also be used to increase the collection of data in the field of psychiatry. In this field, the ability to collect objective information regarding the subject's day-to-day behaviour is particularly important. For example, wearable devices can be used to track the subject's physical movements, health parameters, sleep patterns, and many other relevant factors, including data regarding the subject's social interactions with others. These data can provide an objective measure of psychological health in patients with depressive and/or anxiety disorders, providing a robust platform for studying the effects of antidepressants and anxiolytics. And of course, REMOS can be used to ask subjects to rate their general well-being, to report on their positive and/or negative emotions, and to provide other data regarding their daily experiences. Obtaining this information at regular intervals throughout the day can reveal important insight into the feelings and behaviour of patients with psychiatric disorders, complementing standard questionnaires that simply ask the patient how he/she 'felt' during the past seven days. In coming years, CHDR will further develop the REMOS app for use in psychiatry and other research areas.



Using laser-evoked potentials to study pain with high precision

In 2017, CHDR added a new tool to PainCart®, their comprehensive battery of tests designed to study the effects of analgesic compounds. In this test, laser-evoked potentials are used to measure the electrophysiological signal in the brain (EEG) elicited in response to a mildly painful laser stimulus delivered to the skin.

To measure laser-evoked potentials (LEP), brief laser pulses are applied to a small confined patch of skin while recording brain activity using EEG. The subject perceives the stimulus as mildly painful and is asked to rate the pain. An important advantage of LEP is that it provides the researcher with a direct, objective visualisation of the stimulus' effect on brain activity, in addition to the subjective response given by the participant. This is important because the other tests in PainCart rely solely on the participant's subjective response by measuring a pain detection threshold and/or a pain tolerance threshold. In the future, CHDR will compare between these objective and subjective measurements using a variety of compounds that affect the perception of pain. Another advantage of LEP over other tests in PainCart is that the stimulus activates only nociceptive (i.e. pain) fibres, namely Aδ fibres and C fibres.

Because the laser pulse lasts for just a few milliseconds, the stimulus must be synchronised precisely with the EEG signal. CHDR recently upgraded the EEG systems in both **NeuroCart®** and **PainCart**, allowing researchers to measure electrical signals using up to 32 electrodes with high sampling frequency, providing the high temporospatial resolution needed for measuring LEP.

The LEP setup is fully mobile and can be used to easily stimulate various parts of the skin. Thanks to this feature, LEP is suitable for use in combination with CHDR's capsaicin challenge model. Application of capsaicin to a small patch of skin causes a temporary local increase in sensitivity to painful stimuli (hyperalgesia). The surrounding area can also be sensitised in a phenomenon known as secondary hyperalgesia, which may be useful as a model for studying neuropathic pain.

CHDR demonstrated the power of LEP using a two-part approach. In the first part of the study, the effect of capsaicin-induced hyperalgesia on LEP was measured. After application of capsaicin, a clear increase in LEP was measured in the primary hyperalgesic area, but not in the secondary area. In the second part of the study, researchers measured the pharmacological effects of two compounds currently used to treat neuropathic pain, namely duloxetine (a serotonin/noradrenaline reuptake inhibitor) and tramadol (an opioid compound that also inhibits serotonin reuptake). The use of LEP was therefore validated by demonstrating concentration-dependent effects using the capsaicin challenge model discussed above.

‘CHDR set the bar high’

‘In general, CHDR is extremely flexible and efficient, and their employees are a pleasure to work with. This is why I enjoy working with CHDR so much, and why I plan to continue doing business with them. In the type of study we typically do, there’s usually little room for a ‘wow’ experience. But CHDR surprised me with the excellent way in which they interacted with the ethics and regulatory bodies in the Netherlands. They had promised this, of course, but I was still pleasantly surprised by how quickly they moved things along. They certainly set the bar high!’

Head of Musculoskeletal Diseases
Scientific Leadership, Biotech Company*

**The views expressed here are the sole opinion of CHDR’s sponsors.*

Operations

Maintaining efficiency in the face of increasing complexity

CHDR continues to grow both in terms of the number of studies that we perform and in terms of the complexity of these studies. Moreover, a growing number of laboratory assays for fresh biological samples (i.e. bedside laboratory testing) and recent additions to our DermaToolbox have increased the complexity of our studies even further. Despite this growth, however, efficiency remains high, allowing us to provide sponsors with reliable results as quickly as possible.

At CHDR, science and innovation have always been high on our list of priorities. Just as important is our dedication to meeting the needs of our sponsors, who depend on CHDR to provide high-quality data as quickly and efficiently as possible. The ability to be innovative while conducting a growing number of studies requires the flexibility and ingenuity of our entire staff, including our Operations Department.

Laboratory operations

One of the most significant changes at CHDR in 2017 was the creation of an in-site laboratory in which freshly collected blood samples, biopsies, and other biological materials obtained from study participants can be processed and analysed immediately. As we discuss on page 93, this new laboratory provides our researchers unique opportunities to study drug effects that cannot be measured using previously frozen samples. However, because these assays are extremely time-sensitive, an efficient logistics chain is essential in order to maintain the quality and integrity of the data.

While the Biomarker group at CHDR was establishing this new state-of-the-art laboratory, others at CHDR were just as busy, adding these procedures into the daily operations at CHDR's clinical research unit (CRU). Facilitating such scientific innovations requires something we like to call 'operational intelligence'. Thus, many details had to be changed in the planning and logistics of our clinical studies. When planning a clinical study, in addition to taking into account the availability of personnel and rooms in the CRU, in many cases we may also need to take into account available laboratory resources.

For example, accommodating the growing number of studies in dermatology, which require specific measurements in large numbers of patients, presents a unique challenge to our Operations Department.

Building and expanding

In 2013, when CHDR moved to our current building, we hoped that this larger facility would accommodate our growth for at least a decade or two. But thanks to the growing number of studies, their increasing complexity, and our increased use of dedicated equipment such as NeuroCart®, PainCart®, DermaToolbox, and bedside laboratory testing, we exceeded our building's capacity in just under half a decade.

At the end of 2017, CHDR's Management Team began to search for ways to expand. Starting in Q1 2018, potential study participants will be screened off-site, within walking distance of CHDR and LUMC, next to Leiden Central Station. For volunteers and patients who need to be screened, this location is easy to reach by both public transportation and car. In the coming years, we'll be on the lookout for more possibilities to expand beyond our primary location.

Business development: focus on science and people

At CHDR, a large part of business development is also business maintenance. For example, our researchers have well-established relationships with several large pharmaceutical companies, as well as with many biotech start-up companies. These relationships are often built on personal contacts and shared scientific interests; in looking for new opportunities to collaborate, we ale look for good chemistry and synergy.

Like any contract research organisation (CRO), CHDR has to pay close attention to the bottom line. At the same time, CHDR is different from other CROs in that our main focus is on science, innovation, and education. As a not-for-profit foundation with no shareholders or creditors, CHDR has the freedom to give science priority, sometimes at the cost of finances. Ironically, this approach has become a highly successful business model.

Collaborating with sponsors

Several large pharmaceutical companies have shown an interest in CHDR's R&D programme, including our new R&D Fund (see text box). We routinely share our ideas for future projects and the types of products in their own pipeline, creating optimum synergy. Sometimes, a company will offer to finance one of our projects, if it matches their development agenda.

In addition, CHDR has a growing network of collaborations with smaller companies in the biotech and biopharmaceutical industries. Having access to CHDR's expertise and facilities, as well as our extensive academic network, can help these small companies overcome the many challenges they face when trying to bring a new product to the market. At CHDR, these contacts are extremely valuable and rewarding because they challenge our scientific creativity. When working with these small companies, we are continually aware of their limited resources, particularly in the early stages of development, and we look for ways to work within that framework.

A focus on people

Even after more than 30 years, CHDR still believes that dedication to people and interpersonal relationships should be one of our core values. For example, some of our collaborators have worked with CHDR for decades, some even from the very beginning. When we develop a new business opportunity, our goal is to establish a long-term relationship. We closely monitor new developments

'Even after more than 30 years, our dedication to helping people develop and establish professional relationships remains one of our core values'

in the pharmaceutical industry, and if we see a new product emerging that matches our expertise and interests, we reach out to the developers with a clear proposal. And when we sit down to talk, we often include one of our senior scientists, ensuring that the discussion stays focused on the science. In our experience, this approach to business development is more enjoyable for us and for our potential partners – and it can be quite efficient, too.

Neurology and Pain

Demonstrating the pharmacological effects of new CNS compounds

CHDR has pioneered new methods for developing drugs for neurodegenerative disorders, and our investment in these approaches has already begun to bear fruit. In collaboration with several academic groups, CHDR can now measure the effects of various compounds on hyperexcitability and other neurophysiological parameters. We can also measure whether a test compound affects mitochondrial function in blood, skin, muscle, and brain cells. With respect to pain research, several new sponsored projects were contracted to begin in 2018.

In order to treat and/or prevent neurodegenerative disorders, several new compounds are being developed that may slow – or even reverse – neurodegeneration. Some of these candidate drugs target common pathways in neurodegeneration (for example, mitochondrial dysfunction, microglial activation, and inflammation), whereas other compounds act on specific pathways that act 'upstream' in the neurodegeneration process. These novel compounds differ in their mode of action from traditional drugs designed to restore neurotransmission, so to study the pharmacological action of these new compounds, CHDR researchers needed a new approach.
In addition to measuring neuropsychological and neurophysiological functions using **NeuroCart®**, we needed specific tests to quantify the effect of a compound on the specific physiological process targeted by the drug. Ideally, these tests should provide results rapidly, even within a few hours of dosing.
A good example is CHDR's ongoing study in patients with Parkinson's disease. On **page 57**, we describe how we recruited a large number of patients who have Parkinson's disease and a mutation in the specific gene product targeted by the test compound.

Mitochondria

CHDR is currently developing and validating several methods for measuring the effects of test compounds for treating neurodegeneration. For example, we developed a challenge model that allows us to measure the beneficial effects of a test compound on mitochondrial function in healthy volunteers.
By inducing a slight yet measurable reduction in mitochondrial function using the cholesterol-lowering drug simvastatin, we can test whether the compound can improve mitochondrial function. To analyse mitochondrial function, we use ^{31}P-MRS (magnetic resonance spectroscopy) to measure the time it takes to replenish energy-rich biophosphates such as phosphocreatine in muscle tissue following moderate exertion. In collaboration with Leiden University Medical Centre, CHDR researchers use a similar approach to study mitochondrial function in patients with Huntington's disease (see also **page 60**).

At CHDR's facility, we also study mitochondrial function at the cellular level. For example, in a study funded by CHDR's R&D budget, researchers are studying the effect of mitochondrial function in the muscles on recovery following knee surgery. For one month before surgery and for one month afterward, physical activity is monitored using a wearable sensor; in addition, a muscle biopsy is obtained during surgery. These data are then correlated with clinical information regarding the patients' recovery. The principal goal of this study is to determine whether mitochondrial dysfunction worsens recovery, as well as to demonstrate how wearable sensors can be used to measure the effect of a major intervention such as surgery on physical activity. Given that the effect of most drugs is relatively small compared to surgery, this is an important first test of our approach using wearable devices.

Cortical excitability increases in several neurological conditions, including epilepsy and amyotrophic lateral sclerosis (ALS). In ALS, peripheral motor neurons are hyperexcitable, and this increased excitability has been correlated with disease progression in these patients. CHDR recently studied several compounds that reduce hyperexcitability and are used for – or are currently in development for – treating ALS.

Until recently, the standard method used to measure neuronal hyperexcitability focused on peripheral motor neurons. With this method, two electrical stimuli are applied to the neuron, and the effect is measured using EMG. The first stimulus affects the response to the second stimulus depending on various parameters such as stimulus intensity and refractory time. In addition to these peripheral measurements, researchers at CHDR and Twente University also use transcranial magnetic stimulation (TMS) in combination with EEG and EMG to study excitability in the motor cortex of the brain. In this test, a magnetic coil placed over the motor cortex induces a change in the electric field. Above a specific threshold, the coil induces a motor response comparable to the response induced by directly stimulating the motor neuron. By using a similar dual-stimuli approach, this method can be used to quantify the effects of test drugs on excitability in the cerebral cortex. The aim of one such ongoing

study is to demonstrate the concentration-dependent effects of three anti-epileptic compounds on cortical excitability and other variables measured using TMS-EMG and TMS-EEG.

Pain

At CHDR, we are continually creating new methods and approaches for use in drug development. In recent years, in addition to sponsored studies we invested heavily in the development of **PainCart®**, our automated and standardised test battery used to study the effects of analgesic compounds on pain mechanisms. In 2017, the results of our validation studies were published in *the British Journal of Clinical Pharmacology*, showing how PainCart can be used as a 'biomarker' to measure the analgesic potential of a test drug. In the wake of this publication, CHDR was contacted by several companies developing new analgesic compounds. Meanwhile, we are continuing to develop our pain research toolkit, for example by adding a method to directly measure the effect of a pain stimulus on the brain (see our report on laser-evoked potentials on **page 40**).

'New breakthroughs in the fields of neuronal excitability and pain'

Putting the Monocenter and Ready4Research strategies into practice: Genotyping 3000 Parkinson patients

Imagine that the only way to find a needle would be to search every haystack in the country. And then, imagine that you need to find at least 40 needles. CHDR faced such a challenge when a sponsor asked them to do a study in patients with Parkinson's disease who have a mutation in a specific gene, which according to the literature occurs in 5 to 10% of all patients with the disease. Thanks to our extensive network, we managed to find (more than) enough patients.

Parkinson's disease is the second most common neurodegenerative disorder, affecting millions of people worldwide. In addition to the characteristic motor symptoms, many patients suffer from neuropsychiatric and cognitive symptoms, adding to the overall negative impact on their quality of life. There are no therapies which impact the progression of Parkinson's disease. Several genes have been associated with the disease. One of them, GBA1, the gene encoding the enzyme glucocerebrosidase, is associated with non-familial ('sporadic') Parkinson's disease. In 5 to 10% of all patients, mutations in this gene contribute to disease progression. Patients with Gaucher's disease, an autosomal recessive metabolic disorder, have specific homozygote GBA mutations. The peripheral symptoms of Gaucher's disease can be treated with

enzyme replacement therapy, but as the recombinant human enzyme is not able to penetrate the blood-brain barrier, a large proportion of these patients will develop Parkinson's disease which progresses at a more rapid rate than idiopathic Parkinson's disease and has a higher frequency of cognitive impairment.

CHDR is involved in the clinical development of LTI-291, a compound that aims to restore glucocerebrosidase function in the subgroup of patients with sporadic Parkinson's disease with GBA mutations. First, a test to measure glucocerebrosidase activity in peripheral white blood cells was developed, as a proxy for the enzyme activity in brain cells.

To quantify glucocerebrosidase activity, we measured the concentration of several glycosphingolipids, one of them being its substrate glucocerebroside (GluCer). Validation studies in our laboratory are aimed at showing a relationship between these molecules and glucocerebrosidase activity measured ex vivo. This "phase 0" study was also aimed at quantifying the natural variation of enzyme activity in healthy subjects and in Parkinson patients with and without a GBA mutation over the day and between days.

After these experiments in our laboratory, CHDR was ready to start with the actual clinical drug studies. Healthy volunteers received a single ascending dose and multiple ascending doses of the investigational compound. The candidate drug proved to be safe and well tolerated.

The next step will be to test the candidate drug on actual patients with Parkinson's disease carrying a relevant GBA mutation. These tests are scheduled for the beginning of 2018, but it was quite a challenge to find sufficient numbers of patients. After all, according to the literature, only one in ten patients (maybe even one in twenty) carries the mutation. To find 10 people with Parkinson's disease and a mutated GBA gene, one has to screen 100 to 200 patients. But even that number is not nearly realistic. The clinical studies we have planned will be quite demanding, so we expect that a substantial number of patients will decide not to participate. All in all, our calculations show that we needed to screen the DNA of at least 3000 patients with Parkinson's disease to be certain that we had enough subjects for our first study in patients.

Luckily, we received help from neurologists all over the Netherlands, not only in the region around CHDR, but also from Groningen in the north of our country and several other centres. A great many patients with Parkinson's disease received a letter from their neurologist, informing them about our study and asking them to send a signed informed consent form and a saliva sample to CHDR for DNA analysis. Our collaborators at GenomeScan, a company in walking distance from CHDR, developed a method to quickly search the GBA gene for mutations and did all the necessary analyses of the almost 3000 samples we received. If the compound will be approved, it will be a targeted drug for a specific subpopulation of patients, potentially requiring a companion diagnostic to test for the GBA mutations in Parkinson's disease patients.

As the genotyping of these Dutch Parkinson patients progressed, we found to our surprise that some GBA mutations were more frequent in the Netherlands than in other countries. This is of course interesting from a population genetics point of view, and very fortunate for the study of the specific compound we investigate. CHDR is now ready for the next step: investigating the effects of the candidate drug in the target population of patients. All the patients who choose to participate in our study will come to CHDR. In this way, we can minimise variability in the tests and measurements (including sensitive tests of the enzyme activity in white blood cells): CHDR's **Monocenter** strategy. And of course, the DNA samples of 3000 patients with Parkinson's disease could potentially be used for other studies on the genetics of the disease and related to the development of specific treatments.

'Taking the next step in treating Parkinson's disease'

This project is an early example of a new method to address Neurologic Diseases: applying a Precision Medicine approach. Historically, neurologic diseases were characterized solely by signs and symptoms. As the science of molecular and cellular biology has advanced we now have learned that the same set of symptoms in patients may be the result of different genetic mutations, and thus, different biochemical mechanisms. The converse is true as well: different symptom and signs can be produced by the same genetic mutation. Targeting the specific biology of the underlying mutation/genetics rather than the empiric signs and symptoms hopefully will lead to better therapies for patients with Neurologic Diseases just as it has for patients with oncologic conditions.

Dosing at home: testing a new treatment for Huntington's disease

At CHDR we developed Trial@Home, our innovative approach to conducting a clinical trial. Rather than having to stay on-site at our clinical research unit, study subjects can participate in a trial from the comfort of their own home while monitored via a wearable device connected to their smartphone. This year, CHDR took the Trial@home concept to the next level by treating participants in their own home in a study that involved subcutaneous injections of a novel compound designed to treat Huntington's disease.

In recent years, CHDR has become increasingly involved in studying Huntington's disease (HD) in collaboration with Professor Raymund Roos, an internationally renowned neurologist and expert in the field of HD at Leiden University Medical Centre (LUMC). In the past, CHDR measured neurological symptoms in patients with this progressive hereditary neurodegenerative disorder using NeuroCart® and Green Dino's driving simulator in order to help physicians assess their patients' driving ability. Now, in collaboration with LUMC, CHDR is involved in what may well become the world's first disease-modifying treatment for HD.

Mitochondria

Although the precise pathogenic mechanism underlying HD remains unknown, mitochondrial dysfunction may a play role in the disease process. At CHDR, we are currently studying SBT20, a compound shown to improve mitochondrial function in preclinical testing.

In addition to studying the safety and tolerability of SBT20 in patients with HD, we are also examining its pharmacological effects on mitochondrial function. The first part of the study, which was performed in three cohorts containing eight patients each, was designed to determine the optimal dose of SBT20 based on the time required for muscle tissue to replenish energy-rich biophosphates such as phosphocreatine.

The ratio between inorganic phosphates and energy-rich phosphocreatine levels can be measured using MRS (magnetic resonance spectroscopy) at LUMC. The data obtained from this so-called 'dose-finding study' were then used to determine the dose used in the second part of the study, a placebo-controlled trial involving 24 patients who were treated for 28 days.

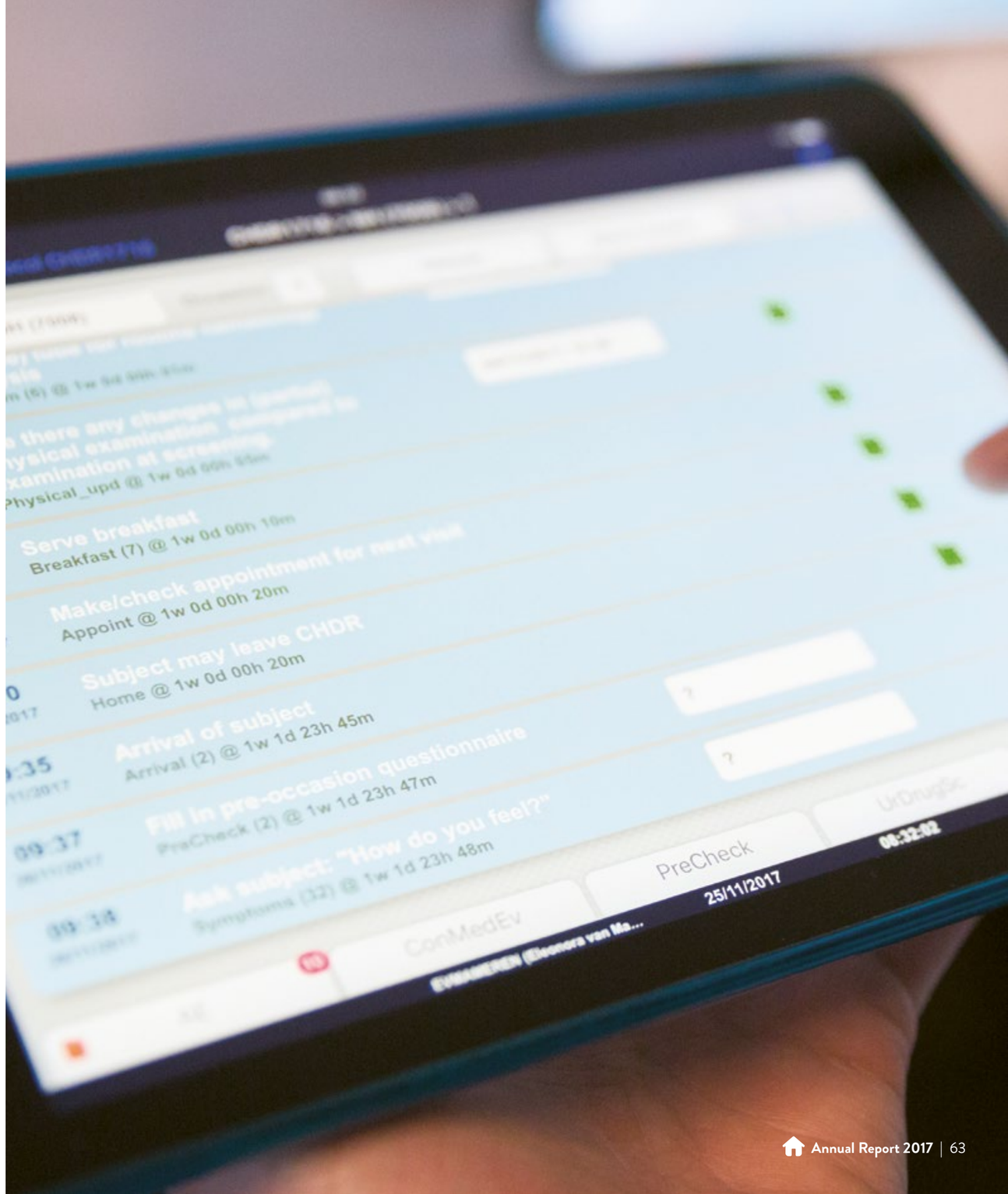
Injections at home

SBT20 currently needs to be administered daily by subcutaneous injection. While designing the protocol for the clinical study, we quickly realised that visiting CHDR every day for treatment would place a significant burden on the patients. We therefore needed to find another way. The solution was to train medical students in GCP (good clinical practice) and how to administer a subcutaneous injection; during the trial, these medical students drove to the patients' homes, where they administered the injections. In addition, when the patients received their daily injection, the medical students asked about their well-being and whether they experienced any adverse effects.

Brain imaging

Prior to the trial, and again after four weeks of treatment, each patient underwent a thorough neurological exam; in addition, mitochondrial function in the brain was measured at LUMC's Radiology Department, one of only a few departments in the world that specialises in this procedure. The group used MRS (magnetic resonance spectroscopy) to measure energy metabolism in the brain. During the scan, the patient views a rapidly shifting checkerboard pattern, which stimulates the visual system and causes a measurable reduction in phosphocreatine levels in the occipital cortex. After the stimulus, phosphocreatine levels return to normal, at a rate that depends largely on mitochondrial function. Although the clinical symptoms of HD are not likely to improve after only four weeks of treatment, it may be possible to measure an improvement in mitochondrial function in this relatively short time frame. The results of this study are currently being analysed and will be submitted for publication in 2018.

'Taking Trial@home to the next level'



‘CHDR is the right choice’

‘CHDR has access to a number of specific and specialised tools such as their NeuroCart, which neither we nor other CROs have. So, for more specialised studies, CHDR is the right choice.’

Experimental Medicine Clinical Scientist,
Top 10 Pharma*

**The views expressed here are the sole opinion of CHDR’s sponsors.*

Psychiatry

Novel targets, innovative methods, and training in psychiatric drug development

Over the past 30 years, CHDR has helped develop several new compounds for treating psychiatric illnesses, including mood and anxiety disorders. Time and again, our researchers are faced with the challenge to demonstrate relevant pharmacological effects as early as possible in the drug development process. Using innovative methodologies such as challenge models and state-of-the-art neuroimaging, we help our sponsors answer important questions.

In psychiatry, there is currently an unmet need for safe and effective treatments, and developing suitable drugs for use in this field is challenging. In recent years, several pharmaceutical companies discontinued their CNS drug development programmes. Luckily however, other companies still focus on developing compounds that target novel mechanisms of action to treat psychiatric disorders, and CHDR is proud to play a role in helping develop some of these compounds. We are also fortunate that a growing number of patients with depressive disorders signed up for CHDR's unique Ready-for-Research database, enabling us to quickly find enough subjects for clinical studies. In the near future, we hope to expand our database with patients suffering from anxiety disorders.

Sleep deprivation

The purinergic P2X7 receptor is a promising new target with a putative role in various psychiatric and somatic diseases. CHDR is involved in the early clinical development of a new P2X7 receptor antagonist for treating mood disorders. Using our pharmacological amphetamine challenge model in healthy volunteers, we previously found that this new compound affects both subjective mood and visuomotor function.

Introducing a new internship programme for psychiatry residents

In addition to contributing to the development of more effective pharmacological treatments in psychiatry, another of CHDR's missions is to contribute to the education of students and residents in psychiatry. In 2017, CHDR was accredited by the Royal Dutch Medical Association to establish a research internship in clinical psychopharmacology for psychiatry residents. The first trainees in this programme will start in 2018 and will participate in early phase studies regarding mood and anxiety disorders and acquiring first-hand knowledge of cutting-edge psychopharmacology research.

Based on these findings, our next step was to demonstrate the compound's properties in patients with major depressive disorder, in order to better explore the compound's clinical potential. However, administering amphetamine to these patients raised both safety concerns and practical issues, so an alternative approach was needed in order to safely improve the mood of these patients.

Skipping a single night of sleep is a well-documented method for temporarily improving the mood of patients with major depressive disorder. We therefore used a standardised **sleep-deprivation** protocol to temporarily improve mood in depressed patients and then examined whether the test compound enhances and/or prolongs the beneficial effect of sleep deprivation on mood. These results can help the sponsor make informed decisions regarding the next phase in the drug's development.

Ketamine

The non-competitive glutamatergic NMDA receptor antagonist ketamine has raised considerable interest within the field of mood research in recent years, particularly with respect to patients suffering from treatment-resistant depression. Interestingly, administering a single or repeated subanaesthetic dose of intravenous ketamine induces a robust antidepressant effect and reduces suicidal tendencies in the majority of these patients. The effect is short-lived, as the depressive symptoms usually return within two to three weeks after the ketamine administration session. Applying ketamine in clinical practice for depressive disorders therefore requires some form of maintenance treatment. However, long-term treatment involving repeated injections of ketamine is rather impractical, and there is currently insufficient data regarding the possible adverse effects of long-term ketamine treatment. In addition, the optimal dose and/or dosing regimen for ketamine in treating depression is unclear. Therefore, despite its high promise, intravenous ketamine is currently not widely used to treat treatment-resistant depression.

To circumvent the issue of repeated injections, alternative formulations for oral and intranasal delivery are currently in development. At the same time, CHDR uses ketamine as a pharmacological probe to study the role of glutamate in mood regulation and in the pathophysiology of mood disorders. As a result, CHDR is currently performing several studies involving patients with major depression. Taken broadly, these studies focus on better understanding the role of glutamate in the pathophysiology of depression by applying innovative methodologies such as resting-state functional magnetic resonance imaging (RS-fMRI) and ascertaining the potential adverse effects of repeated ketamine administration over a prolonged period in depression.

CO_2 inhalation challenge provokes panic attacks

CHDR is currently testing several promising new anxiolytics with novel mechanisms of action. As always, our goal is to demonstrate relevant pharmacological effects as early as possible in the drug development process. Healthy volunteers, however, do not experience anxiety under normal conditions and are therefore not optimally suitable for testing the effects of anxiolytics. That's where the carbon dioxide (CO_2) inhalation challenge can be extremely useful to study fear and anxiety-related phenomena such as panic attacks in health and disease.

A panic attack is an intense but transient episode of subjective dread and discomfort, often associated with cognitive misinterpretation of perceived threat and objective physical symptoms related to activation of the autonomic nervous system. From a research point of view, panic attacks are difficult to study, as they often occur without warning in the naturalistic setting. Thus, in most cases, only a retrospective analysis of drug effects is possible, using questionnaire-based psychometric data collected from the patient and by the clinician. This is obviously not the ideal way to study drugs designed to prevent panic attacks in patients, where it is essential to directly observe the frequency or intensity of panic attacks in real time. In addition, demonstrating an anxiolytic signal with newly developed anxiolytics in healthy subjects obviously provides the confidence to move on to patients with anxiety disorders.

In the past, pharmacological challenges using compounds such as lactate, yohimbine, and cholecystokinin tetrapeptide (CCK-4), as well as self-induced hyperventilation all have been applied in anxiety research. However, these approaches yielded inconsistent results, which made it difficult to interpret their relevance to early drug development. Today, the most widely used challenge model is the carbon dioxide **(CO_2) inhalation challenge**, which experimentally triggers a reaction that closely resembles a panic attack in terms of both subjective symptoms and objective physical signs.

The CO_2 inhalation challenge

The CO_2 inhalation challenge model is a robust tool for experimentally inducing panic attacks in order to test new anxiolytics. Patients with panic disorder are the most sensitive, with more than 90% experiencing a panic attack after inhaling CO_2-enriched air, followed by healthy first-degree relatives of patients with panic disorder. Inhaling air enriched with CO_2 triggers a panic attack in roughly half of healthy volunteers, making them the least sensitive population. Importantly, administering a therapeutic dose of clinically effective anxiolytic drugs such as benzodiazepines reduces the sensitivity to CO_2-induced panic attacks in all such populations. Interestingly, CO_2 inhalation can also induce robust fear-like behaviour in animal models, with physiological changes similar to changes measured in humans during a panic attack. Furthermore, the panic response induced by acutely inhaling CO_2 remains stable and reproducible over time, which curtails concerns about the development of tolerance after repeated challenges. Also, the repeated inhalation of CO_2 by healthy subjects who undergo the challenge carries no increased risk of developing a panic disorder. CO_2 inhalation therefore represents a reliable, translational challenge model in the development of novel anxiolytic drugs.

CHDR applies the CO_2 tolerance tester originally developed by Maastricht Instruments and Maastricht University. This device safely and reliably induces panic attacks by delivering a mixture containing 35% CO_2 and 65% O_2 (by comparison, normal air usually contains less than 1% CO_2) via an oral nasal oxygen mask. In addition, this device simultaneously measures physiological changes associated with CO_2-induced activation of the autonomic nervous system, including changes in heart rate and blood pressure. By doing so, it provides integrated real-time information regarding panic-related somatic parameters, which can be readily combined with subjective assessments of fear and anxiety. Of course, the environment in which the test is performed may influence its outcome; that's why CHDR's clinical research unit provides a safe, comfortable and standardized environment for performing the CO_2 challenge.

CHDR has used the CO_2 challenge to study the pharmacodynamics of several potential novel anxiolytic compounds in healthy volunteers. In the future, it may also be used to test the anxiolytic effects of new drugs in individuals who are at risk of developing an anxiety disorder or even in patients diagnosed with an anxiety disorder. For this purpose, CHDR will expand its collaboration with patient advocacy groups in the field of anxiety in 2018, which is expected to facilitate the recruitment of patients. Ultimately, the CO_2 inhalation challenge model might be applied as an instrument to translate findings from preclinical studies involving animal models to healthy human subjects, and finally to patients in early drug trials.

Dermatology

Cutting-edge tools for a growing research area

A few years ago, CHDR first became interested in research involving the skin. Today, CHDR has a dedicated Dermatology group, which actively collaborates with other CHDR research groups, including Immunology, Pain, and Methodologies. Our unique DermaToolbox includes a wide range of state-of-the-art tools for studying and monitoring a wide variety of skin conditions. The Dermatology group now plays a direct role in the entire drug development process, from *in vitro* and *in vivo* animal studies to extensive patient studies.

The skin is our largest external organ, covering approximately 2 m^2 in an average adult. From the perspective of drug development, this organ is highly relevant, as skin conditions often have a large impact on quality of life, and most patients with a chronic skin disorder have high medical needs. In addition, the pathophysiology of inflammatory skin conditions such as psoriasis has clinical overlap with other inflammatory disorders in the fields of rheumatology and gastroenterology. Importantly, most new anti-inflammatory compounds are tested first on the skin, as these compounds can often be applied locally, and their effects can clearly be seen on the skin's surface and/or monitored using various imaging systems.

The DermaToolbox

When studying the effects of a dermatological drug, researchers used to rely on a clinical evaluation of the patient by an experienced dermatologist. Although this somewhat subjective approach has certain value, at CHDR we believe that objective data is just as important. That's why we developed the **DermaToolbox**, a comprehensive battery of tests designed to objectively evaluate the patient's skin in order to assess the effects of treatment (see the table below). Unlike our NeuroCart® and PainCart® test batteries, which are fully portable, the DermaToolbox actually occupies several rooms.

An important tool included in the DermaToolbox is total body photography, in which digital photography is used to obtain standardised, reproducible images of the subject's entire skin surface. Variables such as position, lighting, and distance are kept constant, allowing the researcher to accurately measure changes in skin lesions over time. Importantly, this tool can be used to electronically determine the lesion's extent and severity; a good example is using total body photography to measure the psoriasis area and severity index (PASI). Another technique, multispectral imaging, provides highly detailed information regarding changes in skin pigmentation and erythema.
The DermaToolbox can also be used to reveal changes that cannot be seen by the naked eye. For example, optical coherence tomography uses coherent light to generate images of structures located up to 400 microns below the skin's surface. This non-invasive procedure can be used to image the epidermis and the upper layer of the dermis in real time.

Another powerful tool is high-definition thermography, which can be used to study various processes such as postsurgical wound healing. Subtle differences in temperature reveal the precise size and location of the wound, providing a highly precise measure of the healing process. CHDR plans to investigate the feasibility of using thermography to monitor the effect of treating inflammatory skin conditions.
The DermaToolbox also includes laser-speckle contrast imaging, which is used to measure blood flow through vessels in the skin.

A multimodal approach

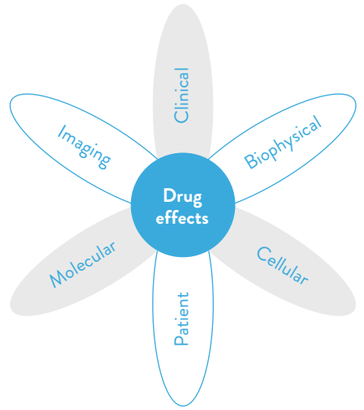
At CHDR, our multimodal approach to drug development allows us to generate a profile of both the drug and the patient from several perspectives and in several dimensions. This is no less true for dermatological drugs. In addition to the 'gold standard' (i.e. the clinician's evaluation and the patient's experience), objective measures can have high value; these measures can include complementary imaging techniques, biophysical measurements such as temperature and water evaporation, and *in vivo* and *ex vivo* cellular and molecular measurements. In some cases, highly sensitive imaging data and/or laboratory results can reveal a pharmacological effect long before the patient or clinician can detect it. In the early stages of clinical drug development, the ability to obtain these objective measures can be highly beneficial in helping decide on the next step.

CHDR's Dermatology group has always worked closely with our Biomarker laboratory (see also **page 93**), particularly in studying inflammatory skin conditions. In many cases, the effect of an anti-inflammatory compound can be demonstrated first using an *ex vivo* challenge model with isolated white blood cells, followed by a skin challenge test in healthy volunteers and effect studies in dermatology patients. When necessary, we can also use skin biopsies to study the epidermal and dermal cells in detail. Alternatively, we can analyse the contents of a 'suction blister' induced by applying local suction to the skin. This procedure was recently added to our array of tools thanks to our collaboration with the Centre for Clinical Pharmacology and Immunology at University College London. This simple procedure is much less invasive than a biopsy, and it can be used to study the local immune response, for example after an intradermal injection of endotoxin or other challenge agent such as histamine, codeine, or a compound that stimulates Toll-like receptors.

CHDR's DermaToolbox

Method/tool/technique	What it measures	What it's used for
Clinical photography	Extension of the lesion	Objectively assess the clinical course
3D photography	Lesion volume and other factors (e.g. roughness)	Obtain additional objective information regarding the clinical course
Aquaflux	Transepidermal water loss	Document the skin's barrier function
Colorimetry	Erythema	Objectively measure erythema in inflammation
Laser-speckle contrast imaging	Blood flow through the dermis	Study capillary flow in circulatory conditions (e.g. sickle cell disease)
Fourier-transformed infrared spectroscopy	Lipid organisation in the stratum corneum	Measure the penetration and effect of interventions on lipid content
Raman spectroscopy	Profiling of epidermal layers	Monitor penetration of the compound into the epidermis
Lipid profiling (LC-MS)	The composition of lipids in the epidermis	Monitor treatment effects
Total body photography	Lesion size and severity	Measure the extent of lesions such as psoriasis (e.g. digital PASI), photo documentation
Mobile app	Treatment compliance, adverse events, target lesions, patient-reported outcome	Obtain skin photos off-site, Trial@home, documentation, quality of life, monitoring
High-definition thermography	High-resolution temperature	Measure wound-healing kinetics, inflammation
Transdermal patch analysis	Skin surface biomarkers	Monitor biomarkers
Punch/shave biopsy	Epidermal/dermal markers, histology	Monitor morphology and biomarkers
Transdermal penetration	Skin barrier function	Measure pharmacokinetics
Multispectral imaging	Lesions size and severity	Study erythema and pigment disorders
Optical coherence tomography	Skin histology	Measure skin structure in real time
Microbiome (gut/skin)	Bacterial and/or fungal composition	Monitor cutaneous/systemic effects
Suction blister	Cell type/content in exudate	Immunophenotyping of skin reactions

LC-MS, liquid chromatography–mass spectrometry; PASI, psoriasis area and severity index



In multimodal drug development, several perspectives and levels are combined to obtain a more comprehensive view of the disease and the treatment. In addition to the clinician's view and the patient's view, objective information can be used to validate drug effects.

Comprehensive drug development

The number of studies conducted at CHDR has grown steadily through the years, but dermatology is now one of the fastest-growing research areas; we conducted more than 20 dermatology projects in the past four years alone. In the future, we plan to focus our efforts on projects in which we can provide added value due to our expertise. Thanks to our new cellular laboratory (see page 93), we can now conduct translational studies that facilitate a more rational transition from preclinical development to clinical testing. In some cases (for example, our ongoing study of a putative immunomodulatory peptide; see page 99), this can provide better insight into the test

Dr Robert Rissmann leads the new Dermatology research group

In 2017, CHDR established a Dermatology research group, with **Dr Robert Rissmann** serving as the first Research Director. In the past seven years, Rissmann was CHDR's Director of Education. In addition to his educational activities, Rissmann became increasingly involved in dermatology. This is of course only natural, given that Rissmann is a licensed pharmacist who studied at the Free University of Berlin and obtained his PhD in translational dermatology at the Leiden Academic Centre for Drug Research (LACDR). Rissmann serves on the board of the Dutch Society of Clinical Pharmacology and Biopharmacy (NVKFB); he is also a member of the Education Committee of the British Pharmacological Society and is an Executive Editor for the British Journal of Clinical Pharmacology. In 2015, Rissmann also became an Associate Professor at Leiden University Medical Centre. He has published more than 35 papers in peer-reviewed journals and is actively involved in supervising and training PhD students.

compound's potential, as well as the condition the drug is designed to treat. This translational phase – in which we perform *ex vivo* tests using human samples – can also help our researchers determine the optimal dose and/or dosing regimen for use in first-in-human studies.

In the early stages of clinical drug development, CHDR uses a combination of *ex vivo* and *in vivo* challenge models to measure the pharmacological effects in healthy volunteers. These models are an important part of the translational process, as they form the bridge between preclinical experiments and studies involving patients. The next step in the development process may involve what we call a 'Phase 0' study, which provides a detailed phenotypic characterisation of a given patient population and spontaneous changes in disease severity over time. This is important, as many skin conditions such as psoriasis and eczema have a highly variable course, and several factors such as stress and weather conditions can affect the size and severity of the lesions. To study the effects of a test compound, CHDR first needs to determine the disease's natural course.

CHDR's studies in dermatology patients helped put our Trial@home approach on the map. With Trial@home, participants first visit the CHDR facility for testing using the DermaToolbox; but they don't need to stay at our facility after testing. Trial@home lets our participants go about their daily lives; at regular intervals, an app on their smartphone reminds them to apply the test medication and send a picture of the medicated lesion to CHDR via a secure encrypted connection. This approach ensures extremely high treatment compliance, typically above 90%; moreover, CHDR has a complete record of each subject's performance throughout the study period. With the Trial@home app, the participant can also be prompted to complete a short questionnaire at regular intervals, providing important information regarding quality of life and the level of symptoms such as pain or itching. Even more data can be obtained through the use of wearable devices.

In short, at CHDR we believe in placing high value on objective measures, performing innovative translational research, and using modern technologies to stay in touch with our research subjects on a daily basis. Thanks to this comprehensive approach, the entire drug development process is more efficient, significantly reducing the risk of costly failure in a later stage.

Drug profiling using a localised skin inflammation challenge in healthy volunteers

CHDR recently developed a robust challenge model involving healthy volunteers in order to study the pharmacology of new therapies for treating inflammatory skin disorders. This challenge model, which was developed in collaboration with researchers at Erasmus Medical Centre in Rotterdam, is based on imiquimod's well-documented effects on the skin Imiquimod activates the body's innate immune system via Toll-like receptor 7, a protein commonly involved in pathogen recognition. Sold under the brand name Aldara®, topical imiquimod is used to treat genital warts, superficial basal cell carcinoma, and actinic keratosis. At CHDR, researchers use imiquimod to induce a localised inflammatory response in the skin of healthy volunteers, which can also be used to study the pharmacological effects of an immunomodulatory compound.

In 2017, after validating this challenge model, we used it to profile the effects of a putative immunomodulatory compound. Up to 11 application 'chambers' containing various concentrations of imiquimod and/or the investigational compound were applied to the subjects' skin; we then used the DermaToolbox to characterise the responses. To our surprise, we observed a synergistic effect when the compound was included with imiquimod; this effect was observed in several dimensions, including imaging data, clinician-reported outcome, and cellular and molecular patterns. These novel findings revealed potential new applications and indications for the investigational compound. Our findings also demonstrate that our challenge model is a sensible translational tool, and the results were well received by the sponsor. These studies clearly show the added value that comes from using our imiquimod challenge model. And the story doesn't end there; we are currently planning the next study in which we will characterise the synergistic properties and efficacy of the combined treatment in patients.

‘Open, transparent communication’

‘CHDR has excellent academic and scientific knowledge and is well-placed to conduct phase I studies properly using cutting-edge, innovative technologies. They are also extremely good at analysing the data that they collect. I am therefore extremely satisfied with their services.

With a study, I expect open, transparent communication throughout the entire process. This ensures that the study is carried out properly, and it ensures the safety of the volunteers. In this respect, CHDR always meets these expectations.’

Consultant
Biopharma company*

**The views expressed here are the sole opinion of CHDR’s sponsors.*

Internal Medicine

Innovative studies in a variety of fields

In the past year, CHDR's Internal Medicine division has been quite busy. In addition to our ongoing projects such as image-guided surgery, our new projects include designing a study to test a promising new drug for treating atrial fibrillation, laying the foundation for developing new treatments for hepatic steatosis, and contributing to the development of new compounds designed to regenerate cartilage.

Internal Medicine has always been one of the most diverse research areas at CHDR, and last year was no exception. These are exciting times, with many interesting new therapeutic approaches emerging to address a wide range of clinical issues. At CHDR, we like to be at the cutting edge of research; that's why – in addition to the many clinical studies that we perform – we also play an active role in preparing for the future clinical testing of compounds that are still in preclinical development.

This approach requires close interactions between Internal Medicine and other research groups at CHDR, as well as with our sponsors and academic partners.

For example, the new cellular laboratory in our Biomarker group will contribute to a variety of studies in internal medicine and dermatology. In addition, we collaborate with clinicians in a wide range of disciplines, designing optimal strategies for selecting patients for early-stage clinical research and determining the ideal method for measuring pharmacological effects in a clinical setting.

Cardiology

Our ongoing collaborations with clinicians at the Leiden University Medical Centre (LUMC) and the Vrije University Medical Centre in Amsterdam (VUmc) have played an essential role in the success of CHDR's **Cardiology Services**. For example, we recently developed a new method for studying the QT interval in the ECG (see **page 90**). In addition, researchers at CHDR and VUmc designed a protocol to study a new compound that was shown in preclinical testing to convert atrial fibrillation to normal sinus rhythm. Atrial fibrillation is the most common form of chronic cardiac arrhythmia in the Western world, affecting approximately 2-3% of the general population; moreover, the prevalence will increase as our population ages. Atrial fibrillation can reduce quality of life and is associated with several debilitating conditions, including stroke and dementia. Given that the current therapeutic approach is to control heart rate, this novel compound, which controls the heart's rhythm, would represent a major step forward.

At CHDR, we plan to study the safety and tolerability of this new compound in healthy volunteers, thereby helping to establish the optimal dose for upcoming pharmacological studies involving patients at VUmc.

Image-guided surgery

For several years, CHDR and the Department of Surgery at LUMC have been developing new fluorescent markers for use in **image-guided surgery**, in which the fluorescent marker is used to increase the visibility of specific structures. For example, these markers can be used to label a tumour or to label a benign structure such as the ureter or a nerve fibre, thereby reducing the risk of damaging these delicate structures during surgery. Several companies are now developing fluorescent markers for labelling a wide variety of tumours and other structures.
At CHDR and LUMC, we're studying the safety and pharmacokinetics of these fluorescent markers, first in healthy volunteers, followed by studies involving patients who will undergo an endoscopic or other surgical procedure.

Last year, we initiated several studies of fluorescent markers that can be used to detect colon cancer using colonoscopy. These projects fit perfectly in the Dutch colon cancer screening programme, in which patients who have a positive stool tests undergo a colonoscopy. These studies are being conducted throughout the Netherlands, including LUMC, Groningen University Medical Centre, Catharina Hospital in Eindhoven, and CHDR. The ultimate goal is to demonstrate the added value of using a fluorescent marker to increase the detection and successful treatment of colon cancer.

Gene therapy

Last year, CHDR also acquired a license that allows us to administer a gene therapy product to human subjects at our facility. We applied for this license in order to conduct an early-stage trial to test an innovative new gene therapy for treating arthritis, in which an adeno-associated virus expressing human interferon beta (IFN-β) is injected into the affected joint in order to locally control the inflammatory response. In the viral vector, the gene expressing IFN-β is driven by a promoter that responds to the presence of inflammation; thus, IFN-β is produced in the joint only during inflammation. Using this promising new approach, the disease burden associated with inflammatory diseases such as rheumatoid arthritis could be significantly reduced with a single injection. Importantly, the gene is expressed only in the presence of inflammation, providing 'on-demand' therapy.

Our study is designed primarily to investigate the safety of the gene therapy product, as well as

to provide proof-of-concept (in other words, to demonstrate that the gene is expressed in the joint only in the presence of inflammation). Our original study was designed for patients with rheumatoid arthritis; however, because we were unable to recruit sufficient numbers of patients, we recently revised the study to include patients with osteoarthritis, which is far more common than rheumatoid arthritis and induces a similar inflammatory response. In addition, we have established a large network of rheumatologists, orthopaedists, and hand surgeons in order to increase the number of patients for our study.

Regenerating cartilage

Regenerative medicine is one of the most promising new medical fields. Although classic treatments can alleviate symptoms, and in some cases may even treat the underlying cause, regenerative medicine can actually restore the tissue or organ to its original disease-free state. For example, in osteoarthritis, medical treatment may alleviate the pain, and surgical approaches such as joint replacement can even restore much of the joint's function; but the only way to truly cure a patient with osteoarthritis is to regenerate the cartilage that has been lost in the joints. CHDR is currently involved in developing a compound that promises to do just that.

In preclinical research, this compound was found to stimulate stem cells in the cartilage to begin dividing, producing more chondrocytes, which produce the extracellular matrix proteins that comprise the cartilage within the joint. Using both X-rays to measure the joint space and MRI to image the cartilage itself, researchers at CHDR are investigating the compound's effects in patients with osteoarthritis. If this compound is found to be effective, it would represent a major step forward in the field of regenerative medicine, as well as significantly improving the quality of life for millions of individuals with osteoarthritis.

Rotator cuff tendinopathy

Rotator cuff tendinopathy is a highly common condition in which the tendons that help stabilise the shoulder joint become damaged and/or inflamed. Some patients with rotator cuff tendinopathy experience chronic pain, particularly at night, resulting in insomnia and reduced quality of life. In many patients, nonsteroidal anti-inflammatory drugs (NSAIDs) fail to provide relief.

Researchers at CHDR are currently studying a monoclonal antibody called secukinumab, which binds to interleukin-17 (IL-17), a cytokine that is believed to mediate tendinitis and therefore may play a role in rotator cuff tendinopathy. In a placebo-controlled randomised trial involving patients with rotator cuff tendinopathy, we are assessing the efficacy of secukinumab in relieving clinical symptoms. To recruit patients, CHDR is working with orthopaedists within our network, radiologists at the MRI Centre in Amsterdam, and local physiotherapists.

How to study fatty liver

Non-alcoholic steatohepatitis (NASH) is one of the most severe forms of fatty liver disease. NASH is characterised by a combination of fat deposits, inflammation, and fibrosis, ultimately leading to cirrhosis of the liver in many patients. In the United States, an estimated 2-5% of the general population is believed to have NASH. The underlying pathogenic mechanism is currently unknown; however, NASH is strong associated with obesity, insulin resistance, and type 2 diabetes. Moreover, although the early stages of non-alcoholic fatty liver disease often respond to weight loss and treatments aimed at type 2 diabetes, there is currently no treatment available for NASH.

Researchers in both academia and industry are currently developing drugs for treating NASH, and at CHDR, we're developing new approaches to study these new drugs. One of the major challenges is based on the diagnostic criteria for NASH. Current guidelines established by regulatory bodies such as the FDA and the EMA state that NASH should be diagnosed based on a liver biopsy. In daily practice, however, most physicians prefer not to perform a potentially high-risk liver biopsy in patients with a suspected diagnosis of NASH, particularly in obese patients; after all, confirming their diagnosis has little practical value, given that no treatment is currently available.

From the perspective of clinical drug development, however, lack of a confirmed diagnosis in the majority of patients can be quite problematic. At CHDR, we're helping to develop algorithms that can be used to diagnose NASH using non-invasive tests, thereby helping stratify patient risk and grade hepatic fibrosis. In addition, CHDR is helping develop new ways to monitor the effects of investigational compounds, including the use of MRI and measuring metabolites and **inflammatory biomarkers.**

Increasing the reliability of measuring the QT interval

When developing a new drug, the primary concern is ensuring that the compound is safe; if the compound has severe adverse effects, it's better to know this as early as possible. One of the most important issues when developing a new drug is its possible effects on cardiac rhythm, particularly ventricular repolarisation time (i.e. the QT interval). That's why CHDR has invested heavily in an innovative new method for measuring the QT interval in an ECG. This new approach is more sensitive and more specific than previous methods, allowing us to better investigate the safety profile of a new compound and decreasing the likelihood of terminating the development of a compound that is actually safe.

In 2016, CHDR's **Cardiology Services** was established in order to provide our sponsors with 'one-stop shopping' for their cardiology needs. Using our in-house expertise together with clinical cardiologists at the Vrije University Medical Centre in Amsterdam and Leiden University Medical Centre, we can provide a wide range of GCP-certified diagnostic procedures for analysing the cardiological effects of test compounds. In addition to electrophysiology, we also provide a wide range of cardiac imaging techniques for use in healthy subjects and patients.

The QT interval

In a clinical study, one of the most important signs to look for is a prolongation of the corrected QT interval in the ECG; this sign is often associated with sudden death due to ventricular arrhythmia, particularly the so-called torsade de pointes. Including a comprehensive assessment of the compound's effect on the QT interval is therefore essential in clinical drug development and is one of the core elements in our portfolio.

The standard approach used to measure a compound's effects on the corrected QT interval is to perform a single measurement at fixed times during the clinical experiment; these time points are usually based on the compound's plasma concentration. At each time point, a 10-second ECG trace is recorded and analysed. Unfortunately, however, this sampling method is not particularly accurate in terms of assessing the compound's effects on the corrected QT interval, which can easily be overestimated and can have dire consequences on the compound's development. At CHDR's Cardiology Services, we developed and validated a new sampling method that provides much higher sensitivity and specificity than standard ECG sampling, allowing us to detect — or exclude — an increase in the QT interval.

Using continuous telemetric ECG registration, we can analyse 5-minute blocks of ECG data in order to accurately measure the QT interval. Importantly, this approach reduces variability in our measurements, providing sponsors with optimal safety data. Our hope is that this new approach will soon become the new industry standard, as it improves the safety profile of new drugs and can help ensure the further development of a drug that is actually safe for use in patients.

Biomarkers and Laboratory

Bedside laboratory testing at CHDR

One of our major advances in 2017 was the expansion of our biomarker laboratory. Thanks to contributions by our sponsors, we now have a state-of-the-art laboratory where we can measure a wide variety of cellular responses in freshly obtained samples. These new facilities have already been used in clinical – and even preclinical – studies.

Although CHDR has always used biochemical and **immunological biomarkers** to measure pharmacological effects, most of these measurements were performed off-site, either in the clinical laboratory at Leiden University Medical Centre (LUMC) or a commercial laboratory. However, some functional measurements using white blood cells, skin biopsies, and other fresh materials are extremely time-sensitive and cannot be outsourced. Even within the CHDR, we need to transport the samples as quickly as possible from the clinical unit to the laboratory.

Timing is everything

To investigate the effect of timing on some of our assays, we performed a series of experiments using well-defined immunological challenge models designed to stimulate peripheral white blood cells (PWBC). The results were highly revealing: even a 30-minute delay between collecting the blood and starting the challenge can reduce the measured response by up to 50%. Interestingly, monocytes were found to be particularly sensitive to this delay. In searching for an explanation for this phenomenon, we ruled out cell death, oxidative stress, and mitochondrial stress. Thus, it seems that monocytes simply become less responsive due to suboptimal conditions, and we're currently investigating which pathways underlie this process. In addition to its purely scientific value, this study also illustrates the importance of having an in-house cellular laboratory with well-oiled internal logistics. And even then, our experiments showed that the delay caused by a simple coffee break can ruin a carefully planned experiment.

A new lab, an expanded network

Throughout 2017, CHDR built the new cellular laboratory almost entirely from scratch. At the start of the year, we had limited facilities for cell-based work. These facilities were upgraded to a dedicated, fully equipped cell culture lab with sufficient space for four technicians. An additional flow cytometer was acquired, the number of flow hoods and incubators was increased, and new equipment was purchased, including a fluorescence microscope, a stereo microscope, and ELISA and ELISPOT readers. Combined with our magnetic cell sorter, our facilities are now well-equipped for studying drug effects at the molecular and cellular levels. Moreover, CHDR's R&D laboratory staff increased from two members to eight. Most of this rapid growth was to address the needs of our sponsors, who requested that we perform specific tests in the context of clinical – and even preclinical – studies. Thus, our new cell culture facilities allow us to accommodate highly specific requests. For example, one of our sponsors was interested in using fibroblasts from Parkinson's patients to characterise the possible underlying molecular pathways. To address this need, we can culture fibroblasts taken from patient skin biopsies. In some ways, CHDR's contribution amounts to simply collecting and preparing the biological specimens for later analysis; however, this seemingly simple step requires a fully equipped cell culture lab and experienced staff who know how to culture specific cells for several weeks – features that are more common in an academic research lab than at a CRO.

Our new laboratory facilities have also had a positive impact on our academic network. Now that CHDR houses and operates a state-of-the-art cellular laboratory and can handle fresh samples collected from both healthy subjects and patients, we have more to offer our academic colleagues. Here in the Netherlands, we've strengthened our collaboration with several groups in Utrecht, LUMC, and the Leiden Academic Centre for Drug Research (LACDR). We also recently began an interesting new collaboration with the Centre for Clinical Pharmacology and Immunology at University College London (UCL) in order to develop state-of-the-art *in vivo* innate immune challenges. One of our first studies with UCL will focus on the effects of an intradermally injected endotoxin.

Focus on neurodegeneration

A major driving force behind the need for a cellular laboratory is our increasing focus on developing new treatments for neurodegenerative disorders such as Parkinson's, Huntington's, and Alzheimer's disease. Recently, changes in peripheral blood mononuclear cells (PBMCs) were found to be correlated with disease progression in several neurodegenerative disorders; thus, pathophysiological processes that affects the central nervous system seem to be reflected by changes in the peripheral circulation. It may therefore be possible to use circulating immune cells as a metric to evaluate the effects of test drugs and predict therapeutic dose levels.

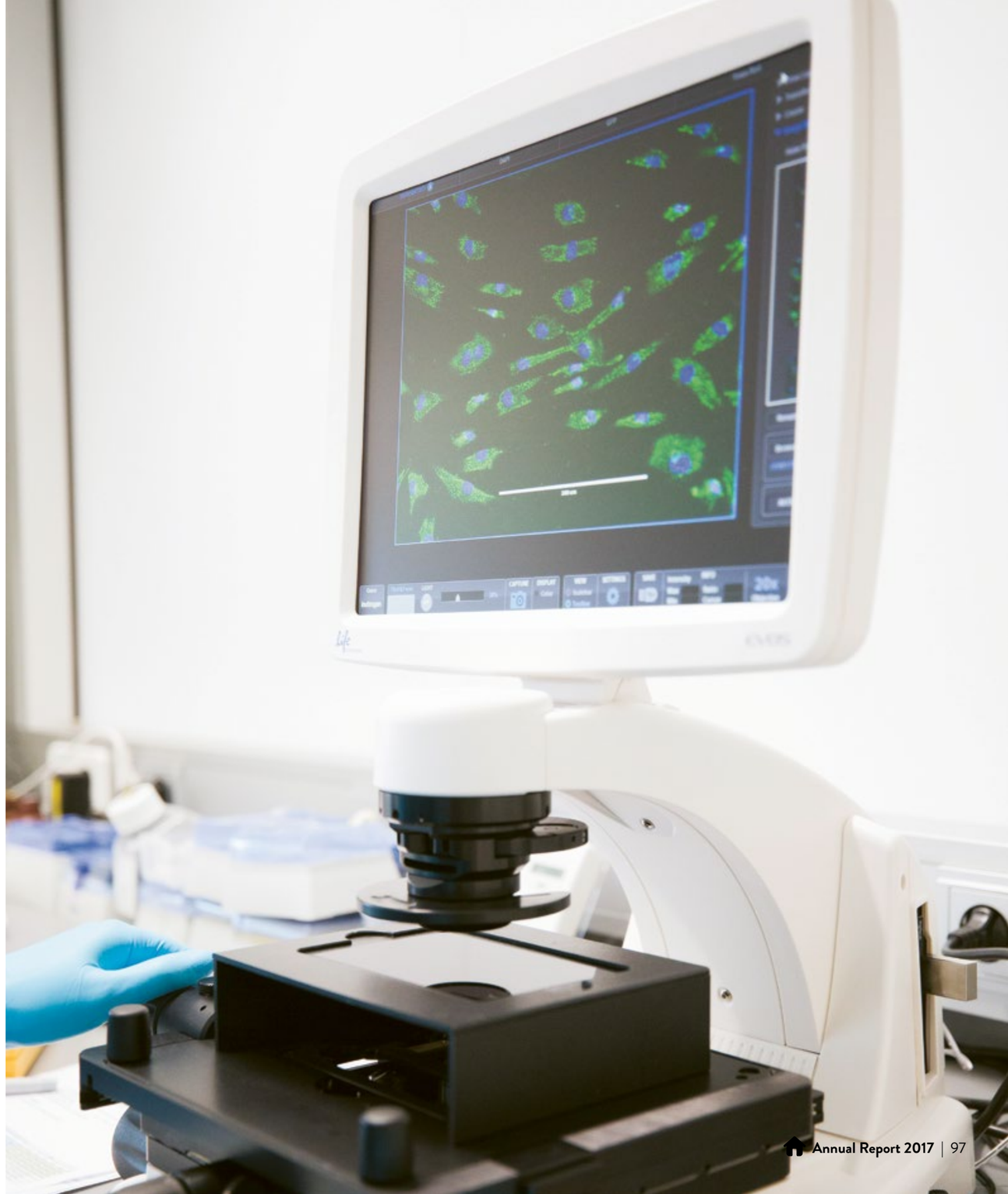
Inflammation, mitochondrial dysfunction, and oxidative stress are all processes that can play a role in specific neurodegenerative diseases and are therefore considered potential therapeutic targets. For example, compelling evidence suggests that mitochondrial dysfunction contributes to the early pathogenesis of Huntington's disease, making mitochondrial function an interesting target for new interventions. CHDR is currently involved in the clinical development of a promising new treatment for Huntington's disease that targets mitochondria (see **page 60**).

In our new cellular laboratory, the biomarker group introduced several new procedures in order to meet the demands of these cutting-edge studies. For example, we developed a battery of tests designed to measure mitochondrial dysfunction and oxidative stress; these assays can be used to measure the baseline stress levels in living cells. In addition, we developed a series of *ex vivo* stress challenges in which the cells are stressed with toxic compounds. This approach can be used to test the effects of mitoprotective compounds. Importantly, our group has extensive experience using a similar *ex vivo* approach to study inflammatory pathways and their modulators.

Entering new territory

Thanks to this new laboratory, and with a rapidly growing number of standard operating procedures to describe the new tests and methods, CHDR has now begun to enter completely new areas of research. One exciting example is the putative immunomodulatory effects of antibiotics. It has been suggested that in addition to their direct effect on bacteria, antibiotics may also directly affect our innate immune response. However, this theory has yet to be tested. CHDR designed an integrated set of tests using *in vitro* and *ex vivo* preparations, dermal inflammatory challenges in healthy volunteers, and an extensive characterisation of drug responses in subjects with acne. Using this combined approach, CHDR hopes to definitively challenge this long-standing hypothesis regarding the effects of antibiotics on the immune response.

In the future, we plan to contribute to the study of pharmacological modulation of T cell function, a growing point of interest in the development of drugs for use in viral infection, transplantation medicine, and oncology. New compounds are currently being developed to target the co-stimulatory pathways activated when a T cell makes contact with an antigen-presenting cell. From a technical perspective, measuring the T cell response is more complicated than measuring the innate immune response, because the T cell response is driven by specific antigens, so only a relatively small fraction of T cells is involved in the immune response to a given antigen. We are currently optimising our bioanalytical approaches to characterising and quantifying the T cell response, and we hope to be able to report our progress in this fascinating line of research in next year's annual report.



Preclinical drug development at CHDR using human cells

A few years ago, CHDR began a collaboration with an innovative US-based pharmaceutical company. In clinical studies, we investigated one of their new compounds, a cationic peptide that has bactericidal properties as well as possible immunomodulatory properties. Although the results were interesting, they were not particularly compelling; thus, CHDR's advice was to conduct additional preclinical research in order to increase their understanding of the compound's mechanism. Their response to this advice was to provide CHDR with sufficient funds to conduct these additional studies over the next two years.

At the end of 2016, a team of researchers began to study the effects of the cationic peptide on a variety of immune responses, using several lines of enquiry. At CHDR, the ability of the peptide to modulate the innate immune response is being investigated in primary immune cells obtained from subjects' blood.

In collaboration with an external company, CHDR has also been studying the interaction between the cationic peptide and cultured primary human keratinocytes. In addition, to support the mechanistic findings obtained in human samples, the peptide's effects on tumour-infiltrating mononuclear cells was also studied in animal models in collaboration with Professor Sjoerd van der Burg, an immunologist at LUMC interested in cancer treatments. Within the framework of this project, collaborations are now being established with Erasmus Medical Centre in Rotterdam and other research groups.

Taking the translational step

The insights gained from these preclinical studies will likely open new lines of enquiry with respect to the clinical development of this immunomodulatory peptide. The first translational step has already been taken: CHDR's Dermatology group studied the possible synergistic effects of combining the peptide with imiquimod (Aldara®), a drug used to treat genital warts, superficial basal cell carcinoma, and actinic keratosis. Imiquimod activates Toll-like receptor 7 (TLR7), which plays a central role in pathogen recognition. The first results of our early-stage clinical studies in healthy volunteers confirm the findings from our preclinical challenge models, showing that the new peptide may indeed potentiate the effect of imiquimod on TLR7. The next step is to test whether this drug combination has added value in treating skin disorders.

Education

Building an international platform for teaching clinical pharmacology

At CHDR, one of our core values is educating and guiding the professional development of our students and staff. As with our approach to drug development, we pride ourselves in our innovative approach to teaching pharmacology. Through our collaborations with partners both near and far, we're building a flexible yet powerful platform based on blended learning.

In academia, teachers often ask, 'What happened to my students' motivation?' Early in their studies, students are eager to learn new things and are willing to go the extra mile. But after just a few semesters, many students start to complain about all the daily reading that's required to keep up with the curriculum, and their motivation tends to wane.

Of course, this phenomenon has always been part of university life, due in part to the many distractions that students face in their daily – and nightly – lives. But another factor may be the way in which today's students digest and process large amounts of information regarding a wide range of subjects. For example, students today find it easier to read and then connect a hundred separate facts presented on different media platforms than to read three chapters in a textbook.

To first capture – and then keep – our students' interest, we need to present them with information in an entirely new way. That's one of the main reasons that CHDR invests heavily in blended learning, a relatively new concept in education that combines multimedia, printed text, and face-to-face classroom teaching.

Increasing importance

CHDR plays an active role in educating physicians, pharmacists, biomedical scientists, nurses, and other professionals in healthcare and biomedical sciences, providing both basic and clinical pharmacology training. In the Netherlands and abroad, the importance of receiving solid training in pharmacology is growing, particularly among physicians. For example, a significant number of hospital admissions are caused by inadequate pharmacotherapy or complications associated with drug-drug interactions. As our global population ages, the importance of our doctors' pharmacological skills also increases. In elderly patients, complications are more likely to occur due to polypharmacy, inadequate compliance, and/or age-dependent changes in pharmacodynamics and pharmacokinetics.

Recognising that physicians must have a solid grasp of pharmacology, a new national pharmacology exam will be introduced for medical students in the Netherlands; this exam will be administered at the end of the theoretical part of their study and is being developed by all eight medical schools in the Netherlands. CHDR – in collaboration with Leiden University Medical Centre (LUMC) – is helping develop this exam.

The Netherlands, the UK, and beyond

At CHDR, we have always contributed to education, both locally and internationally. Our Teaching Resource Centre (TRC) app and website have been used by more than 300,000 medical students and residents worldwide for learning pharmacology and applying it in clinical practice. The TRC was first developed back in the 1990s. Since then, it has been updated for use on mobile devices; and thanks to a recent update, the TRC is now compatible with the US Micromedex database. But we're not stopping there...

In collaboration with LUMC, Leiden University, the University of Applied Sciences Leiden, and several other Dutch universities and university medical centres, we are now developing a new, expanded version of the TRC for teaching clinical pharmacology. In addition to containing information aimed at students, this new TRC will also contain a vast library of audio-visual materials (e.g. lectures, case presentations, short videos, etc.), animated information, texts, and other resources; this library can be used by educators to help design their own courses for specific groups of students. Educators can suggest additions to the platform, and they can comment on outdated items, ensuring that the database is always up-to-date. Because the platform covers a wide range of topics on many levels, it can be used to design a basic pharmacology course for first-year medical students, as well as advanced courses, for example teaching cardiology residents essential information regarding antiarrhythmic drugs. CHDR will use this new TRC for teaching a wide range of students, as well as for our in-house clinical pharmacology training programme.

Recently, CHDR and the British Pharmacological Society agreed to collaborate in developing this new platform. Working closely with this large, well-respected organisation will greatly accelerate the platform's development and facilitate its future use in academia.

Blending theory and practice

We asked medical students to share their thoughts about the increased amount of pharmacology training included in the current curriculum, and the answers were quite revealing. Initially, they viewed pharmacology as just another obligatory component in a specific course. But over time, as they drew closer to their future profession, they began to place a higher value on pharmacology. This is particularly true among senior students who spend most of their time in internships, as they quickly become aware of the importance of providing their patients with safe and effective pharmacotherapy.

Therefore, in developing our new platform for teaching pharmacology, we are careful to ensure that we connect the theory with practice. The most effective approach to education is often to first pose a question or challenge the students with a dilemma commonly encountered in research and/or clinical practice. This approach encourages the students to find the solutions themselves and to develop a proactive attitude towards learning, rather than simply absorbing information. This so-called 'blended learning' approach provides an additional layer of education; in addition to blending online resources with face-to-face education, it also blends theory and practice.

The use of teaser questions, multimedia, and short informational clips, as well as providing the link to professional practice, are all tools that can help keep students motivated and can stimulate an active learning process. At the same time, teaching students how to find state-of-the-art information – and how to apply this information in practice – is just as important. All students require a solid frame of reference, for example a thorough understanding of receptor-ligand interactions, pharmacokinetics, and the practical implications of these concepts. But because science and clinical practice are continuously changing, simply memorising facts is not necessarily very useful. After all, many of the facts that students learn may become outdated by the time they start to practice. So in addition to having a basic framework, healthcare professionals need to be able to quickly locate the most up-to-date information.

Postgraduate education

In addition to teaching students, CHDR also provides continuing education for postgraduates. For example, we provide training in clinical pharmacology in accordance with the latest guidelines established by the Dutch Society for Clinical Pharmacology and Biopharmacy (NVKFB). In the 2017 NVKFB guidelines, more emphasis is now placed on practical applications, with visits to the CCMO (the Dutch central medical ethics committee) and the Dutch Pharmacovigilance Centre. In addition, the guidelines stipulate that trainees should receive more education regarding complex cases that involve polypharmacy and/or vulnerable patient groups such as children, elderly patients, and patients with kidney and/or liver failure. CHDR has addressed all of these guidelines in our Clinical Pharmacology training programme.

In 2017, CHDR had a direct role in helping launch Paul Janssen Futurelab Leiden, a new blended learning programme for teaching entrepreneurial skills to biomedical scientists around the globe using a combination of online and on-campus learning. For more information, please visit **www.PaulJanssenFuturelab.eu.**

Meet Dr Jeroen van Smeden, CHDR's new Director of Education

In August 2017, **Dr Jeroen van Smeden** became the new Director of Education at CHDR. Like his predecessor, Dr Robert Rissmann, Van Smeden obtained a Master's of Pharmacy degree, followed by PhD training at the Leiden Academic Centre for Drug Research (LACDR), where he studied the role of lipids in the stratum corneum in mediating the skin's barrier function. Van Smeden has always been interested in both education and science. At LACDR, he taught physical pharmacy to Bachelor's students, rising to the challenge of making this potentially 'dry' subject interesting. When CHDR posted an opening for a new Director of Education, Van Smeden quickly applied. 'At CHDR, education remains a high priority,' says Van Smeden. 'And I think this is an exciting time to be the Director of Education here, as we introduce new innovations in education, collaborating with so many people here in the Netherlands and abroad. Just like my predecessor, I will continue to play an active role in research here at CHDR, staying connected to the entire drug development process. This way, rather than teaching yesterday's news, I'll be able to spark our students' enthusiasm while helping them prepare for the future.'

Working with CHDR

‘A CRO that listens to our needs’

‘Normally, we encounter a lot of issues when we work with a new party for the first time. This was definitely not the case with CHDR. They are very ‘Dutch’ in the sense that they were always respectful, open-minded, and trustworthy. And their staff – at all levels – were very pleasant to work with. They always listened to us, implemented what we asked, and allowed us to put all relevant and appropriate things in place. Because of this, all went very smoothly. ’

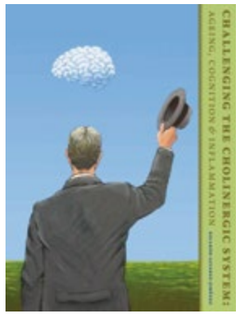
Director of Operations,
Business Development,
Collaborating company*

**The views expressed here are the sole opinion of CHDR’s sponsors.*

Recent PhDs

Dr Ricardo Alvarez Jimenez

‘My “Dutch adventure” has worked out quite nicely’



In 2011, Ricardo Alvarez-Jimenez had just finished medical school in Mexico and was looking for opportunities in scientific research. Today, he’s a clinical pharmacologist with a PhD and is training as an anaesthesiologist at Vrije University Medical Centre in Amsterdam. ‘I learned a lot at CHDR, and I really enjoyed my time there.’

Click to download

NeuroCart and Alzheimer’s disease

‘Thanks to a scholarship,’ says Alvarez Jimenez, ‘I was able to study pharmacology as a Master’s student at Leiden University, where I learned the details of PK/PD modelling, which became very useful later on when I was doing my PhD research. At that time, however, I wanted to learn more about drug development, so I was delighted when Prof Adam Cohen invited me to join CHDR; later, Dr Geert Jan Groeneveld asked me to join the CNS group as a project leader, focusing on the cholinergic system as a target for new treatments for Alzheimer’s disease. We started by validating the cognitive tests available in NeuroCart using our scopolamine challenge model to induce cognitive impairment in healthy elderly volunteers.

Next, we investigated the difference between younger and older people with respect to their response to scopolamine. We expected to find differences in pharmacokinetics using a PK/PD model; however, in addition to the unexpected finding that plasma concentrations of scopolamine were higher in elderly subjects, we also found that elderly subjects were ‘primed’ to the effects of scopolamine in specific tests. Based on these findings, we concluded that our sensitivity to scopolamine increases as we age. Interestingly, the functions that are affected most by this process are associated with brain areas that diminish in size with ageing, possibly explaining the increased sensitivity to anticholinergic drugs such as scopolamine.’

EEG

‘In our next project, we focused on the early clinical development of a nicotinic compound that had promising results in preclinical studies. In this case, our scopolamine challenge was not entirely appropriate, given that scopolamine is a muscarinic antagonist. To investigate the nicotinic system, we developed the mecamylamine challenge based on this nicotinic antagonist. Interestingly, we found out that mecamylamine is more efficient than scopolamine, particularly in terms of inducing cognitive deficits, with fewer side effects such as dizziness.

‘In our final project,’ continues Alvarez Jimenez, ‘we analysed the effects of a cholinergic medication on brain activity measured using an electroencephal ogram (EEG). We identified distinct patterns in patients with dementia and in healthy elderly and young subjects, possibly providing a reliable biomarker for use in drug development.

‘So, it’s been quite a ride, and an interesting intellectual challenge. Currently, I’m focusing mainly on my anaesthesiology training, with research as a side project; but I hope to return to scientific research again in the near future. In the field of anaesthesiology, there is still much work to be done with respect to the cognitive effects of various drugs, and I’m looking forward to applying the skills learned at CHDR.’

Dr Marlous Dillingh

‘I enjoy contributing to both science and drug development’

Click to download

‘Clinical Pharmacology of Immuno-modulatory Biotherapeutics’ was the title of Marlous Dillingh’s PhD thesis, in which she describes several studies focusing on the development and validation of inflammation biomarkers for use in drug development. ‘I covered a lot of ground,’ explains Dillingh, ‘ranging from *in vitro* experiments to studies involving both healthy volunteers and patients. The common denominator was the optimisation of the drug development process, particularly in the development of immunomodulators.

‘We were involved in developing a promising new drug for pulmonary fibrosis,’ continues Dillingh, ‘and we performed the early studies both in healthy volunteers here at CHDR and in patients at the Erasmus Medical Centre in Rotterdam. This was one of my first clinical studies, and what impressed me most was talking with patients who have such a severe medical condition but were glad to contribute to the search for a cure, even though they were well aware that they likely wouldn’t benefit directly from our research.

‘I coordinated the study using our *in vivo* LPS challenge in healthy volunteers. In this challenge, LPS (lipopolysaccharide) induces the release of a wide variety of cytokines into the blood, causing mild fever and other symptoms, depending on the dose. As the coordinator of this study, I was perhaps even more anxious than the volunteers themselves. Unlike the usual situation in the standard drug development process, in which you hope that the compound won’t cause any adverse effects, we knew that LPS would make our subjects sick. Even given this knowledge, our volunteers were remarkably stoic. And I was glad that we were able to use a relatively low dose of LPS, which induces a measurable response without causing too much discomfort for the subject.

‘I first came into contact with CHDR when I was a Master’s student. I did an internship at the intensive care unit at Leiden University Medical Centre, where I collaborated on a project with Prof Koos Burggraaf, who is now the CEO at CHDR. After I graduated, I worked for two years as a clinical research associate at what was then called Quintiles (now IQVIA). Although I enjoyed being involved in coordination and logistics, I felt that I also wanted to contribute to clinical science. Luckily, I was offered a job at CHDR. At first, I had no intention of obtaining a PhD; I just knew that I wanted to do scientific research. But then, after I collected a sufficient amount of data, writing a PhD thesis was the logical next step. I’m now working as a clinical scientist at CHDR. Many things have changed in the seven years since I started here; for example, we moved to a new building, and the organisation has grown considerably. I like being in such a dynamic environment because it offers me and my colleagues many opportunities to develop ourselves both personally and professionally. What I also like about CHDR is the atmosphere, which manages to be both light-hearted and extremely professional at the same time. We’re involved in cutting-edge research, and everyone here is highly dedicated, but we also know how to have fun. And I like to be challenged; for example, if I’m told that something cannot be accomplished in a relatively short time, I’m determined to prove them wrong. That’s why I enjoy working at CHDR.’

Dr Hélène van Meir

‘It was both a pleasure and – sometimes – a challenge working with so many highly intelligent people’

Click to download

Hélène van Meir was based at CHDR when she studied a therapeutic vaccine for treating cervical cancer. Most of her time, though, was spent at local hospitals in Leiden and Amsterdam, and in the Immunology Laboratory at Leiden University Medical Centre (LUMC).

‘I was in the middle of a collaboration between CHDR in several departments at LUMC,’ she explains, ‘so essentially I had several bosses. I must admit, that took some getting used to. But I can see now that it was worth it, as the results we obtained were valuable both scientifically and clinically. I met a lot of extremely smart people who were also dedicated to the research. So yes, I’d have to say that the experience was quite rewarding.

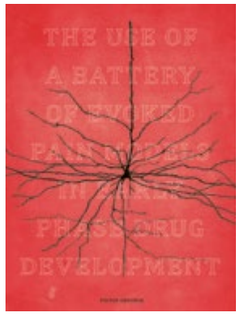
‘In this project,’ Van Meir continues, ‘we investigated the effects of chemotherapy and/or radiotherapy on the immune system’s response to a therapeutic vaccine designed to treat cervical cancer. Both chemotherapy and radiotherapy are commonly used to treat metastatic cervical cancer, and we wanted to investigate whether they interfere with an immunotherapeutic vaccine being developed by a Leiden-based biotech company, a spin-off of LUMC. Because both chemotherapy and radiotherapy can reduce the body’s production of white blood cells, they might interfere with the immune response. For this project, we studied patients who had an extremely poor prognosis, a commonly used approach in the development of new treatments for cancer. But thanks to the extensive early screening programme here in the Netherlands, it was difficult to find sufficient numbers of patients with metastatic cervical cancer in Leiden; to get enough patients for our study, I had to go to Amsterdam as well. It was worth the extra effort, as we found a clear answer to our question: radiotherapy reduces the immune system’s response to the therapeutic vaccine, whereas chemotherapy increases the response. The enhanced effect of immunotherapy when combined with chemotherapy is due to the fact that chemotherapy improves the balance between the cytotoxic T cells and inhibitory immune cells that are often present both in and around the tumour.

‘After I finished my PhD studies, I went on to become a gynaecologist. I just started the final 18 months in my training, in which I’m focusing on the treatment of gynaecological cancer. During my time at CHDR, I also completed the clinical pharmacology training programme. Although few gynaecologists are also clinical pharmacologists, I think the combination can be extremely useful, particularly for communicating with clinical oncologists.

‘Meanwhile,’ continues Van Meir, ‘others are working to further develop the therapeutic vaccine, including studying the effects of repeated vaccinations in combination with chemotherapy. My hope is that one day this therapeutic vaccine will help increase the survival and quality of life of patients with cervical cancer. I expect that the vaccine will be most effective when used as an adjuvant therapy in an early stage in patients who are eligible for surgery. But for now, I’m focusing on my own future as a doctor and – possibly – a clinical scientist as well.’

Dr Pieter Okkerse

‘CHDR is a great place to learn how to do research’



Click to download

At CHDR, Pieter Okkerse obtained his PhD for his thesis entitled ‘The use of a battery of evoked pain models in early phase drug development’, in which he used the test battery called PainCart. ‘I did most of my research between 2011 and 2014,’ says Okkerse, ‘when we were validating the various tests that are now included in PainCart. We needed to know the test results were reproducible, and we wanted to ensure that we were actually measuring pain and analgesia, not consciousness or sedation. Once the basic test battery was established, we performed validation studies in order to measure the analgesic profile of various drugs. For example, we tested three orally delivered drugs – ibuprofen, pregabalin, and imipramine – against placebo in a four-way crossover study. Using a similar setup, we also tested three intravenous drugs – fentanyl, ketamine, and phenytoin – against placebo. I then used these profiles to study new compounds and new drug combinations. For example, I studied a new neurotrophic compound, and I studied a combination of the opioid buprenorphine and the serotonin-norepinephrine reuptake inhibitor milnacipran.

‘Thanks to my work at CHDR, I’m now a clinical pharmacologist, and I recently received my PhD. I’m now in training at Leiden University Medical Centre (LUMC) to become an anesthesiologist. My training in clinical pharmacology is of course useful, as anaesthesiologists typically give patients combinations of drugs, and these patients can have several clinical conditions. In the future, I hope to continue performing scientific research in addition to my work as a doctor.

‘In a way, the circle is now complete,’ continues Okkerse. ‘When I was a medical student at LUMC, I participated in a research project in the Anesthesiology Department. When I finished medical school, I chose to do scientific research. Professor Albert Dahan in the Anesthesiology Department suggested that I get in touch with Geert Jan Groeneveld, and that’s how I came to CHDR. While at CHDR, I applied to LUMC for a residency programme in anesthesiology and was accepted. And so now, I’ve returned to the Anaesthesiology Department at LUMC.

‘I feel as though I’ve learned quite a lot at CHDR. Their work is largely project-based, so as an investigator you focus on the big picture, but you never lose sight of the finer details that require your attention. In an academic laboratory, you’re usually busy doing the measurements yourself. I think that CHDR manages to be dedicated to both science and their sponsors’ interests. Although they are more “business-like” than most academic institutions, they’re also highly interested in finding out what works, and why. Importantly, they give young people the chance to learn something new while contributing to medical research. That’s why at CHDR, I felt that I could prove myself by being responsible for clinical studies while receiving excellent training.’

Crossing borders, bridging cultures

Ahmad Skineh

‘I want to contribute to society’

Ahmad Skineh is a pharmacist originally from Syria. Through a programme organised by the city of Leiden, he came into contact with CHDR, and he is now a member of their staff. ‘I’m working towards getting my license to practice as a pharmacist here in the Netherlands.’

‘After I studied pharmacy in Aleppo,’ says Skineh, ‘I worked there as a pharmacist, first in the local hospital, then in my own pharmacy at a pharmaceutical company, where I researched hormones and related compounds. Unfortunately, the situation in Aleppo became unsafe, and my family and I moved to Turkey. My wife and three children then stayed in Turkey while I went to the Netherlands. After a year in the Netherlands, I received a permit to stay here, and my family joined me. I immediately started to learn Dutch, and I also wanted to get a job, preferably one in which I could use my knowledge and training as a pharmacist. But it wasn’t easy. I worked at a nearby hospital for three months, but they couldn’t offer me a fixed job because I didn’t have my licence to practice here. But ironically, I was unable to study in order to get my pharmacist’s license as long as I was collecting unemployment benefits. So, I started to think about how I could solve this dilemma. Around that same time, the city of Leiden organised a meeting at CHDR for people with a background in medicine or pharmacy, which I attended. I was then invited by Adam Cohen, CHDR’s CEO at the time, and he gave me the opportunity to perform scientific research at CHDR for six months. I was involved in a study on wound healing, working with the project leader to write the protocol. I also assisted by taking photographs of the wound-healing process.

‘After that initial six months, I was offered a part-time contract at CHDR, where I can continue my research on wound healing and study the central nervous system as well. I really like working here, and I’ll always be grateful for the opportunity that they’ve given me; at the same time, I’m also eager to obtain my Dutch language certificate so I can become a pharmacist here in the Netherlands. I’m now applying to the Master’s programme in Biopharmaceutical Sciences here at Leiden University. If I’m accepted, I’ll start this September. Of course, combining my studies with my work here at CHDR will be hard work, but it will be worth it if it allows me to return to working as a pharmacist.’

Dr Osamah Albitar

‘At CHDR, I became interested in scientific research’

Osamah Albitar is a Palestinian physician born in Syria. Looking for a new challenge, he contacted CHDR and was offered an internship. ‘I became interested in conducting scientific research,’ says Albitar, ‘so now I’m applying to the Master’s programme in biomedical sciences at Leiden University. Once my command of the Dutch language is sufficient, I hope to work as a physician here in the Netherlands.

‘I studied medicine at Alzaiem Alazhari University in Sudan. After receiving my medical degree in 2010, I worked in Sudan for about two years, then returned to Syria, hoping that the situation there would improve. Unfortunately, things didn’t improve, but grew worse, so I came to the Netherlands. When I received my permit to stay here, I contacted the city of Leiden to see if they knew of any volunteer work that I could do. They recommended that I try to find something in my field of expertise. I was invited for a meeting that the city organised at CHDR, and that’s how I came to do an internship here.

‘It’s been a really interesting experience,’ continues Albitar. ‘I first worked as a medical assistant in dermatology, taking photographs of the subjects’ skin and analysing the images. I then grew increasingly interested in CNS research, working with CHDR’s NeuroCart. I was also involved in writing several SOPs (standard operating procedures). Much of my work was done together with my colleague Achmad Skineh, a pharmacist who’s also from Syria.

‘In the future, I hope to become an orthopaedic surgeon. But that will take some time. First, I need to learn enough Dutch to communicate with my patients. For now, I’m focusing on scientific research here at CHDR and studying at Leiden University. This combined approach allows me to continue contributing to research.’

CHDR and the CCMO

‘I use my experience at CHDR to maximise research ethics in the Netherlands.’

As a neurologist with a keen interest in developing CNS drugs, including psychiatric drugs, Professor Joop van Gerven has been with CHDR for nearly 25 years. He’s still with CHDR, but most of his time is now dedicated to the CCMO, the Dutch central medical ethics committee. In 2016, Van Gerven was the Interim Chair of the CCMO, and in 2017 he became the Chair. Here, Van Gerven talks about his new job and how it relates to his work at CHDR.

‘I’m still on the staff at CHDR, but I don’t spend much time here these days,’ says Van Gerven. ‘I’m still involved in many of the CNS trials, particularly in psychiatry, even though I’m mainly in the background. And I still visit sponsors to discuss new studies or potential lines of enquiry at an early stage. That’s where my expertise is useful, and it’s what I enjoy most – contributing to the scientific discussion from the beginning and helping find the best approach to studying a new CNS compound in the earliest phases of clinical development.’

In his many years at CHDR, Van Gerven developed and fine-tuned a method to collate all of a new compound’s preclinical data in order to maximise safety and make informed decisions in early-stage clinical development. Based on this method, CHDR developed the IB-Derisk analyser (see page 128), a convenient tool that integrates all available knowledge contained in the investigator’s brochure (IB). This tool can also be used to train clinical pharmacologists serving on a medical ethics committees (MEC) and to help them analyse the IB, if included in the protocol submitted to the MEC.

A mutually beneficial interaction

In choosing Van Gerven to serve as their Chair, the CCMO elected someone who is still actively involved in medical research. In the past, this position was usually filled by a retired professor who could devote much of his time to the job. Van Gerven is well aware that his roles at both CHDR and the CCMO could lead to a possible conflict of interest. ‘I need to be both transparent and responsible,’ he explains, ‘and I hope that the people around me won’t hesitate to ask questions when needed. If the CCMO is asked to evaluate a protocol from CHDR, I will of course recuse myself. And if a protocol involves a sponsor with whom I’ve worked in the past, we’ll discuss the situation and decide on my involvement. If I do anything as the Chair of the CCMO that may seem to be unduly in CHDR’s favour, I hope I’ll be called to task.’

Of course, those who know Van Gerven know that he has high integrity. At the same time, the authorities have good reason to want a CCMO Chair who is still active in scientific research. The fields of medical science and drug development are changing faster than ever, and many new approaches and research tools are developed each year, all with their own potential consequences with respect to the ethical considerations and the practice of research involving human subjects. Moreover, the rules and regulations are changing just as fast, with many governing bodies issuing their own sets of rules. Van Gerven explains: ‘At CHDR, we often have to deal with the challenges of following new rules and new regulations. By maintaining a wide network of researchers, pharmaceutical companies, and biotech start-ups, I can experience first-hand the effects of all of these developments. So I hope to use my past experience and my current network in serving both research ethics and science.’

Improving communication

‘As Chair of the CCMO,’ says Van Gerven, ‘one of my goals is to improve communication between all parties involved in drug development in the Netherlands, including various legislative and regulatory bodies. I think it’s important that each party recognises each other’s opinions and priorities in order to maximise clarity and minimise bureaucracy.’

For example, a pharmaceutical company developing a new drug can ask the CBG (the Dutch Medicines Evaluation Board) for scientific advice. In reply, the CBG may recommend that the company use a certain procedure or design in their clinical trial in order to provide the CBG with the information they’ll need for ultimately registering the product. At the same time,

the CCMO – or another MEC – may object to that same procedure for ethical reasons. Understandably, receiving conflicting information from two governing bodies can cause confusion for the study's investigator and/or sponsor.

'That's why communication between different institutions and regulatory bodies is so important,' explains Van Gerven. 'One of my aims is to improve communication among the entire chain of institutions involved in drug development, including post-marketing evaluation, so we can prevent these kinds of time-consuming problems.

Working with the rules, not against them

Of course, not all studies that require ethics approval involve drug development. In addition, a large percentage of the clinical research conducted at university medical centres in the Netherlands is investigator-initiated. Here, Van Gerven hopes to help ease tension between the requirements of science and regulatory pressure. 'At CHDR,' he explains, 'we have a great deal of experience conducting clinical research while meeting high regulatory demands. I believe it's entirely possible to use these regulatory demands to improve the quality of your research. The steady flow of publications and PhD theses produced by CHDR shows that we have found a way to maintain high scientific output and satisfy regulators' requirements.

'As a researcher,' continues Van Gerven, 'I understand the difficulties that all of these rules can cause. And I can use our experience – and the solutions we've found – to help academic researchers. I think it's in everyone's best interest – including CHDR's – that there's minimal distance between academic research and contract research. That's why I'll continue to do whatever I can to keep academic clinical research going strong. We need to be critical of new rules that add a lot of paperwork but have little added value in terms of safety, reliability, or ethics. So in academic science – as in drug development – communication can help prevent many problems.'

The IB-Derisk analyser: A practical tool for integrating preclinical findings

The first time a new compound is administered to human subjects is always an important milestone. In order to design a study that is both safe and informative, the researcher must have a clear overview of all of the preclinical data. This body of data is usually compiled in the investigator's brochure (IB), a massive document often hundreds of pages long. To help the researcher extract the key data from the IB, CHDR developed the IB-Derisk analyser.

Preclinical drug development typically includes studies conducted in a wide range of conditions, often involving both *in vitro* and *in vivo* experiments using a wide variety of species. For example, in some cases, a time course may be performed to monitor the blood levels of the drug; in other experiments, cardiovascular safety or the drug's effects on its molecular target may be studied, without obtaining detailed information regarding pharmacokinetics. The results of all of these experiments – as well as other findings such as mortality, adverse effects, changes in behaviour, etc. – are then compiled to create the IB. Before making the transition to human trials, the investigator must somehow organise all of this data in order to design the first-in-human trial in such a way that it's both safe and informative.

Safe and informative

Having a thorough understanding of the IB's contents is essential in order to maximise the safety of the volunteers who will be the first subjects to receive the new drug. In particular, unexpected events in preclinical studies and/or differences in species' response to the test compound can be warning signs of possible complications in early clinical studies.

Preclinical data are also needed in order to determine which tests and measurements should be performed in the early clinical studies, as well as the initial dose, dosing range, and route of administration. These tests can also be valuable for indicating which methods can provide key information regarding pharmacology and the putative drug-target interaction. Often, intended and/or unintended effects can be studied in healthy volunteers by using drug-sensitive tests, sophisticated challenge models, *ex vivo* studies, and other approaches.

To maximise safety and design the most informative early clinical studies, investigators must use the wealth of preclinical data to generate predictions regarding the test compound's pharmacokinetics and pharmacodynamics in human subjects. Thanks to CHDR's new IB-Derisk analyser, this process is now much simpler.

C_{max} and colour codes

To organise all of the preclinical data contained in the IB and reduce the risk of overlooking important results, CHDR's IB-Derisk tool arranges all preclinical experiments in a convenient table according to the maximal concentration (C_{max}) achieved after administration of a single weight-corrected dose.

For most species used in preclinical research, C_{max} is determined from pharmacokinetics experiments. The C_{max} value is then used to rank all of the findings with respect to pharmacological effects in various species. The outcomes are then colour-coded, providing a visual overview of the compound's intended and/or unintended effects. These colour codes provide additional structure and can help reveal irregularities. Importantly, this visualisation also helps the investigator detect possible risks that might otherwise go unnoticed in the IB.

At CHDR, we have been working with this approach for years. Of course, this approach may not necessarily predict all possible issues that can arise in early drug development, nor should it replace a thorough review of the preclinical information. However, it provides a practical method for organising all of the information contained in the IB and helping reveal irregularities in the preclinical data. For more information, see our recent publication by Van Gerven and Cohen[1] and visit our website at www.ib-derisk.org.

[1] Integrating data from the IMPD/IB. A new tool for translational integration of preclinical effects. 2018. *British Journal of Clinical Pharmacology*. Jan 30. doi: 10.1111/bcp.13529

Working with the new EU guideline

New European guideline regarding early-stage clinical trials

In the wake of the tragic events that occurred in 2016 during a clinical trial conducted in Rennes, France, the European Medicines Agency (EMA) revised their guideline with respect to early-stage drug development. A draft version of their 'Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products' was discussed thoroughly at CHDR.

At CHDR, our entire research staff discussed the draft EMA guideline, as this was a good opportunity to educate our junior staff members regarding the process of reviewing and critiquing such guidelines. Our PhD students and other junior staff members actively participated in these discussions, and as a result CHDR delivered extensive comments and suggestions to the EMA. We were pleased to find that most of our suggestions were included in the EMA's final version of the guideline[1], which was published in July 2017 and took effect in early 2018.

The guideline also provided us with the opportunity to take a critical look at our own operations. Overall, we concluded that no major changes were needed. At CHDR, we have always emphasised the importance of using a scientific, question-based approach built on a thorough knowledge of the compound's pharmacology. In keeping with this approach, the new EMA guideline states that each step in the drug development process must be supported by well-documented scientific rationale, and the process must also be responsive to new data that may emerge during the course of the clinical trials. When designing the first-in-human and other early-phase trials, the data obtained from preclinical studies should play an important role.

Of course, ensuring the safety of the study subjects is of paramount importance in the entire drug development process. That's why CHDR is pleased to contribute to the dissemination of the new EMA guideline and its underlying principles, principles that we share as well. A good example is our new IB-Derisk analyser tool (see also page 128), which provides a clear and comprehensive overview of the preclinical findings contained in the Investigator's Brochure (IB), thereby helping the investigator develop protocols that have a strong scientific basis. To facilitate the dissemination and implementation of the new EMA guideline, Prof Joop van Gerven, a Research Director at CHDR and the Chairman of the Dutch Central Committee for Medical Ethics (in Dutch: *Centrale Commissie Mensgebonden Onderzoek*, or CCMO), co-authored a commentary that was published recently in the *British Journal of Clinical Pharmacology*[2]. We will also include the new guideline when educating students, clinical pharmacologists, and trainees at Paul Janssen Futurelab Leiden.

[1] The entire guideline is available for download at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/07/WC500232186.pdf.

[2] van Gerven, J and Bonelli, M (2018). Commentary on the EMA Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1. *British Journal of Clinical Pharmacology*. doi: 10.1111/bcp.13550.

Volunteering at CHDR

Marianne, study volunteer at CHDR

‘I feel it’s important that new drugs are being developed; that’s why I want to contribute’

‘People sometimes ask me why I volunteer for research studies at CHDR,’ says Marianne. ‘They don’t see why anyone would invest so much of their time and take the possible risks involved in drug research. But when they’re sick, they’re certainly glad that there’s an effective medication for them to take. And I know that many disorders – for example, Alzheimer’s disease – still have no cure. So that’s my main motivation; I don’t really care what other people think. And sometimes, I deliberately provoke a reaction from my friends, for example by posting a picture of myself at CHDR with all kinds of wires attached to my head.

‘When I volunteer at CHDR, I always feel like they really care about us. I can’t really think of anything there that I don’t like; it’s been a positive experience in all respects. I appreciate the personal care I receive, as well as their dedication and the professional way in which they conduct their studies. Everything’s usually on a tight schedule, and they make sure that I receive the study medication and perform all of the tests at the scheduled times. In some ways, this can be quite intense. For example, on some study days, we might start at 8 in the morning, and they may keep us busy until late in the evening, doing all kinds of tests on the computer, measuring our eye movements and brain activity… Those days can be really tiring. But for me, it’s not a problem, and I’ve never considered leaving a study because of it. CHDR always maintains a nice balance between what they ask of their volunteers and the level of care that they provide.’

‘The last time I was at CHDR for a study,’ continues Marianne, ‘I had a sudden emergency situation at home. I absolutely had to go home to take care of the situation, but I didn’t want to just leave in the middle of the study, knowing that all of my efforts – and the efforts of CHDR – would have been in vain.
So I discussed my dilemma with CHDR staff, and they decided that it would be alright for me to go home for a couple of hours. They called a taxi for me, and I was able to do what I needed and then return to finish the study. That’s when I realised – and not for the first time – how much CHDR cares for me as a person, seeing me as more than just a subject in their study.’

Herman, study volunteer at CHDR

‘They treat you with respect’

‘I was in the military,’ says Herman, ‘so retirement came relatively early for me. I was 50 when I stopped working. My niece – my younger sister’s daughter – is a student in Groningen, and she sometimes volunteers as a subject in drug studies. My sister suggested that I could participate in a study as well. I was already doing some volunteer work, so I decided to give it a try. And I liked it. I’ve been in four different studies so far, at CHDR and at other CROs; but I honestly like CHDR the best. The nurses and other staff members at CHDR are always friendly, polite, and highly professional. I like the location as well; it’s really comfortable, and you have a great view thanks to all the glass.

‘Of course,’ continues Herman, ‘it’s not always easy. For example, if the study requires a stay of two weeks or more, it can become a bit of a challenge dealing with all the different people. And relatively small things may tend to irritate you. For example, in my last study at CHDR, our diet was somewhat restricted due to the study medication. After a while, people started complaining, especially if you were the last to receive the medication, as you were also last to arrive at the dinner table. But in all fairness, once we pointed this out, they did what they could to improve this.

‘For me personally, I find it difficult to stay indoors for such a long time. When I’m at home, I go out every day to walk, jog, or ride my bicycle – rain or shine. But at CHDR, I’m not even allowed to go down the stairs unaccompanied; this is for my own safety, of course, and because of liability issues. On the other hand, they do what they can to provide plenty of entertainment. They have a variety of games, as well as several newspapers and other reading material. Each room also has a television, with headphones available so you don’t disturb the others. So, I usually enjoy my time at CHDR.’

Henk, study volunteer at CHDR

‘Time flies when I’m in a study at CHDR’

‘I’ve been a study volunteer for quite some time now,’ says Leering, ‘first at another CRO and then at CHDR for the past five or six years. When I joined the first study at CHDR, they had just moved into their new building. I found them to be quite friendly and service-oriented, and there’s a very hospitable atmosphere. When I’m in the “living room” at CHDR, I really feel at home. There are always other volunteers to talk to, and I can also read a book or watch television. And of course, during the study itself, the researchers keep you busy performing various tests. So even a study that requires a stay of two or three weeks is no big deal for me, as the time flies by.

‘The last time I was at CHDR was in early December, and as usual we were a very close group of volunteers, having a lot of fun. Early December is the time of year when children in the Netherlands put a shoe by the fireplace at night so that Saint Nicholas will put a little present in it. One night, we all put a shoe outside the door of our room. My room was close to the nurses station, and I overheard them saying, “Looks like we should give Saint Nicholas a call.” Sure enough, the next day we each had a little present in our shoe. That’s what I really like about CHDR – they truly care and have a light-hearted, fun way of treating their study volunteers.

‘Over the years,’ continues Henk, ‘I’ve participated in several trials. Sometimes you have to take the medication for several weeks at home. They give you an iPhone, which you use to send them a picture of the medication at the time you take it. That way they know that you’re following their instructions.

‘I think it’s important that people volunteer for drug studies. When friends ask me about it, I say, “If you need to take medication, don’t you want to be sure that it’s safe?” I’ve been a blood donor for quite some time as well, so for me this was the next logical step. But I started to volunteer for research studies for a far more personal reason. In 2004, two of my brothers were hospitalised, and unfortunately one of my brothers passed away. That’s when I started to think about my own health, and I asked my family doctor for a check-up. He told me that if I didn’t have any symptoms, my health insurance wouldn’t pay for the tests. But then I realised that if I became a volunteer in a drug study, I would receive a thorough medical test as part of the screening process. Luckily, I was healthy enough to participate in the study, and that’s how it started. These days, it’s just something I do, and I’m also glad when I get a clean bill of health.

‘Most of the time, the study drugs don’t have much of an effect on me. But I remember one study where we tested a nasal spray; I think it was a new drug for Alzheimer’s disease. I was the last in line, and I had seen the others experiencing minor problems such as a runny nose. When I received the spray, I didn’t have any problems, so I thought, “I probably got the placebo.” But then I suddenly felt quite nauseous. Immediately, a nurse came to me and asked me if I was all right. I had to lie down, and I could not participate in all of the tests that day. During the day, someone was always there to check on me, so I felt completely safe.

‘Of course, you should realise that there is always a small risk associated with this kind of research. After the problems with a study in France a couple of years ago, some people asked me why I still wanted to be a volunteer. I told them that I find it to be an acceptable risk. After all, driving a car carries far more risk than participating in a research study, but we still drive, right?’

Ron, study volunteer at CHDR

‘The medical students who gave me the injections at home were nice and showed a genuine interest in me as a person’

‘I recently participated in a trial at CHDR to study a new drug for Huntington’s disease,’ says Ron.
‘I have Huntington’s myself, as did my mother, my grandmother, and several other family members. Of course, I hope they will find an effective treatment for HD; that’s the main reason I participated in this study. The study consisted of two parts. In the first part, I stayed at CHDR for about two days, where they gave me the study medication and performed all kinds of measurements and tests, including blood pressure, temperature, an ECG, and blood test. They also did a wide range of tests on the computer, and they performed an MRI scan. In the second part of the study, I was visited every day for four weeks by students from CHDR who gave me an injection. Once a week, I returned to CHDR, where they took a blood sample and did some tests. And again, I received several MRI scans.

‘I had never been in an MRI machine before,’ continues Ron, ‘but it was no big deal. People had told me beforehand that these scanners can make a lot of noise, but it didn’t bother me. They gave me earplugs and headphones to use, which made a difference. Normally, you have to lie very still during an MRI scan, but I was instructed to tense my calf muscles during the scan. And that was it... I wouldn’t mind doing it again.

‘I enjoyed my stay at CHDR. They did whatever they could to make us comfortable – within limits, of course; it’s not like we could walk down to the pub. There was another patient with Huntington’s disease when I was there, as well as other volunteers who were there for other studies. I had a nice room, so when they didn’t need me, I could go there for some alone time, or I could spend time with the other volunteers in the common room, what they call the “living room”. I met some people there who were staying for several weeks; but we just were there for two days.

‘The medical students who came to my home were really nice and friendly. They didn’t just come in, give the injection, and then dash away; they took the time to talk to me, and they were clearly interested in me as a person. It was obvious that these medical students were eager to learn more about Huntington’s disease, and I learned a few things from them as well.

‘I’m looking forward to learning the outcome of the study; I think they’ll have the results soon. I didn’t feel any different during the study. It’s possible that I was in the placebo group; of course, they don’t tell you during the study, and they don’t even know themselves. After the study is finished, they break the code; so I hope to know within a few weeks whether I had the placebo or the study drug.’

Scientific output

Bibliometric analysis

As in previous years, CHDR commissioned the Centre of Science and Technology Studies in Leiden to performed our bibliometric analysis for our 2017 annual report. This analysis provides insight into CHDR's publication performance, as well as our impact in the research field.

Publication output (P)

Many research activities can be quantified, but the most common measure is to simply count the number of publications, which provides a basic measure of research output.

Ranking an institution based solely on the number of publications makes it possible to compare output among institutions. However, because the number of publications depends to a large extent on the number of researchers, assessing the impact of these publications can provide a more appropriate measure of scientific impact.

Citation impact (MNCS)

Citations are used in publications to refer the reader to previously published work, and tracking these citations provides a useful measure of the impact of your research. The Mean Normalised Citation Score (MNCS) is commonly used to measure citation impact over a four-year window

PP(top10%)

This score reflects the proportion of an oeuvre in the top 10% of the most frequently cited papers. A value of 10% (0.1) or higher indicates a relatively high proportion of frequently cited papers. Importantly, unlike MNCS, this indicator is less sensitive to outliers (i.e. papers cited an extremely high number of times).

Summary

Once again, our bibliometric analysis reflects a steady increase in scientific output. This increase in the number and impact of our publications is likely due to CHDR's growth both in research staff and in the number of studies performed. Our current publication impact score (MNCS) of 1.11 is higher than the global average of 1.0. This means that CHDR – a full-service CRO – performs as well as most research-driven institutes and academic departments. We're proud to report that our publications are cited by researchers around the world and that currently 15% of our articles are in the top 10% of the most-cited publications in their respective fields.

Figure 1: Number of CHDR publications from 2005 through 2017

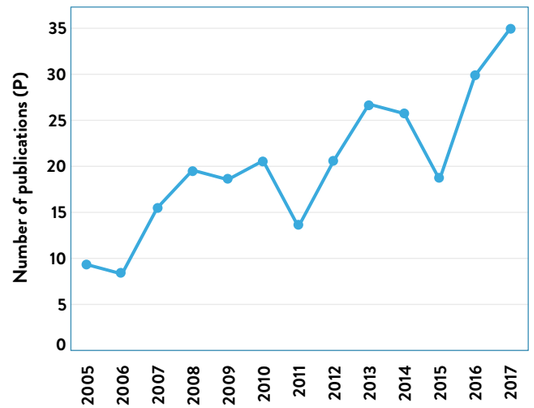


Figure 2: Citation impact (MNCS) for CHDR from 2001 through 2016

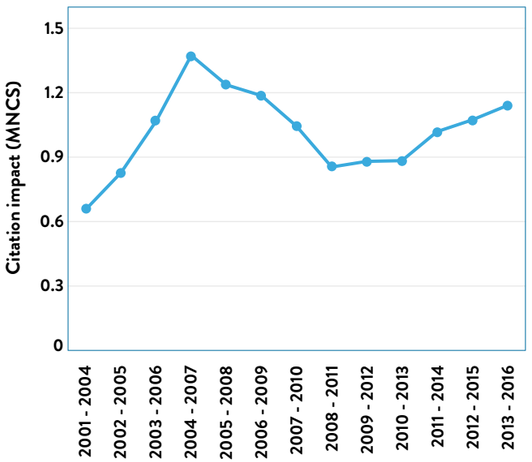
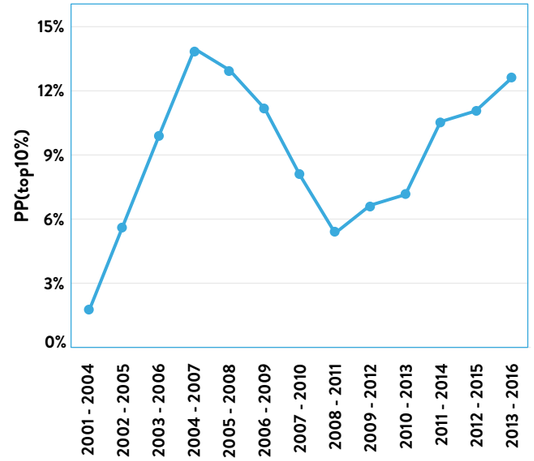


Figure 3: Proportion of high-impact papers published by CHDR from 2001 through 2016



Publication list

Alvarez-Jimenez R, Baakman AC, Stevens J, Goulooze SC, Hart EP, Rissmann R, van Gerven JMA, Groeneveld GJ. Pharmacokinetics and pharmacodynamics of oral mecamylamine - development of a nicotinic acetylcholine receptor antagonist cognitive challenge test using modelling and simulation. *Journal of Psychopharmacology.* 2017; **31:192-203**.

Baakman AC, Alvarez-Jimenez R, Rissmann R, Klaassen ES, Stevens J, Goulooze SC, den Burger JCG, Swart EL, van Gerven JMA, Groeneveld GJ. An anti-nicotinic cognitive challenge model using mecamylamine in comparison with the anti-muscarinic cognitive challenge using scopolamine. *British Journal of Clinical Pharmacology.* 2017; **83:1676-1687**.

Balak DMW, van Doorn MBA, Arbeit RD, Rijneveld R, Klaassen E, Sullivan T, Brevard J, Thio HB, Prens EP, Burggraaf J, Rissmann R. IMO-8400, a toll-like receptor 7, 8, and 9 antagonist, demonstrates clinical activity in a phase 2a, randomized, placebo-controlled trial in patients with moderate-to-severe plaque psoriasis. *Clinical Immunology.* 2017; **174:63-72**.

Bergheanu SC, Bodde MC, Jukema JW. Pathophysiology and treatment of atherosclerosis: current view and future perspective on lipoprotein modification treatment. *Netherlands Heart Journal.* 2017; **25:231-242**.

Chen X, Broeyer F, De Kam M, Baas J, Cohen A, van Gerven J. Pharmacodynamic response profiles of anxiolytic and sedative drugs. *British Journal of Clinical Pharmacology.* 2017; **83:1028-1038**.

Dahan A, Boom M, Sarton E, Hay J, Groeneveld GJ, Neukirchen M, Bothmer J, Aarts L, Olofsen E. Respiratory effects of the nociceptin/orphanin FQ peptide and opioid receptor agonist, Cebranopadol, in healthy human volunteers. *Anesthesiology.* 2017; **126:697-707**.

Ducore J, Lawrence JB, Simpson M, Boggio L, Bellon A, Burggraaf J, Stevens J, Moerland M, Frieling J, Reijers J, Wang M. Safety and dose-dependency of eptacog beta (activated) in a dose escalation study of non-bleeding congenital haemophilia A or B patients, with or without inhibitors. *Haemophilia.* 2017; **23:844-851**.

Emanuel AL, Nieuwenhoff MD, Klaassen ES, Verma A, Kramer MHH, Strijers R, Vrancken AFJE, Eringa E, Groeneveld GJ, Serne EH. Relationships between type 2 diabetes, neuropathy, and microvascular dysfunction: evidence from patients with cryptogenic axonal polyneuropathy. *Diabetes Care.* 2017; **40:583-590**.

Goulooze SC, Franson KL, Cohen AF, Rissmann R. Clinical pharmacology research internships at the interface between academia and industry: students' perceptions and scientific output. *Basic & Clinical Pharmacology & Toxicology.* 2017; **121:22-28**.

Handgraaf HJM, Boonstra MC, Prevoo HAJM, Kuil J, Bordo MW, Boogerd LSF, Mulder BGS, Sier CFM, Vinkenburg-van Slooten ML, Valentijn ARPM, Burggraaf J, van de Velde CJH, Frangioni JV, Vahrmeijer AL. Real-time near-infrared fluorescence imaging using cRGDZW800-1 for intraoperative visualization of multiple cancer types. *Oncotarget.* 2017; **8:21054-21066**.

Heuberger JAAC, Rotmans JI, Gal P, Stuurman FE, van 't Westende J, Post TE, Daniels JMA, Moerland M, van Veldhoven PLJ, de Kam ML, Ram H, de Hon O, Posthuma JJ, Burggraaf J, Cohen AF. Effects of erythropoietin on cycling performance of well trained cyclists: a double-blind, randomised, placebo-controlled trial. *Lancet Haematology.* 2017; **4:E374-E386**.

Jacobs M, Hart EP, Roos RAC. Driving with a neurodegenerative disorder: an overview of the current literature. *Journal of Neurology.* 2017; **264:1678-1696**.

Khalili-Mahani N, Rombouts SARB, van Osch MJP, Duff EP, Carbonell F, Nickerson LD, Becerra L, Dahan A, Evans AC, Soucy JP, Wise R, Zijdenbos AP, van Gerven JM. Biomarkers, designs, and interpretations of resting-state fMRI in translational pharmacological research: a review of state-of-the-art, challenges, and opportunities for studying brain chemistry. *Human Brain Mapping.* 2017;**38:2276-2325**.

Klaassens BL, van Gerven JMA, van der Grond J, De Vos F, Möller C, Rombouts SARB. Diminished posterior precuneus connectivity with the default mode network differentiates normal aging from Alzheimer's disease. *Frontiers in Aging Neuroscience.* 2017; **9:97**.

Klaassens BL, Rombouts SARB, Winkler AM, van Gorsel HC; van der Grond J, van Gerven JMA. Time related effects on functional brain connectivity after serotonergic and cholinergic neuromodulation. *Human Brain Mapping.* 2017; **38:308-325**.

Kruithof AC, Watanabe S, Peeters PAM, de Kam ML, Zuiker RGJA, Stevens J, van Gerven JMA, Stockis A. Pharmacological interactions between brivaracetam and ethanol in healthy males. *Journal of Psychopharmacology.* 2017; **31:915-926**.

Landray MJ, Bax JJ, Alliot L, Buyse M, Cohen A, Collins R, Hindricks G, James SK, Lane S, Maggioni AP, Meeker-O'Connell A, Olsson G, Pocock SJ, Rawlins M, Sellors J, Shinagawa K, Sipido KR, Smeeth L, Stephens R, Stewart MW, Stough WG, Sweeney F, van de Werf F, Woods K, Casadei B. Improving public health by improving clinical trial guidelines and their application. *European Heart Journal.* 2017; **38:1632-1637**.

Continued on next page

Monnet E, Lapeyre G, van Poelgeest E, Jacqmin P, de Graaf K, Reijers J, Moerland M, Burggraaf J, De Min C. Evidence of NI-0101 pharmacological activity, an Anti-TLR4 antibody, in a randomized phase I dose escalation study in healthy volunteers receiving LPS. *Clinical Pharmacology & Therapeutics.* 2017; **101:200-208**.

Okkerse P, van Amerongen G, de Kam ML, Stevens J, Butt RP, Gurrell R, Dahan A, van Gerven JM, Hay JL, Groeneveld GJ. The use of a battery of pain models to detect analgesic properties of compounds: a two-part four-way crossover study. *British Journal of Clinical Pharmacology.* 2017; **83:976-990**.

Okkerse P, Hay JL, Sitsen E, Dahan A, Klaassen E, Houghton W, Groeneveld GJ. Pharmacokinetics and pharmacodynamics of intrathecally administered Xen2174, a synthetic conopeptide with norepinephrine reuptake inhibitor and analgesic properties. *British Journal of Clinical Pharmacology.* 2017; **83:751-763**.

Okkerse P, Alvarez-Jimenez R, Hay JL, Tehim A, Kumar R, de Kam ML, Groeneveld GJ. No evidence of potentiation of buprenorphine by milnacipran in healthy subjects using a nociceptive test battery. *European Journal of Pain.* 2017; **21:494-506**.

Reijers JAA, Moerland M, Burggraaf J. Remarkable pharmacokinetics of monoclonal antibodies: a quest for an explanation. *Clinical Pharmacokinetics.* 2017; **56:1081-1089**.

Reijers JAA, Kallend DG, Malone KE, Jukema JW, Wijngaard PLJ, Burggraaf J, Moerland M. MDCO-216 does not induce adverse immunostimulation, in contrast to its predecessor ETC-216. *Cardiovascular Drugs and Therapy.* 2017; **31:381-389**.

Schrier L, Zuiker R, Merkus FWHM, Klaassen ES, Guan Z, Tuk B, van Gerven JMA, van der Geest R, Groeneveld GJ. Pharmacokinetics and pharmacodynamics of a new highly concentrated intranasal midazolam formulation for conscious sedation. *British Journal of Clinical Pharmacology.* 2017; **83:721-731**.

Schutte T, Tichelaar J, Reumerman MO, van Eekeren R, Rissmann R, Kramers C, Richir MC, van Puijenbroek EP, van Agtmael MA. Pharmacovigilance skills, knowledge and attitudes in our future doctors - a nationwide study in the Netherlands. *Basic & Clinical Pharmacology & Toxicology*. 2017; **120:475-481**.

Simpraga S, Alvarez-Jimenez R, Mansvelder HD, van Gerven JMA, Groeneveld GJ, Poil SS, Linkenkaer-Hansen K. EEG machine learning for accurate detection of cholinergic intervention and Alzheimer's disease. *Scientific Reports.* **2017; 7:5775**.

Treiber A, de Kanter R, Roch C, Gatfield J, Boss C, Von Raumer M, Schindelholz B, Muehlan C, van Gerven J, JENCK F. The Use of physiology-based pharmacokinetic and pharmacodynamic modeling in the discovery of the dual orexin receptor antagonist ACT-541468. *Journal of Pharmacology and Experimental Therapeutics.* 2017; **362:489-503**.

Wilhelmus MMM, HAY JL, Zuiker RGJA, Okkerse P, Perdrieu C, Sauser J, Beaumont M, Schmitt J, van Gerven JMA, Silber BY. Effects of a single, oral 60 mg caffeine dose on attention in healthy adult subjects. *Journal of Psychopharmacology.* 2017; **31:222-232**.

Wopereis S, Stroeve JHM, Stafleu A, Bakker GCM, Burggraaf J, van Erk MJ, Pellis L, Boessen R, Kardinaal AAF, van Ommen B. Multi-parameter comparison of a standardized mixed meal tolerance test in healthy and type 2 diabetic subjects: the PhenFlex challenge. *Genes and Nutrition.* 2017; **12:21**.

van de Loo AJAE, Bervoets AC, Mooren L, Bouwmeester NH, Garssen J, Zuiker R, van Amerongen G, van Gerven J, Singh J, van der Ark P, Fedgchin M, Morrison R, Wajs E, Verster JC. The effects of intranasal esketamine (84 mg) and oral mirtazapine (30 mg) on on-road driving performance: a double-blind, placebo-controlled study. *Psychopharmacology.* 2017; **234:3175-3183**.

van der Kolk T, Dillingh MR, Rijneveld R, Klaassen ES, de Koning MNC, Kouwenhoven STP, Genders RE, Bavinck JNB, Feiss G, Rissmann R, Burggraaf J. Topical ionic contra-viral therapy comprised of digoxin and furosemide as a potential novel treatment approach for common warts. *Journal of the European Academy of Dermatology and Venereology.* 2017; **31:2088-2090**.

van Diemen MPJ, Berends CL, Akram N, Wezel J, Teeuwisse WM, Mik BG, Kan HE, Webb A, Beenakker JWM, Groeneveld GJ. Validation of a pharmacological model for mitochondrial dysfunction in healthy subjects using simvastatin: A randomized placebo-controlled proof-of-pharmacology study. *European Journal of Pharmacology.* 2017; **815:290-297**.

van Esdonk MJ, Burggraaf J, van der Graaf PH, Stevens J. A two-step deconvolution-analysis-informed population pharmacodynamic modeling approach for drugs targeting pulsatile endogenous compounds. *Journal of Pharmacokinetics and Pharmacodynamics.* 2017; **44:389-400**.

van Meir H, du Burck IJ, de Kam ML, Welters MJP, van der Burg SH, Trimbos JBMZ, de Kroon CD, van Poelgeest MIE. The identification of patients at high risk for recurrent disease after treatment for early-stage cervical cancer. *European Journal of Gynaecological Oncology.* 2017; **38:25-32**.

van Meir H, Nout RA, Welters MJP, Loof NM, de Kam ML, van Ham JJ, Samuels S, Kenter GG, Cohen AF, Melief CJM, Burggraaf J, van Poelgeest MIE, van der Burg SH. Impact of (chemo)radiotherapy on immune cell composition and function in cervical cancer patients. *Oncoimmunology.* 2017; **6:e1267095**.

Governing bodies

Supervisory Board
Frans Eelkman Rooda, MSc, MBA *(Chair)*
Dr Peter Leijh *(Vice-Chair)*
Dr Bernard Cohen
Dr Jan Hendrik Egberts
Prof Dr Marcel Levi

Executive Board
Prof Dr Koos Burggraaf, CEO
Dr Geert Jan Groeneveld, CMO / CSO
Dr Pierre Peeters, COO

Scientific Advisory Board
Prof Dr Noortje Swart *(Chair)*
Dr Bert de Boer *(Vice-Chair)*
Prof Dr Meindert Danhof
Prof Dr Piet Hein van der Graaf
Prof Dr Thomas Hankemeier
Dr Laura Heitman
Prof Dr Tom Huizinga
Prof Dr Ron Kloet
Prof Dr Cees Kluft
Prof Dr Cees Melief
Dr Ram Sukhai
Dr Rebecca ten Cate
Prof Dr Frans Zitman

Prof Dr Frans Zitman

Directors

Prof Dr Koos Burggraaf, Internal Medicine

Prof Dr Adam Cohen, InnoS

Prof Dr Joop van Gerven, CNS

Dr Geert Jan Groeneveld, CNS

Dr Gabriël Jacobs, Psychiatry

Dr Matthijs Moerland, Translational Biomarkers

Bart Mooy, MSc, RA, Finance

Dr Pierre Peeters, Operations

Dr Robert Rissmann, Dermatology

Dr Jeroen van Smeden, Education

Credits

Annual Report 2017

Text	Pieter van Megchelen
Editing	English Editing Solutions
Photography	Michiel Plas
	Rob Overmeer
Design	Just, Leiden
Print	Puntgaaf drukwerk, Leiden

CHDR
Centre for Human Drug Research

Centre for Human Drug Research
Zernikedreef 8
2333 CL Leiden
The Netherlands

+31 (0)71 5246400
info@chdr.nl
www.chdr.nl

chdr.nl