CHDR
Centre for Human Drug Research

Annual Report 2019

The Heart of Science

The front and back covers of this 2019 Annual Report depict the recently-installed sculpture *Heart of Science*, created for CHDR by Isabel Ruys.

Isabel Ruys (1957) trained as a physician in Leiden and worked at CHDR as a paediatrician for four years. Almost 20 years ago, she decided to pursue a career as a sculptor, and has been successfully doing so ever since.

The sculpture *Heart of Science* is a combination of high-tech and nature, medicine and heart, modern stainless steel and timeless bronze. The sculpture's form is reminiscent of a tablet or drug. The outer shape was designed with the help of computer technology and forged from stainless steel, a modern alloy. This shape is divided in two to reveal an encapsulated bronze heart at its centre, which is moulded from a knot of a 100-year-old linden tree that once grew in Leiden. The heart is cast in a bronze alloy made of copper and pewter, metals known for their use among early civilisations.

'The form of the sculpture expresses the innovation in medicine and pharmacology that CHDR brings forth. The heart of the sculpture symbolises the human healing made possible by CHDR's scientific work. With a history going back over 30 years, CHDR represents the scientific lifeblood at the heart of the Leiden Bio Science Park. I hope that *Heart of Science* will stand as a beacon of their work for many years to come.'

Isabel Ruys, May 2020

Foreword

2019 was another good year for CHDR. The organisation thrived on all relevant levels – operations, scientific output, education and finances. Several factors underpin this success, but in this year's Annual Report, we would like to highlight one factor in particular: our network of collaborators, both in the Netherlands and abroad. Their contribution to CHDR's data-rich early phase drug trials cannot be overstated. Thanks to these synergistic collaborations, our Clinical Scientists and their colleagues in method development and biomarker research can stay ahead of rapid developments in the pharmaceutical and biotech industries. This means that we can offer sponsors specific biomarker readouts which are tailored to their product, even if it is a first-in-class compound.

Collaborators fulfil a range of different roles in our work: contributing ideas and methodologies, participating in in-depth scientific discussions, helping to recruit patients, performing cutting-edge measurements and developing models to analyse data and prepare studies. Other collaborators are crucial to our educational activities, or to day-to-day operations. To showcase these vital contributions, this Annual Report includes interviews with a number of our collaborators. Of course, this is just a selection – we have many more valued collaborators, and we would like to take this opportunity to thank them all equally for their invaluable work.

As a growing organisation, we have recently implemented operational changes, with more changes still to come soon. We've also expanded our workforce, with many talented and enthusiastic people joining CHDR in 2019, a number of whom are interviewed in this Annual Report. One crucial decision taken in 2019 was to relocate some of the administrative teams to a nearby building. This move will provide CHDR – and particularly the Clinical Research Unit – with the necessary space to grow.

2019 also saw the establishment of our Management Team, which provides vital support as our operations expand in both scope and complexity. With their fingers on the pulse of the organisation, the members of the Management Team play a key role in operational planning and strategic decision-making. They also contribute to the changes that are needed as our organisation continues to grow. In many cases this has meant reviewing and refreshing our processes to improve efficiency and structure – the move to a cloud-based ICT infrastructure and the introduction of a comprehensive Enterprise Resource Planning system are just two examples. At the same time, however, we are all keenly aware of how important it is to maintain CHDR's unique, open organisational culture. Informal exchange, individual initiative and intrinsic motivation bring just as much value to our work today as when CHDR was founded.

While we were preparing this Annual Report, the COVID-19 pandemic swept across the planet, providing a stark reminder of the vulnerability of individuals, organisations and societies. As we scrambled to respond to these challenges, we were even more grateful for the spirit, commitment and resilience of our staff and the support of our network of collaborators. We will need this synergy and strength more than ever in the months and maybe even years to come. The pandemic has put the world economy under great strain, affecting almost everything we do. Amid these uncertainties, it is important to prepare CHDR for the challenges that we face until a resolution to the pandemic is found. Thanks to CHDR's financial health, we have been able to invest – and will continue investing – in measures to optimally serve our clients. These investments include expansion of our clinical capacity, capabilities for at-home monitoring of study participants, and top-notch facilities for virtual meetings. These initiatives, together with risk-mitigation measures, help ensure the business continuity of CHDR, allowing us to play our role as a key contributor to innovations in global health.

As always, we remain committed to our social responsibility, devoting ourselves to our mission to translate cutting-edge scientific progress into tangible improvements in medical care. This dedication is embodied by the sculpture featured on the cover of this Annual Report, *The Heart of Science*, which was installed in front of our building in 2019.

We would like to thank everyone who plays a role in our endeavours, from the patients and volunteers who participate in our studies, to our sponsors, our staff and our collaborators.

Leiden, May 2020

Prof. Koos Burggraaf, CEO Dr Geert Jan Groeneveld, CMO/CSO

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The year in perspective

2019 was another dynamic year for CHDR on many levels. The organisation continued to evolve, while staying true to its roots: a science-driven contract research organisation dedicated to operational excellence, where talented people love to work, teach and learn together.

Thriving in a network of collaborations

CHDR's Executive Board can once again look back on a prosperous year, with a range of operational and scientific successes. Organisational changes were brought in to accommodate and consolidate the growth of recent years, and steps were taken towards a much-needed expansion of the Clinical Research Unit. Directors Prof. Koos Burggraaf (CEO) and Dr Geert Jan Groeneveld (CMO/CSO) are proud of the organisation's accomplishments, but are quick to emphasise the roots of CHDR's success in its vibrant collaborative networks across industry and academia.

'Our stakeholders are our raison d'être,' says Burggraaf, CHDR's CEO. 'Improving patients' quality of life, educating clinical and life-science professionals, contributing to the scientific community and delivering value for our sponsors – these are the concerns that drive us.' 'That's why we've always nurtured our collaborative networks, which extend far into research and healthcare,' adds CMO/CSO Groeneveld, who is also in charge of operations. 'Thanks to these collaborations, we're able to deploy cutting-edge methods to test new treatments, both in healthy volunteers and in patients. These connections also help us attract bright young professionals who bring vitality to our research and operations. People who undertake PhD research at CHDR often have a thesis adviser at one of the nearby universities, which continually reinforces our links with academia.'

Thriving collaborations with clinicians in various fields play a key role in CHDR's work on treatments for a range of diseases. Successful patient studies of recent years have been made possible by the dedication of networks of dermatologists (such as CONNECTED, see page 62), neurologists (as in the Parkinson's disease studies, see page 40) and mental healthcare professionals (such as Transparant, see page 54). Besides providing essential clinical experience and expertise, these clinical networks play an important role in recruitment.

Situated in the middle of the so-called Randstad area – an urban agglomeration which is home to more than 8 million people – CHDR's location is particularly beneficial for reaching out to professional networks, as well as for attracting research talent and recruiting study participants. At the heart of Leiden's Bio Science Park, CHDR is just a stone's throw from Leiden University with its prestigious Academic Centre for Drug Research (LACDR) and the Leiden University Medical Center (LUMC). Within an hour's drive are the cities of Amsterdam, Rotterdam and Utrecht, all of which have highly-ranked universities with renowned university medical centres. Complementing these key academic and clinical partners are the many vocational training colleges in the region, some specialising in healthcare training. And just across the road from CHDR, the life sciences division of the Netherlands Organisation for Applied Scientific Research, TNO, is currently building its new headquarters, promising new opportunities for collaboration in coming years.

Accommodating growth

'We're in an excellent position to contribute to cutting-edge drug development, as demonstrated by our growth in recent years,' says Burggraaf. As CHDR is a not-for-profit foundation, investing 10% of its turnover into its own R&D Fund, this recent growth has offered the organisation many opportunities. But of course, growing brings new challenges too. Groeneveld: 'This period of rapid growth has been an interesting time, raising issues that range from the practical to the managerial. The most pressing practical questions at the moment concern building capacity. Although operating at full capacity means we're maximising resources, being fully booked can have a negative impact on our ability to be flexible. That's why we've taken the decision to relocate some of our administrative teams to a nearby building. Once this move takes place in 2020, we'll be free to start converting the vacated office space into an expanded Clinical Research Unit.'

After the expansion, CHDR's Clinical Research Unit will have 74 beds instead of the current 60: an increase in capacity of almost 25%. 'Of course, things won't stop there. We're continuing to plan how we will accommodate growth in the years ahead. One option on the table is of course to scale up our premises with new buildings, but there are other possibilities too, such as relocating some of our activities to hospitals in the vicinity. Trial@home, our integrated approach for conducting outpatient studies, also has an important role to play here: the more we can safely and effectively conduct studies off-site, the less pressure there is on the Clinical Research Unit,' says Burggraaf. 'In any case, operational capacity looks like it will be high on the agenda for some years to come.'

Several organisational changes took place in 2019, aiming to support growth and streamline operations. A Management Team was established, consisting of Financial Director Bart Mooy, Human Resources Director Yvette Akkermans, Compliance Director Margreet Rienstra, Director of Clinical Operations Ard Vink and Technology Director Bart van der Kroef. Changes have also taken place at the Board level. Burggraaf: '2019 saw the departure of our COO Dr Pierre Peeters, whom we like to thank for his contributions during the seven years that he served CHDR. After extensive discussions with

our Supervisory Board and our Management Team, the decision was taken to share the operational responsibilities between Geert Jan and myself for the time being. In our Board roles we can also rely on the support of the Management Team.'

Supporting success

A natural consequence of the growing number of studies conducted at CHDR is an increase in research output. Groeneveld: 'The number of scientific publications continues to grow. Of course, it's important that our staff – especially our project leaders – maintain a good balance between their operational duties and their research activities. With the help of Karen Broekhuizen, our medical writer, staff are able to produce timely manuscripts while still staying on top of operations. Thanks to Karen's systematic approach, we have also been able to identify a number of potential new publications based on studies that have already been carried out.'

At the end of 2019, CHDR had 36 project leaders, and this number is expected to grow to more than 40 in 2020. Project leaders are an essential part of operational activities, but at the same time, they play a vital role in generating the research output which places CHDR at the cutting edge of early-phase drug development. Many of these project leaders go on to pursue careers elsewhere, becoming medical specialists or scientists at other organisations. Others stay to build their career at CHDR, or return to the organisation at a later stage in their professional lives. In 2019, new career paths were developed to provide senior scientists with a clear professional pathway (see also page 122). Groeneveld: 'We now offer career development plans for scientists with different backgrounds, incorporating new functions such as Associate Director and Associate Research Director. These new roles have concrete descriptions, providing clarity for those wishing to attain these positions.'

A crucial component of both scientific and operational excellence is the efficient collection, analysis and management of quantitative data. Until now, this vital role has been shared between the Statistics and Pharmacometrics groups. Groeneveld: 'In 2019, we merged these to form one SPx group, which is led by Dr Kirsten Bergmann. She's now reviewing their procedures, checking where validation of statistical steps is necessary.'

Future directions

'Recent reports show that the market for CROs is expected to grow in coming years. This is particularly true for CROs who specialise in early-phase clinical drug development,' says Groeneveld. 'We are constantly evaluating how best to position ourselves in this growing international market. Of course, we will continue to do what we're best known for: innovating, validating and deploying state-of-the-art methods to explore the pharmacology of new compounds in the early stages of clinical drug development. But we're also looking to broaden our scope, for example by including new therapeutic areas.'

One potential new therapeutic area for CHDR is the treatment of cancer. 'In the past, oncology was off-limits for us, because it was synonymous with toxic chemotherapeutics that were never tested in healthy volunteers,' says Burggraaf. 'But in the last decade, this picture has been changing rapidly. In fact, we have already performed a number of interesting studies in this field. An inventory of those studies, made by our Associate Research Director Dr Naomi Klarenbeek, reveals that our efforts in this area already cover quite a wide range – there's work by Dr Robert Rissmann and Dr Matthijs Moerland studying various treatments for HPV-induced tumours, and of course, Matthijs' work in immunology is closely related to the kind of immunotherapy currently being developed in oncology. We also have an ongoing collaboration with the LUMC Surgery department on image-guided surgery, which chiefly concerns the treatment of cancer. Another area we're considering expanding into is the treatment of infectious diseases – the importance of which has proven itself very clearly in recent times.'

Whatever strategic choices CHDR ultimately makes, the organisation remains committed to supporting the development of innovative treatments, to improve the lives and prospects of patients worldwide. Burggraaf: 'Both the world of our clients and the world of science are undergoing rapid changes. On the one hand, we're seeing technological development continue at an unprecedented pace; on the other hand, societal demands are evolving in unforeseen ways. Our strength is our flexibility and creativity: not only can we quickly adapt to a changing world, but as innovators we can lead the way forward. Of course, none of this is done in isolation. Achieving progress in science is a joint effort, which is why collaboration will always remain one of CHDR's core values as an organisation. Whatever form our future endeavours take, effectively responding to the needs of our sponsors and connecting with our networks of expertise will remain the key ingredients of success.'

'Scientific progress is a joint effort - that's why collaboration will always remain one of CHDR's core values'

Corporate social responsibility

'We want to contribute to society on many levels,' says Burggraaf. 'Of course, we play a role in developing treatments that can change the lives of people worldwide, but we find it important to be a force for good closer to home as well. We are one of the benefactors of the Boerhaave Museum, Leiden's museum for the history of science. Following a complete renovation in the last couple of years, the Boerhaave Museum won the 2019 European Museum of the Year Award. And our commitment to the museum is not just financial – we're also pleased to be able to lend our expertise. Geert Jan Groeneveld will be a guest curator for one of the Museum's exhibitions in 2020.'

CHDR is also looking for ways to minimise its environmental impact as an organisation. Recent steps include the elimination of single-use plastic utensils from the cafeteria and the introduction of a weekly Meatless Monday. 'As an organisation, it's important not to lose sight of the myriad ways we can be a positive influence on the world around us. Besides our core mission of contributing to better healthcare, medical science and education, we are sensitive to the need to run operations in a way that's sustainable in the long term. We have our open, collaborative culture to thank for this, too: with many minds thinking together, we can always find creative ways to do what we do even better.'

Dr Jeroen van der Grond, associate professor of Radiology and head of the Research Consultancy Center, Leiden University Medical Center

'We cherish our collaborative relationship with CHDR'

'We perform studies with CHDR on a regular basis,' says Dr Jeroen van der Grond, radiologist at the Leiden University Medical Center (LUMC). Alongside his associate professorship in Radiology, Van der Grond is also head of the Radiology department's Research Consultancy Center (RCC). 'The RCC is involved in all the scientific research conducted by the Radiology department, including our contract research. Our staff are trained in Good Research Practice, and offer advice on study design. We're also responsible for quality assurance, data integrity, optimal image processing and statistical analysis.'

CHDR's collaboration with the LUMC Radiology department mainly concerns MRI scanning. 'We have a 3T MRI scanner which is dedicated to research, meaning that we can schedule scan time as we wish without interfering with clinical activities. If we get a request to scan in two weeks, all we have to do is check our calendar to see if there's availability,' says Van der Grond. 'Our research scanner is also located separately from the regular diagnostic scanners. It has dedicated clinical research rooms for taking blood samples and other tests, and with CHDR these are typically used for conducting NeuroCart testing.

'We provide a range of different services to CHDR. For some studies we just deliver images, while for others, we provide additional analysis. Thanks to scientific progress, there are increasingly sophisticated techniques available for analysing images. I'm really excited about the use of artificial intelligence in this field, which will revolutionise our work in the coming years. The RCC also provides consulting services – such as attending teleconferences between CHDR and a sponsor to support discussions about study design. We're also able to offer radiological support – for example, scanning potential study subjects if there are specific MRI criteria for selection.

'Much of our collaborative work focuses on the central nervous system, but we can perform scans of any body part: thorax, abdomen, finger joints – you name it! Our team has a broad range of experience – whatever CHDR has asked us for, we've always been able to deliver.' In addition to the wide range of services that Van der Grond and his team provide to CHDR, the two organisations also engage in collaborative work to achieve shared scientific goals. These common interests include the development of resting-state fMRI as a tool for pharmacological research, and the use of fMRI in the study of Alzheimer's disease. Van der Grond: 'For us, the relationship with CHDR represents more than just service provision or research collaboration. We cherish our personal contact with the people at CHDR – we're friends, keen to work together on shared interests.'

Linda van der Hulst, trial manager, Central Pharmacy of the Leiden University Medical Center

'People often see me as part of CHDR'

The Pharmacy department of the Leiden University Medical Center (LUMC) is an important partner for CHDR. Not only does the pharmacy deliver all the study medications used in CHDR's trials, but there are also a range of collaborative projects in research and education. Linda van der Hulst, the pharmacy's trial manager: 'CHDR has no pharmacy or storage facilities of its own, so all trial medication is supplied by our department. Sometimes, it's just a matter of delivering pre-packaged drugs. Most of the time, however, there are more complex requirements such as blinded repackaging, preparation for use, or even manufacturing. In some of CHDR's first-in-human studies, for example, we receive the active pharmaceutical ingredient (API) and produce the capsules containing either placebo or a dose of the investigational compound. Once the data have been analysed, we prepare the next dose. Occasionally, we manufacture the compound here in our GMP-compliant facility.'

Van der Hulst became trial manager at LUMC's Central Pharmacy in 2009. All medication for trials at the LUMC and studies at CHDR fall under her responsibility. Over the years, the number of studies conducted at CHDR has grown rapidly. 'Our workload has increased as well, so we've hired extra personnel. The knock-on effect of this is that the pharmacy has the capacity to offer more services. For example, we're now open during the weekends too. It's a dynamic, enjoyable job.'

Studies at CHDR, especially those with healthy volunteers, differ from most in-house patient trials at LUMC in that the timelines are much faster. Van der Hulst: 'In a patient trial, the medication is only needed as and when new patients agree to participate. Healthy volunteer studies, by contrast, follow a tight schedule. So if anything goes awry – say, if we don't receive the medication in good time – we work hard to try and make sure that the first dose can still be given according to schedule, while still abiding by the strict rules of Good Manufacturing Practice.' Van der Hulst has a tradition of giving new project leaders at CHDR a tour of the LUMC pharmacy, so that they are aware of all the steps required to deliver study medication to schedule.

The way Van der Hulst talks about the planning of clinical trials, you could be forgiven for thinking she's a member CHDR's staff. 'Yes, staff members at CHDR often think that! It's good to be part of the community,' she says. 'I enjoy being involved in these studies. By making sure things operate smoothly at the LUMC, I feel I'm contributing to the success of operations at CHDR too.'

Prof. Gerard van Westen, professor of AI and Medicinal Chemistry at Leiden University and the Leiden Academic Centre for Drug Research

'Our AI tools and CHDR's rich datasets are a perfect match'

'My primary research interest is the use of computational methods in drug development,' says Prof. Gerard van Westen, whose work focuses on computational drug discovery including the application of artificial intelligence approaches. 'We use AI approaches to tackle various problems in drug discovery, such as getting a handle on the enormous space of possibilities when it comes to chemical compounds. The number of possible organic compounds is in the order of magnitude of 10^{33}, far more than anyone could dream of analysing in a lifetime. With our algorithms, however, we can generate new molecules and select those that interact with a specific target,' says Van Westen. 'We're also interested in the later stages of the drug development process, including clinical drug development. In our collaboration with CHDR, we have the interesting task of developing methods to analyse their trial data.'

In recent years, Van Westen has been involved in the analysis of various datasets at CHDR, along with his PhD student Hein van der Wall, who is co-supervised by CHDR's Dr Robert-Jan Doll and Prof. Koos Burggraaf. As part of this work, Van Westen and Van der Wall contributed to the analysis of ECG data gathered in the course of screening volunteers, as described by Dr Pim Gal on page 77. Currently, they are analysing a skin microbiome dataset collected by Dr Robert Rissmann and his team, looking for correlations between microbiome composition and specific skin conditions such as eczema.

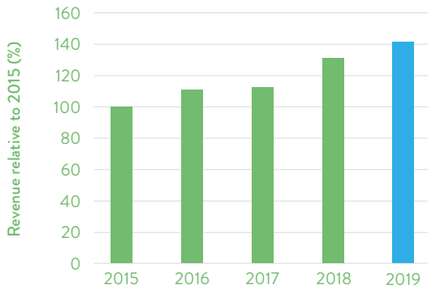
'Computational approaches such as machine learning have diverse applications, depending on the question you want to answer,' says Van Westen. 'In some cases, we can build a model to predict certain events, which can help to improve different aspects of trials, including safety. But these approaches can equally be used to explore datasets that have already been gathered. Both of these dimensions can be beneficial for CHDR, and I enjoy the opportunity to contribute to addressing problems on the practical side of drug development.

'At Leiden University, there are various groups working on novel computational approaches, including AI, across the whole spectrum from social sciences to natural sciences and mathematics. Our university participates in many European-level projects, developing what's known as human-centred AI. It's crucial to maintain this human-centred perspective, in order to anticipate issues relating to the practical application of these techniques in society. Key considerations here include the conditions for societal acceptance, such as explainability and accountability,' says Van Westen. 'Those aspects certainly have relevance for clinical drug development, too. This further underscores the value of the collaboration for both us and CHDR, as we look to a future where AI plays an increasingly central role.'

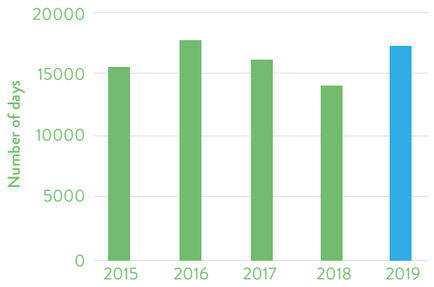
2019 at a glance

Learn about the breadth and depth of CHDR's activities in 2019 in the next few pages, and experience CHDR's unique perspective on early-phase drug development. Find out about the key areas of research and innovation, and the dynamic networks that help to make it happen.

CONTRACT REVENUE



ACCOMMODATION DAYS



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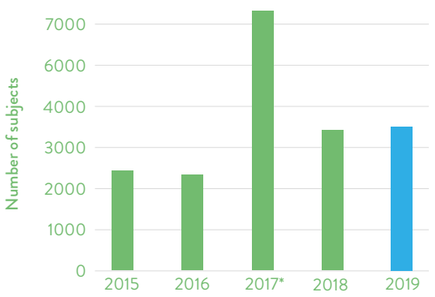


*includes approximately 4000 patients with Parkinson's disease

OVERALL CLIENT SATISFACTION

8.4

★★★★½

2019 IN NUMBERS

54 studies

38 contracts signed

58 articles published

4 PhDs graduated

> 33,000 volunteers available

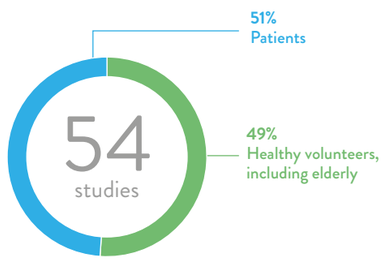
> 19,000 patients available

17 nationalities

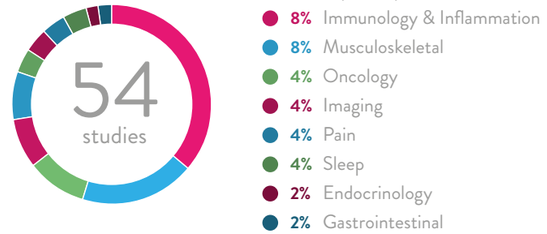
6% turnover of clinical research staff

17% growth in personnel

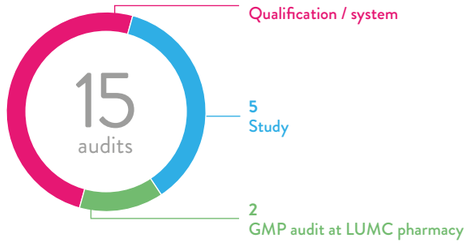
STUDIES WITH SUBJECTS



STUDIES PER RESEARCH AREA



EXTERNAL AUDITS



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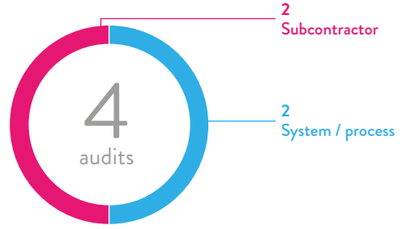

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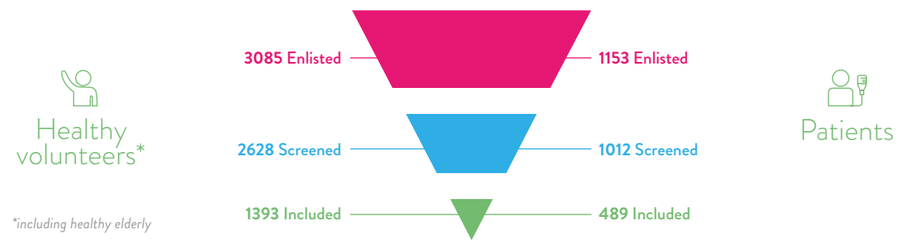
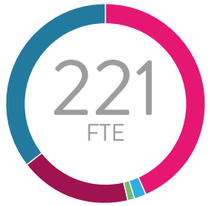


EMPLOYEES BY DEPARTMENT



- 43% Clinical operations
- 2% Education
- 1% Executive & Supervisory Board
- 18% Internal services
- 35% Science & Research

CLINICAL RESEARCH STAFF

- 4% Prof
- 59% MD
- 32% PhD
- 100% MSc
- 16% Clinical Pharmacologist
- 47% Clinical Pharmacologist in training

TYPES OF PATIENTS

- 21% Parkinson's disease
- 9% Major depressive disorder
- 9% Atopic dermatitis
- 6% HPV-induced lesions
- 6% FSHD
- 3% Actinic keratosis
- 3% Alzheimer's disease
- 3% Amyotrophic lateral sclerosis
- 3% Atopic diathesis
- 3% Colorectal cancer
- 3% Cutaneous T-cell lymphoma
- 3% Episodic migraine
- 3% Essential tremor
- 3% Facial seborrhoeic dermatitis
- 3% Inflammatory acne
- 3% Non-alcoholic steatohepatitis
- 3% Opioid tolerance
- 3% Osteoarthritis
- 3% Ovarian cancer
- 3% Overuse tendinopathy

TYPES OF STUDY

- 23% Single ascending dose
- 21% First-in-human
- 13% Multiple ascending dose
- 10% PK/PD
- 6% Biomarker
- 6% Food effect
- 4% Drug-drug interaction
- 4% Exploratory
- 4% Proof-of-concept
- 2% Biocomparison
- 2% Driving
- 2% Ethanol interaction
- 2% Method development

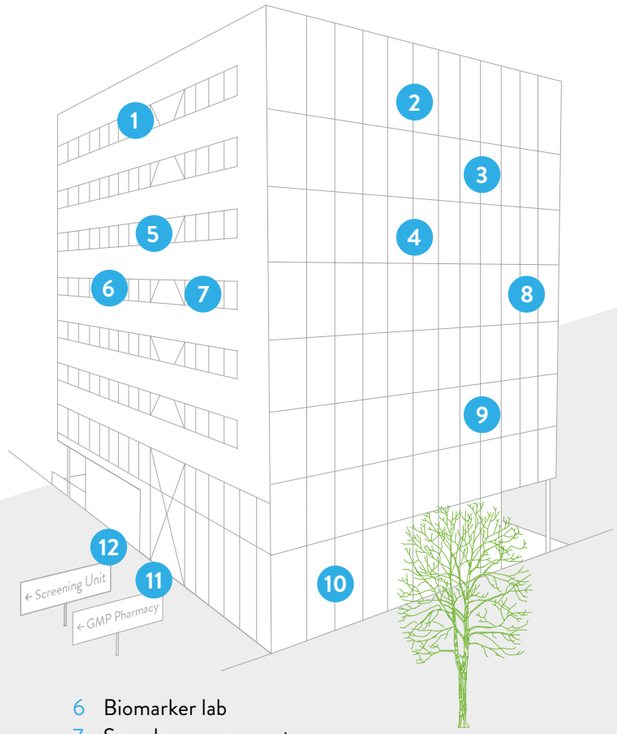
Designed to facilitate research

Our facility is purpose built to streamline everything we do. From our modern First-in-Man unit and top-notch volunteer accommodation, down to dedicated research rooms and efficient sample management, our key processes inspire the unit's design.

With a light and open work environment, we aim to stimulate collaboration and innovative thinking. Our modern office space offers flexible working and meeting areas, and a dedicated auditorium for educational activities.

Let us show you around.

Start the video tour



1 Private volunteer accommodation & research rooms
2 Volunteer relaxation
3 CNS Multifunction research rooms
4 Multifunction research rooms
5 First-in-Man unit
6 Biomarker lab
7 Sample management
8 Recruitment department
9 Open office space
10 Auditorium
11 GMP Pharmacy
12 Screening Unit

A full-service clinical research organisation

Collaborative patient networks

CHDR's strategic location and collaborations with top medical centres across the Netherlands provide a rich environment for knowledge exchange, as well as aiding the recruitment of diverse patient populations.

- **Dermatology (CONNECTED)**
  LUMC (Leiden), Erasmus MC (Rotterdam) & 10+ dermatological clinics
- **Vascular medicine & inflammation**
  Amsterdam UMC
- **Immuno-oncology**
  LUMC, Amsterdam UMC
- **Parkinson's disease**
  LUMC, Alrijne Hospital, UMCG (Groningen), Erasmus MC, Amsterdam UMC, St Antonius Hospital (Nieuwegein) and Meander MC (Amersfoort)
- **Huntington's disease**
  LUMC
- **Amyotrophic lateral sclerosis**
  UMC Utrecht
- **Mood, anxiety and stress-related disorders**
  LUMC, Transparant Centre for Mental Health (Leiden), Netherlands Organisation for Scientific Research

...and many others.

Early-phase drug development

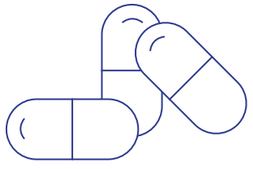
CHDR PERSPECTIVE

At CHDR, the early stages of clinical drug development are seen as vital opportunities to learn more about a compound, gaining valuable insights that make the next steps smoother, safer and more successful. Building on the results of preclinical studies, the candidate drug's pharmacology and putative mechanism of action are investigated thoroughly in human subjects. This prepares the ground for well-informed larger clinical trials, or provides the information needed to decide on other options. Learn more about CHDR's unique perspective on early-phase drug development on page 30.

Method validation

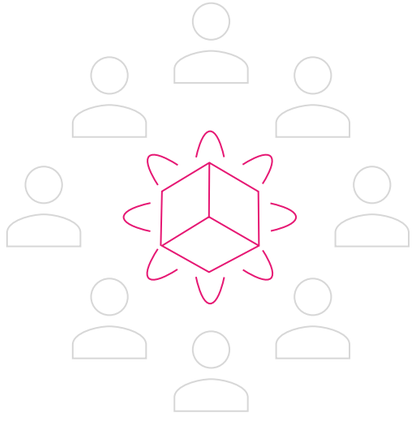
HEALTHY VOLUNTEERS (SAFETY / PKPD)

Single ascending dose



Multiple ascending dose

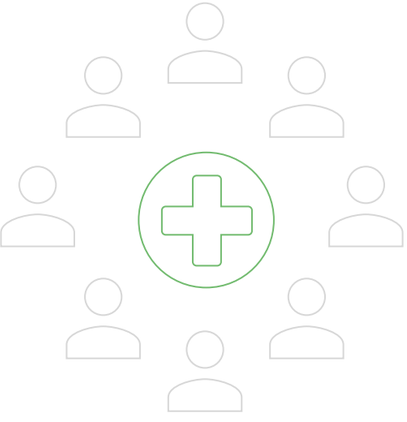
INTERMEDIATE POPULATIONS



Pharmacological challenges

Behavioural challenges

TARGET POPULATIONS (MONOCENTRE APPROACH)



Surrogate endpoints in patients

Efficacy in patients

POP: Proof-of-Pharmacology

POM: Proof-of-Mechanism

POC: Proof-of-Concept

Information-rich clinical trials

Early-phase drug development offers a unique opportunity to gain deep insight into both intended and unintended effects of new compounds. The typically small number of subjects per study means that these effects can be examined in intricate detail. Moreover, at this stage of development, the candidate drug is administered in a wider range of doses than at any subsequent point in clinical research or practice, using a **single ascending dose (SAD)** or **multiple ascending dose (MAD)** regimen. The potential for early-phase trials to yield detailed insight into new compounds is enormous, and yet this opportunity is rarely exploited: most first-in-human trials focus exclusively on toxicity, safety and pharmacokinetics.

Since its founding more than three decades ago, CHDR's mission has been to perform data-rich trials that increase subject safety and offer clients the chance to gain more detailed knowledge about their products. The CHDR perspective on early-phase drug development is defined by the quest for both safety and insight, and this integrated approach can be seen across the many services CHDR offers. This includes the in-house Cardiology Services, where advanced analyses of the cardiovascular effects of novel drugs are leveraged not only to better assess safety but also to learn more about the compound under study.

Questions and methods

Fundamental to CHDR's philosophy is the belief that trials should be about answering questions, not just ticking boxes on a linear path towards market authorisation or failure. Using a systematic and critical evaluation of the available (preclinical) knowledge about a compound, experiments are designed around essential questions, such as: does the compound reach the site of action? Does the compound have the intended effects?

The **question-based drug development (QBD)** approach at CHDR is supported by an extensive range of methods. CHDR reinvests 10% of its turnover to fund in-house R&D, with a focus on the **development and validation of methods** to measure drug effects. This ceaseless process of innovation keeps CHDR in sync with the latest developments across the biopharmaceutical industry.

CHDR's clients can choose from a wide variety of readouts to measure the effect of their compound. Effect readouts include state-of-the-art laboratory biomarkers, (neuro)physiological and behavioural measurements, and imaging. In this way, even in first-in-human trials, data can be gathered about drug effects (**pharmacodynamics**) in relation to drug concentrations (**pharmacokinetics**). In some cases, clients (co-)fund the validation of a specific biomarker to better measure their compound's effects.

CHDR's question-driven, data-rich approach also has important advantages for **subject safety**. The systematic review of preclinical data using CHDR's IB-Derisk analyser facilitates safe trial design, while the use of biomarkers enables the early recognition of adverse drug effects.

CHDR PERSPECTIVE

Challenges

In some cases, a compound has no measurable effects in healthy individuals. To still be able to gather relevant data from healthy volunteers, CHDR makes use of **pharmacological and behavioural challenges** to mimic particular symptoms or physiological disturbances. Prior to administering the investigational compound, subjects are given a substance that induces the physiological state or symptom of interest. Alternatively, a behavioural task or intervention is applied that changes the subject's homeostatic functioning. If the investigational compound is able to redress the symptom or disturbance, this is a promising sign that it will be effective in treating the same symptom in patients.

Such **intermediate studies** – between first-in-human studies and studies in patients – are sometimes also performed in specific populations. For example, to study candidate drugs for Parkinson's disease, Alzheimer's disease or other conditions primarily occurring in people over 60, intermediate studies are performed in healthy volunteers of the same age group. In combination with challenge tests, these trials reveal a comprehensive picture of the compound's properties before embarking on patient studies.

These intermediate studies and their sophisticated readouts, rooted in a thorough understanding of the underlying physiology, are a hallmark of CHDR's approach. Clients can use the results of these studies to decide how to proceed with clinical development. Meanwhile, ongoing method development and validation studies continue to improve and expand the range of possibilities for such trials.

Patients

CHDR conducts research in an ever-expanding variety of patient groups, in order to investigate the potential of a given drug in its target population. In addition to innovative methods for exploring effects using **surrogate endpoints**, CHDR has various strategies to add value in this step.

- The **Ready-for-Research approach** means that cohorts of patients have already been identified and characterised, for swift study recruitment where patients with a specific diagnosis and disease characteristics are required.
- Besides studies in the Clinical Research Unit, remote monitoring with the **CHDR MORE® platform** makes it possible to collect naturalistic data while patients go about their day-to-day lives. MORE® is implemented as part of CHDR's overall strategy for conducting outpatient studies, **Trial@home**.
- CHDR's **Monocentre approach** brings patients to one central facility instead of conducting trials across several locations. Multicentre approaches face limitations on the range of possible tests, and introduce extra variability resulting in unnecessary noise in the data. By contrast, the Monocentre approach promotes sophisticated, precise measurements, with everything taken care of under one roof by dedicated teams.

Data-rich studies provide clients with broader and deeper insights into a compound's pharmacology, its therapeutic potential, and of course, its risks. As the costs of large clinical trials continue to rise, information-rich early-phase studies promise more value than ever before.

Neurology and Pain

The increasing number of patients with neurodegenerative conditions and pain calls for innovative solutions. In the clinical development of new treatments, CHDR uses novel approaches such as virtual reality for pain research and transcranial magnetic stimulation to study brain excitability, in addition to the tried-and-tested NeuroCart® and PainCart® test batteries.

Future-focused neurology and pain research

Together with sponsors, CHDR continues to invest in innovative neurology and pain research. A key achievement in recent years has been the establishment of a large cohort of genotyped Parkinson's patients, which was made possible by the collaboration of neurologists throughout the Netherlands. Work has also continued on the validation and expansion of PainCart®, CHDR's unique toolbox of tests for pain research. Meanwhile, new techniques are currently under development for the study of neurodegenerative diseases. In 2019, this future-focused research approach attracted yet more interesting projects and collaborations.

'I'm proud of what our team has accomplished,' says Chief Medical Officer / Chief Scientific Officer Dr Geert Jan Groeneveld, who also heads the Neurology and Pain group. 'We conducted more studies than in 2018, including both sponsored and self-funded studies. Due to my role on the Board, my personal involvement in these studies is of course less than it used to be. However, our senior scientists and the rest of the team have adapted well to the new situation and CNS research continues to be one of the pillars of CHDR's work.'

PainCart

The success of pain research at CHDR shows the value of persistence. Just a few years ago, the PainCart® – a unique battery of evoked pain model tests – only featured in self-financed validation studies using well-known analgesic compounds. Despite its potential for data-rich insights, sponsors rarely showed interest in incorporating the PainCart into their studies. Nonetheless, with a firm belief in PainCart's capacity to benefit research, the team continued to invest in the tool and publish studies demonstrating its performance. Things began to change once the publications of Groeneveld and his group started to attract the attention of sponsors and the pharmaceutical industry. CHDR's pain researchers have since been involved in the early-stage clinical development of several new compounds, some of them with unique mechanisms of action. One novel compound tested in 2019 was an antibody acting on inflammatory pathways in the body. The hope is that this compound could be used not only in pain caused by inflammation, but possibly also in neuropathic pain. Recent research on neuropathic pain has shown that neuro-inflammation is involved in the pathogenesis and persistence of the condition.

Nowadays, the search is on for compounds that can replace opioids – ideally, compounds that have an equally strong impact on pain, but without the addictiveness, respiratory depression and drowsiness that make opioids so problematic. In a study conducted in 2019, a dual enkephalinase inhibitor (DENKI) - a potential alternative to opioids - was given to human subjects for the first time. Enkephalinases are enzymes involved in the degradation of endogenous enkephalins, the naturally occurring painkillers in our brains. Reducing the elimination of enkephalins should increase their availability, strengthening the brain's own mechanism for dealing with pain. Studying this DENKI compound meant thinking creatively to overcome design challenges. Groeneveld: 'PainCart measurements need to be compared within subjects, due to the natural variability in pain thresholds between subjects. PainCart can therefore be used in a first-in-human study with a single ascending dose, but only as long as it is possible to use a design that allows for within-subject comparison. To achieve this for the DENKI compound, we used a leapfrog design.' A leapfrog design employs a dosing regimen that alternates between cohorts as it increases: the first cohort receives a dose, the second cohort gets a higher dose, then the first cohort is tested again with yet a higher dose, and so on. The basic principle is thus the same as in a regular single ascending dose (SAD) study, but through the 'leapfrog' principle, the reaction to one dose of the drug and the reaction to placebo can be compared within an individual subject. This is essential when the variability of a certain pharmacodynamic measurement (in this case, thresholds for evoked pain) varies considerably more between subjects than within subjects. The advantage of this design, therefore, is that it allows ascending dose levels to be tested sequentially, while also allowing within-subject comparisons between the compound and placebo.

In 2020, CHDR hopes to investigate yet another intriguing compound, a so-called biased opioid agonist. Groeneveld: 'Like regular opioids, it engages the mu opioid receptor. However, it does so in a way that is biased towards one of the downstream pathways – namely, the one leading to analgesia – and circumvents some of the unwanted side effects of opioids. It's promising not only as a potential way to reduce pain without the other effects of normal opioids, but also as a way to do so without leading to tolerance, which typically arises in chronic treatment with morphine. We're looking forward to the chance to explore this interesting new candidate analgesic drug.'

Preventing respiratory depression

Even if alternatives do become available, opioids will still be part of the pharmacological landscape for a long time to come. These compounds represent a valuable tool in pain management and anaesthesia, and of course,

opioid abuse is expected to remain a widespread problem. One of CHDR's many long-established collaborations is with Prof. Albert Dahan of the Leiden University Medical Center (LUMC) Anaesthesiology department, who has been investigating opioids for many years. Prof. Dahan's research primarily focuses on the effects of opioids on breathing. Due to their effect on the part of the brain which regulates breathing, opioids in high doses can lead to potentially fatal respiratory depression. This is the main cause of death in the case of an opioid overdose.

In 2019, Dahan collaborated with CHDR to perform a study on the partial opioid receptor agonist buprenorphine, assessing its potential for preventing fatal respiratory depression in opioid addicts. People who regularly use opioids gradually become accustomed to the depressive effects on breathing, meaning that they can tolerate quite high doses. However, if they start using again after a period of abstinence, they are once again at risk of overdosing and suffering from fatal respiratory depression. This study aimed to establish whether buprenorphine could prevent this. Groeneveld: 'This is a textbook example of how a partial agonist can work as an antagonist at high dose levels. Buprenorphine has a very high affinity for the mu opioid receptor – which is involved in many of the effects of opioids, including respiratory depression – but it is a partial agonist. If you give someone enough buprenorphine, all mu opioid receptors will be occupied, so even a very potent opioid such as fentanyl won't be able to activate enough new opioid receptors to cause fatal respiratory depression.' Read more about this interesting approach, as well as the outcomes of the study, in the interview with Prof. Dahan on page 38.

Parkinson's disease

A few years ago, CHDR became involved in the development of a next-generation treatment for Parkinson's disease (PD), aimed at a subgroup of PD patients with a mutation in the GBA1 gene. To find PD patients with this specific mutation, it was necessary to genotype a large group of PD patients. This resulted in a fruitful collaboration with many neurologists throughout the Netherlands, and the establishment of a large cohort of PD patients with known genotypes and phenotypes. 'Just as we hoped, more and more companies developing new treatments for PD are finding their way to CHDR. In the past year, we've launched no fewer than seven clinical PD studies, with both symptomatic treatments and disease-modifying therapies. In some of these, we were able to undertake the entire early-phase development process, from first-in-human work in healthy volunteers to early studies in patients.'

The study involving PD patients with GBA1 mutations has given rise to a collaboration with PD researchers at the LUMC's Neurology department. Groeneveld: 'Prof. Bob van Hilten at the LUMC is one of the authorities in the field of PD research. He is currently establishing a new research cohort of 1,250 PD patients, who will be genotyped and phenotyped in depth using a variety of techniques. As a collaborator in that study, we will also be able to draw on this well-described patient cohort for recruitment in our own studies.' Learn more about collaborative PD research between CHDR and the LUMC in the interview with Prof. van Hilten on page 40.

ALS and Huntington's disease

In addition to PD studies, CHDR also aims to contribute to the development of therapies for other neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS). There are an increasing number of compounds being developed that focus on pathways leading to ALS. One such pathway concerns an integrated stress response which may be the result of problems with protein synthesis in the cell. As a result of this response, cells can go into necroptosis, a form of semi-programmed cell death. In the case of ALS, this happens in the motor neurons, causing the characteristic signs of this disease. Groeneveld: 'Last year we investigated a compound that aims to stop this stress response. We hope it will be able to help the motor neurons to remain active longer, and to slow down the necroptosis of motor neurons.'

Meanwhile, CHDR's toolkit for studying the CNS effects of compounds is continuing to expand. Existing tools at CHDR include the NeuroCart and PainCart, as well as a variety of imaging techniques. To build on this, the Method Development group is busy testing new approaches to quantify changes in CNS functioning. In collaboration with researchers from the University of Twente, the team tested a method to measure CNS excitability. 'Hyperexcitability of the motor cortex is a characteristic phenomenon in ALS and other conditions, including epilepsy, so it's valuable to be able to quantify it,' says Groeneveld. The test involves applying transcranial magnetic stimulation (TMS) to the motor cortex, measuring the effects on motor responses using electromyography (EMG), and on the brain itself using electroencephalography (EEG).

See page 42 for a more in-depth description of these TMS-EMG and TMS-EEG techniques, in the interview with Dr Michel van Putten and Dr Annika de Goede from the University of Twente.

In 2020, the team are looking forward to participating in the development of a promising treatment for Huntington's disease. Specifically, the aim is to use antisense oligonucleotides to suppress the production of the toxic form of the huntingtin protein that causes disease. This treatment is already being tested in large-scale, randomised controlled phase 3 trials. Groeneveld: 'In parallel with these clinical studies, we will run a smaller study to elucidate the relationship between pharmacokinetics and pharmacodynamics. We will collaborate with our colleagues at the LUMC's Neurology department, who have an impressive track record in studying Huntingdon's. With projects like these in the pipeline, there are exciting times ahead.'

Prof. Albert Dahan, professor of Anaesthesiology at the Leiden University Medical Center

'Our collaboration with CHDR made this complex study possible'

'The collaboration between CHDR and the Leiden University Medical Center goes back decades,' says Prof. Albert Dahan, anaesthesiologist at the Leiden University Medical Center (LUMC). 'Our shared interests include the relationship between pharmacokinetics and pharmacodynamics, the use of pain models, and the effects of ketamine on the human brain. My own research group at the LUMC studies respiratory regulation, with a special interest in the respiratory depression caused by opioids. We've already uncovered new insights in this area in collaboration with the team at CHDR.'

In 2019, Dahan and his colleagues collaborated closely with the Neurology and Pain group to perform a study on opioids and respiratory depression. Alongside a group of healthy volunteers, CHDR recruited a group of people who regularly use opioids, either as a treatment for chronic pain or through opioid addiction. Measurements took place in Dahan's dedicated respiratory laboratory, located in close proximity to the operating theatres in the LUMC. The rest of the time, subjects stayed in CHDR's modern and comfortable clinical unit, where they could be monitored before and after their visits to the lab. Dahan: 'Everything went very smoothly. This was a complex study, with a lot of measurements. It's thanks to this collaboration that we can conduct a study like this while ensuring that it's not too demanding for the subjects.'

The study focused on a phenomenon that causes tens of thousands of deaths every year, especially in the United States: the effects of opioid overdose on the breathing reflex. Taking a high dose of an opioid can lead to cessation of the brainstem signal that tells the body to take another breath. Without adequate intervention, the result is death by asphyxiation. Respiratory depression due to opioid overdose is fairly common, partly due to the fact that street drugs often contain powerful synthetic opioids, such as fentanyl.

In the study conducted in Dahan's lab, the main trigger of the respiratory centre – the carbon dioxide concentration in the arterial blood – was kept at a constant level. The subject was then given fentanyl at an increasing dose, until spontaneous breathing stopped. 'In our laboratory, it's completely safe to go that far. As anaesthesiologists, we know how to deal with apnoea. After all, that's our expertise,' says Dahan. On the second day of the experiment, subjects were given a dose of buprenorphine first. Buprenorphine acts on the same mu opioid receptor as fentanyl, but has different properties: it is an opioid agonist, with a very strong affinity for the receptor. 'Buprenorphine is also well-known for its use in the treatment of opioid addiction. It alleviates withdrawal symptoms but doesn't give a subjective high,' says Dahan.

Dahan and his colleagues were able to demonstrate that buprenorphine could be used to protect opioid users from the dangerous respiratory depression caused by fentanyl. 'People with an opioid addiction who manage to get clean in rehab tend to relapse sooner or later. What most of them don't realise, however, is that their usual dose when they were regular users is far too much for someone who has been clean for some time.' This pattern was reflected in the study: healthy volunteers with no tolerance for opioids went into apnoea at a much lower dose than regular opioid users. The regular users needed a dose at least four times higher to stop spontaneous respiration. In combination with buprenorphine, however, even very high doses of fentanyl did not cause apnoea in either group.

'Our experiments show that giving buprenorphine as a depot preparation may protect against fatal respiratory depression in case of relapse'

'Buprenorphine is often given as a depot preparation after rehabilitation, to reduce the chances of relapse. Our experiments show that this treatment may in fact save lives: if users relapse, the buprenorphine can protect them from fatal respiratory depression in the case of overdose.' There is, of course, a potential downside to buprenorphine depot preparations, which as an anaesthesiologist Dahan is well aware of: if someone has had a buprenorphine injection, will they still respond to an opioid analgesic, in an operation for example? 'That's going to be our next study with CHDR. Our plan is to use the PainCart to find out what buprenorphine does to pain perception, and establish whether opioid analgesics are still effective in someone using buprenorphine. I'm looking forward to exploring this further,' says Dahan. 'And in fact, this is only one of many projects that we have in mind. The richness of this collaboration means there's a lot in store for the future.'

Prof. Bob van Hilten, professor of Movement Disorder Neurology at the Leiden University Medical Center

'Our new cohort of Parkinson's patients will help us lead the way to better treatments'

Prof. Bob van Hilten is a neurologist at the Leiden University Medical Center (LUMC) specialising in movement disorders, especially Parkinson's disease (PD). 'Classification and clinimetrics have always been interests of mine,' he says. 'I was one of the first to use wearables – back in the 1990s, I used accelerometers to objectively measure the movement of patients in their daily lives. Later on, I turned to the clinimetrics of rating scales used for PD. In the 2000s, we started the Scales for Outcomes in Parkinson's disease (SCOPA) study, with the aim of developing better rating scales for the wide spectrum of impairments and disability seen in PD. Although we learned a lot from those studies, we didn't succeed in identifying clinical subtypes of the disease. That's why we've now turned to molecular profiling using genetics, the faecal microbiome and more basic cellular research to unravel the different pathways that may be involved in the pathobiology of PD. The ultimate goal here is to find characteristics that can help us to tailor the treatment for these patients. We've also set up a movement analysis lab, using wireless technology to help us achieve a more precise characterisation of movement disorders.'

Van Hilten was brought into contact with CHDR through work on techniques for assessing movement characteristics of patients, as well as PD drug development studies. Within these domains of shared interest, the collaboration has primarily been driven by CHDR's interest in sensor technologies, and drug trials with specific genotypes of Parkinson's disease, respectively. 'In recent years, we've participated in the study of a new compound aimed at a subgroup of PD patients with mutations in the gene that encodes glucocerebrosidase. We were one of several neurology departments recruiting patients known to have this GBA genotype, and we also helped to search for new carriers of these mutations. As part of this project, an impressive 3,000 PD patients were genotyped,' says Van Hilten. 'Geert Jan Groeneveld and his team are a pleasure to work with. Recently, a new opportunity arose to start a collaboration of hospitals and other organisations, aimed at profiling Parkinson's disease patients (ProPark). It was obvious to us from the start that CHDR should be part of the consortium.'

Van Hilten is in charge of the collaborative ProPark project, which aims to establish a cohort of 1,250 Parkinson's patients and follow them for at least 2–3 years. Recruitment will take place in the university hospitals of Amsterdam, Rotterdam and Leiden, as well as in the general hospitals of Amersfoort and Woerden. As well as a thorough clinical evaluation, blood samples, skin biopsies and stool samples will be taken. Van Hilten: 'The blood samples will be used to do a whole genome sequence. We hope that a genomics approach will yield better predictors of outcome than phenotype alone. With the skin biopsies, we will analyse the degree of alpha-synuclein aggregation in nerve fibres and harvest skin fibroblasts to study the involvement of various pathways. Parkinson's is often thought of as a brain disease, but this is a misnomer: it affects the whole nervous system. That means that we don't need to do lumbar punctures, as it's enough to have peripheral nerves from the biopsies. The skin fibroblasts could also be used to generate induced pluripotent stem cells. Finally, the stool samples will be used to investigate the microbiome. We believe that the gut microbiome may not only play a role in metabolising medication such as L-dopa, but also influence disease progression in some PD patients.'

Patients from the cohort may go on to participate in studies evaluating new therapies. In such studies, CHDR's remote monitoring platform MORE will be used in conjunction with wearables to follow the therapeutic and adverse effects of medication. 'Combining data from wearables with the expertise of motion scientists, we hope to gain a better understanding of different motor impairments, as well as insight into L-dopa off-periods and side effects such as dyskinesias,' says Van Hilten. 'Measurements in daily life are an important addition to the assessments we perform in the consultation room, as they enable us to get a better overall picture. Patients often do things here at the hospital which family members say they never do at home!'

The sheer variety of data gathered from this cohort holds promise for addressing a range of specific pharmacological questions. For example, pharmacogenetics research has the potential to contribute to better dosing and a more personalised approach to medication. Van Hilten: 'Some patients experience difficulties with impulse control when they use dopamine agonists. Dopamine is involved in the natural reinforcement system in the brain. When exposed to these drugs, susceptible patients fail to inhibit their impulses, and find themselves overeating or engaging in inappropriate behaviour. Hopefully, with enough data, we'll be able to identify patients who are more at risk of such unwanted side effects.'

Once this cohort has been established and characterised, it will also have much to offer for future research at CHDR, complementing the cohort of 3,000 genotyped PD patients gathered in the glucocerebrosidase study. A whole new chapter in the treatment of PD is unfolding, with the rise of new therapies aiming to modify disease progression. Van Hilten: 'Given what's already known about the various pathways towards PD, I expect that most patients would need a combination of drugs to slow down the progression of the disease. The first step of this journey is to see what this new wave of medications can do. There's still a lot to be done to find the optimal treatment for each PD patient, but we'll get there. I'm an optimist at heart.'

Prof. Michel van Putten, professor of Clinical Neurophysiology at the University of Twente, and **Dr Annika de Goede**, postdoctoral researcher in Clinical Neurophysiology at the University of Twente and CHDR

'When everything is so well organised, you can really focus on the science'

Prof. Michel van Putten is a neurologist with a strong focus on clinical neurophysiology, who divides his attention between his patients in the Medisch Spectrum Twente hospital and his research at the University of Twente. Under his supervision, Dr Annika de Goede, a technical physician, wrote her PhD thesis about the use of transcranial magnetic stimulation (TMS) as a biomarker for epilepsy. She studied the brain's excitability by measuring TMS-evoked potentials in the electromyogram (EMG) or electroencephalogram (EEG), when stimulating the motor cortex using magnetic pulses. At CHDR, De Goede is currently involved in developing the application of TMS-EMG and TMS-EEG in clinical drug research. Van Putten: 'Geert Jan Groeneveld was interested in our work on TMS, and we both thought that it could be a very useful biomarker to demonstrate drug effects on CNS excitability. It also has potential uses in the evaluation of treatments for conditions such as epilepsy and ALS, in which CNS hyperexcitability plays an important pathophysiological role. It could be useful for investigating other neurotropic drugs too, in psychiatry as well as neurology – or, conversely, as a tool to demonstrate that a compound aimed at other organs does not affect the brain.'

The team's collaborative grant proposal was successful, and while finalising her PhD thesis, De Goede was involved in a series of experiments at CHDR using TMS-EMG and TMS-EEG. 'Over the past few years, we've explored using these techniques to measure the effects of several drugs that are already on the market for the treatment of epilepsy, such as valproate, levetiracetam and lorazepam. In these studies, healthy subjects were given a single dose of each of those compounds, or a placebo, in a four-way crossover design. The next step will be to repeat those experiments in patients with epilepsy. Ultimately, the idea is to be able to predict if a drug will be effective,' says De Goede. 'We also used TMS in sponsored studies investigating two novel compounds which may find applications in psychiatry. The recruitment and planning went very smoothly: all I needed to do was focus on the technology and the science.'

Of course, the development of such a new tool does not come without challenges. De Goede: 'The magnetic pulse can disturb EEG readings, so you need special equipment and specially-trained personnel to perform these measurements. I regularly attend the actual measurements at CHDR, to verify the quality.' Once the measurements have been obtained, the next challenge is to analyse the complex data yielded by these techniques.

Initial results of the study show that the drugs that were tested do indeed affect brain excitability. Even more importantly, the patterns of change are characteristic for the pharmacological properties of the compounds tested. De Goede: 'After averaging a series of EEG responses, we see a characteristic pattern in the TMS-evoked potentials. Based on previous research, we know how specific troughs and peaks correlate with the engagement of specific receptors in the brain – such as the $GABA_A$ and $GABA_B$ receptors, or the various glutamate receptors. The amplitude of these evoked potentials is a measure of brain excitability. Each compound has its own "fingerprint", which we can then use as a reference for investigating novel compounds using these TMS-based techniques.'

Clearly TMS-EMG/EEG has much to offer to drug development, but could it also be useful in clinical neurophysiology? Van Putten: 'Our ongoing research has two goals. On the one hand, we use the TMS-based technique to verify the diagnosis of epilepsy, and on the other hand, we're aiming to evaluate the efficacy of the prescribed medication. We see promising results at the group level, but I'm still not sure this will be a useful diagnostic technique – if only because it's rather time-consuming.' De Goede: 'A number of countries have now approved TMS for therapeutic applications in the treatment of conditions such as depression. If more centres in the Netherlands start using TMS for therapeutic purposes, maybe diagnostic applications will follow. In the short term, however, there's still plenty to discover using TMS as a research tool.'

‘Together, we’re a team with shared goals’

Working with CHDR

‘We have been working with CHDR for almost a year. They contributed patients to our study, and they were a very active participant. They gave a lot of thoughtful feedback on the clinical protocol and were very involved, participating in all the study calls. The way they cared about the trial, and were accountable, was really outstanding. I think of CHDR as a partner, because we collaborate and share the same goals – we work as a team.’

Clinical Operations Programme Leader, Big Pharma Company *

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

Psychiatry

Psychiatric conditions hinge on subjective experience, making it difficult to objectively measure drug effects in this field. CHDR draws on a combination of NeuroCart®, pharmacological challenge tests and remote monitoring to gain better insight into pharmacodynamics in healthy subjects and patients.

Exploring and validating new methods in mood disorder research

Psychiatry researchers at CHDR enjoy a long-standing collaboration with the Psychiatry department of the Leiden University Medical Center (LUMC). In 2019, a new partnership came about with the mental health organisation Transparant, who helped contribute to the validation of CHDR's MORE remote monitoring platform by collaborating in a study with patients suffering from major depressive disorder (MDD). Ongoing collaborations with sponsors included the exploration of a novel compound acting on the glutamate system.

'The main takeaway of the MORE study is that we can go ahead and explore the possibilities of the platform for future drug trials,' says Dr Gabriël Jacobs, Research Director of Psychiatry at CHDR. 'When developing new techniques, there's always the potential for unforeseen challenges. With this self-funded study, we were determined to iron out these problems at an early stage. Having this under our belt, we are now in a position to deploy MORE for applications such as monitoring behavioural effects of investigational compounds in daily life, outside the clinical unit.'

Mutually beneficial collaboration

The evaluation of the MORE platform in the MDD study was a collaborative effort between CHDR and Transparant, an innovative mental healthcare provider in the region that offers outpatient services to patients with various psychiatric disorders. The two organisations decided to collaborate in 2018, and in 2019 a master service agreement was signed. Jacobs: 'Transparant is a great partner for us. It's a dynamic organisation without the red tape of some larger institutions. Their team consists of knowledgeable and approachable psychiatrists, psychologists and psychotherapists, who are supported by highly-motivated administrative staff. We're looking forward to expanding our collaboration further to include education and training initiatives.' According to Jacobs, the successful MORE study proved the strength and the reciprocity of the collaboration. 'This wasn't just a request to deliver patients for our study, but a complementary partnership. We couldn't have done this study without Transparant's input. Their expertise enhanced the quality of the study protocol we wrote together. A particularly rewarding aspect of the experience was organising brainstorming sessions together to engineer scientific and operational aspects of the study protocol.' Jacobs sees many possibilities for the future: 'Our colleagues at Transparant are dependable partners and creative thinkers. We're on the same page in terms of our ideas about developing innovative treatments and modernising patient care, as psychiatry moves into the digital age.' Read more about Transparant in the interview with Transparant's CEO, Dr Liesbeth van Londen, on page 54.

Research Domain Criteria

The project with Transparant drew guidance from the Research Domain Criteria (RDoC) concept developed by the US National Institute of Mental Health. The RDoC approach involves assessing common domains of functioning across diagnostic categories in order to quantify how the functioning of individuals with psychiatric disorders differs from that of healthy individuals. Relevant RDoC domains to MDD are the so-called positive and negative valence systems which govern how individuals respond to rewarding and aversive situations, arousal systems that regulate circadian rhythm, and sensorimotor systems that dictate physical activity. Jacobs: 'Although we limited ourselves to the boundaries of the DSM for this first study, we were interested in mapping behavioural correlates of the negative valence, arousal and sensorimotor systems. We did this by using the MORE mobile application and wearable devices to monitor 30 healthy subjects and 30 MDD patients over a period of three weeks.' Alongside objective measurements such as physical activity, sleep and blood pressure, participants were asked to respond to mood-related questions twice a day using MORE's electronic patient-reported outcome (ePRO) functionality. Participants also returned to the clinic once a week for structured DSM-based interviews and neuropsychological and neurophysiological characterisation with NeuroCart. Jacobs: 'Compared with the traditional questionnaires that assess symptoms over the preceding week or two, the twice-daily reporting via ePRO provides a higher temporal resolution, which may yield a more refined picture of symptoms as they occur. When combining subjective reports with the objective data, contradictions between the two can reveal further insights still.'

Recruitment

CHDR believes that clinicians who collaborate in drug trials should not be burdened with the logistics associated with clinical research. Therefore, in the collaboration with Transparant, recruitment remained primarily CHDR's responsibility, with Transparant facilitating the process in several ways. 'We approached recruitment from various angles,' says Jacobs. 'Our leaflets and brochures could be found in all Transparant waiting rooms, so patients would see them there and have the chance to discuss them with their attending psychiatrist or therapist. Secondly, like most mental health organisations, Transparant isn't usually able to help newly-referred patients straightaway. The coordinator in charge of the waiting list was aware of our study, so if a new patient did have to wait a month or two, he or she could be invited to consider participating at CHDR. We also used CHDR's tried and tested recruitment strategy via (social) media to advertise the study to potential participants. Patient organisations got involved too, distributing information to their members.'

Every potential participant in a patient study at CHDR undergoes a thorough physical and psychiatric screening. Jacobs: 'The physical screening of participants is the responsibility of our dedicated screening physicians. The researchers who perform the psychiatric screening discuss participation in a study with the attending general practitioner, psychiatrist or psychotherapist. Safety considerations and desirability for a subject to participate play a vital role in our selection process. For instance, participation in a CHDR study is only possible if a patient is already receiving treatment and if the risk that participation will disturb their current treatment is minimal. To adequately perform a risk assessment for a given individual, it's important to go beyond the results of the traditional questionnaire. Depending on the study protocol, it may also be important to verify other aspects, such as whether the attending healthcare professional is planning to alter the current treatment during the course of the study. In our MORE study, for example, we wanted to rule out any changes in medication or other treatments during the study period. This meant assessing, in consultation with the patient and their practitioner, whether it was sensible to keep the treatment the same for those three weeks.'

Ketamine and beyond

High on the list of potential future collaborative projects with both LUMC and Transparant is to understand ketamine's mechanism of action, from a pharmacological perspective, as a rapidly acting antidepressant in patients suffering from treatment-resistant MDD. 'CHDR has been studying the pharmacology of ketamine and its relevance to the treatment of depression for some time already,' says Jacobs. 'It's an interesting approach, with the potential to help patients whose condition doesn't respond to any of the currently available treatment options. When it turns out that a patient does respond to ketamine, however, there is still the issue that the effects are transient, and we don't yet have an understanding of the outcomes of using ketamine as a long-term maintenance treatment. The relationship between acute NMDA receptor modulation and mood regulation also remains largely obscure. So there's still much to explore – firstly, in healthy volunteers to understand the pharmacology better, and then in patients to ascertain its effectiveness.'

One of the putative pathways of ketamine's therapeutic effect in depression may offer an alternative approach. In collaboration with the Japanese pharmaceutical company Takeda Pharmaceuticals, CHDR has studied a so-called ampakine compound, which acts allosterically on the postsynaptic AMPA receptor for glutamate. Jacobs: 'Ampakines modify the action of glutamate, which is the main excitatory neurotransmitter in the brain. Their mode of action makes them potential candidate drugs for several psychiatric and neurological conditions. They trigger several cascades of cellular reactions in the limbic system, which may be beneficial to more distal effects such as regenerative processes and neuroplasticity. Interestingly, the antidepressant effects of ketamine very likely also involve the AMPA receptor. Selectively blocking the AMPA receptor in animal models for depression seems to result in ketamine losing its antidepressant-like effect. So this is an intriguing class of drugs that may well offer new horizons for the treatment of depression.'

Transcranial magnetic stimulation

The scientific collaboration with Takeda began at the 2018 World Conference of the International College of Neuropsychopharmacology (CINP) in Vienna, where Jacobs and his colleagues presented a poster. Jacobs: 'During a poster session I came across a presentation on the preclinical findings on this ampakine, by a team of Takeda's scientists from Cambridge, Massachusetts. We had an interesting conversation about the possibilities for demonstrating the compound's pharmacodynamic effects and relating these to its pharmacokinetics in human subjects – which is, of course, CHDR's core expertise. My colleagues and I introduced NeuroCart and its potential application to explore the neuropharmacology of the compound. And that's how things started.'

Soon afterwards, during one of CHDR's regular visits to the Boston area, the exchange of ideas regarding a potential study continued. It turned out that Takeda had measured transcranial magnetic stimulation elicited mechanomyogram (TMS-MMG) responses in their preclinical studies in rats, and had shown that this compound increased neuronal excitability. By that time, CHDR had already started to validate the use of TMS in combination with EEG and EMG, measuring motor-evoked potentials (MEP) to quantify the effects of various drugs on neuronal excitability in the brain. Jacobs: 'Interestingly, TMS-MEP in humans can be considered analogous to TMS-MMG in rodents. This led us to apply both NeuroCart and TMS as a potential translational biomarker bridging preclinical and early clinical studies with ampakines.'

Both the NeuroCart and the TMS data yielded compelling results. Similar to its effects in rodents, at a certain plasma concentration the compound increased neuronal excitability, as indicated by an increased MEP amplitude after stimulation of the primary motor cortex. The NeuroCart results were equally informative,

showing a clear effect on various neurophysiological variables which was remarkably consistent with the TMS response, suggesting acute stimulatory effects. Jacobs: ‘Overall, it was a vibrant, multi-way collaboration between Takeda’s scientists, our own psychiatry team and researchers from the University of Twente. Regardless of how our sponsor decides to proceed with this compound, it has already proven to be a very valuable and informative experience.’ The University of Twente researchers Prof. Michel van Putten and Dr Annika de Goede talk more about the use of TMS-based techniques at CHDR in the interview on page 42.

Training and sharing expertise

‘Over the years, we have always maintained close ties with the LUMC Psychiatry department. I followed my training there, and currently see outpatients with therapy-resistant depression on a weekly basis,’ says Jacobs. ‘Between CHDR and the LUMC, there is a lively exchange of scientific ideas. Research at the LUMC focuses on various conditions caused by trauma and stress, including depression and anxiety disorders. So there’s considerable overlap in our areas of interest.’ Read more about the team’s collaboration with the LUMC Psychiatry department on page 56, in the interview with Prof. Nic van der Wee, professor of Biological Psychiatry at LUMC and member of CHDR’s Scientific Advisory Board.

‘At CHDR, we also offer a research traineeship for doctors specialising in psychiatry,' continues Jacobs. 'In 2020, we will welcome the third trainee to take up that position. Engaging more psychiatrists in clinical pharmacology and drug development is very important for the field. The more we stimulate the exchange of knowledge between clinicians, academics, drug developers and patients, the better equipped we will be to improve treatments for mood disorders.’

Dr Liesbeth van Londen, CEO of Transparant Centre for Mental Health

'Participating in research motivates our team and contributes to quality of care'

'At Transparant, we place the primary process – the interaction between the patient and the practitioner – at the centre of everything we do,' says Dr Liesbeth van Londen, Transparant's CEO. Transparant is a non-profit mental healthcare organisation, working in the area local to CHDR. It was set up in 2005 by Van Londen, who brought together a group of mental healthcare professionals who shared a dissatisfaction with the way most organisations are run. 'In many mental healthcare organisations, administrative and bureaucratic matters end up impacting the primary process of providing patient care. We're determined to do things differently, running the organisation in a way that supports the primary process without constraining it. Of course, every organisation entails some degree of bureaucracy in order to remain accountable, but quality of care must always remain the top priority.'

Van Londen came into contact with CHDR in 2018, when Dr Gabriël Jacobs was looking for partners to collaborate on studies in the field of psychiatry. Van Londen was struck by the dedication and professionalism she saw at CHDR, and Jacobs was in turn impressed by Transparant's approach to mental healthcare. The discussion continued, and in 2019 a formal collaboration agreement was signed. Van Londen: 'From the outset, we aimed for cooperation across a range of areas – not just in research, but also in training and knowledge exchange. For an organisation like Transparant, participating in scientific research can really contribute to the quality of care. As healthcare professionals, research can also add an interesting dimension to our day-to-day work and provide new avenues for professional development.'

The first joint study, on characteristics of depressive behaviour, was launched in 2019. This study used CHDR's remote monitoring platform MORE to compare the behavioural characteristics of patients suffering from major depressive disorder with those of healthy volunteers. The goal of the study was to validate MORE, and to assess its added value over classic measurements such as the Hamilton scale. Recruitment focused on patients on Transparant's waiting list, and by the end of 2019, the data collection phase of the study was almost complete. 'The collaboration was remarkably smooth. I liked that there was flexibility on both sides, and I enjoyed the collaborative approach to solving the challenges involved,' says Van Londen.

One such challenge discovered in this study was that, as Transparant's patients tend to have very complex problems, they are often not suited for participation in CHDR's studies. 'For a scientific study, patients with a single diagnosis are preferred. However, the focus at Transparant is on patients with complex psychiatric disorders, often suffering from comorbidities,' says Van Londen. Nonetheless, this hurdle too can be overcome thanks to Transparant's companion organisation, Transparant Next. Van Londen: 'Within the Dutch mental healthcare system, patients with regular depressive disorder are typically treated in primary care, which may include counselling and GP-prescribed antidepressants. In practice, however, many of these patients have problems that require assessment by a skilled psychiatrist.' Seeing this gap, the enterprising Van Londen established Transparant Next as a foundation to provide these specialised assessments. 'General practitioners can refer a patient to us, and within three weeks, the patient is referred back to them with a detailed recommendation for treatment.' After almost 2,000 consultations, Transparant Next has shown that with these recommendations, 60% of patients can be successfully treated in primary care, saving the cost of referral to specialised mental health organisations. For CHDR, Transparant Next offers a valuable connection to patients in primary care who may be better suited for clinical trials than many of Transparant's patients.

What about Van Londen's plans for the future? 'I'd love to establish a "Mood Lab": an infrastructure to facilitate the study of mood disorders from a range of angles. CHDR has already expressed interest in collaborating, and I hope others will follow suit. The LUMC Psychiatry department would be a particular asset to this project, as they have a tremendous amount of expertise in this field,' says Van Londen. 'There's still much work to do to improve the diagnosis and treatment of mood disorders, but with the right partners, we can really drive things forward.'

'With the right partners, we can really drive improvements in the diagnosis and treatment of mood disorders'

Prof. Nic van der Wee, professor of Psychiatry (Biological Psychiatry) at the Leiden University Medical Center

'We share an interest in exploring novel approaches in psychiatry'

'The collaboration between our department and CHDR goes back a long way,' says psychiatrist Prof. Nic van der Wee, who holds a chair in Biological Psychiatry at the Leiden University Medical Center (LUMC). In 2019, he joined CHDR's Scientific Advisory Board, following in the footsteps of several of his LUMC colleagues. 'CHDR's Dr Gabriël Jacobs works here at the LUMC outpatient clinic, with patients suffering from therapy-resistant depression. Prof. Joop van Gerven also holds a chair in our department. Although he's less involved in our day-to-day work since he became chair of the Netherlands' central medical ethics committee (CCMO), we still see him regularly in the context of European studies.' Besides the exchange of expertise, the collaboration extends to include joint ventures in education and training. Van der Wee: 'Talented students often go on to do an internship at CHDR, and we have PhD students who do part of their research there. There's also the special scientific traineeship in clinical psychopharmacology at CHDR for resident psychiatrists. It's a multifaceted collaboration with a lot of mutual benefits.'

LUMC's Psychiatry department conducts research into various aspects of stress and trauma related disorders, including mood disorders, anxiety disorders and post-traumatic stress disorder. Researchers study the development of these disorders across the lifespan, from childhood to old age, and the factors that influence an individual's susceptibility or resilience. Van der Wee: 'Our research interests have a broad overlap with those of Gabriël Jacobs and Joop van Gerven. We are all interested in exploring and developing innovative psychopharmacological treatments. Besides ongoing research into the use of ketamine to help patients with persistent depressive disorder, in our group we are also studying the use of psilocybin and MDMA in the treatment of post-traumatic stress disorder. In exploring such innovative treatments, having someone like Gabriël Jacobs on board, with extensive clinical pharmacological expertise, is invaluable.' Following early-phase clinical development, as carried out at CHDR, new medicines must subsequently be tested in larger groups of patients. Van der Wee: 'We are very interested in conducting those subsequent clinical trials, together with our partners from mental healthcare organisations. For patients with an unmet clinical need, such as treatment-resistant depression, we're keen to facilitate the introduction of novel treatments into clinical practice.

'My research focuses on the biology of psychiatry,' says Van der Wee. 'Of course, that's not to imply that all of psychiatry can be reduced to biology, but we can learn much from exploring the biological aspects of anxiety, mood and compulsive spectrum disorders using imaging techniques, genetics and other approaches. For example, in collaboration with our Endocrinology department, we study the effects of high cortisol levels on the brain in people with Cushing's disease. Even many years after their hormone levels have normalised, you can still detect measurable changes in cerebral functions. We use these findings as a model for the impact of stress hormones on the brain, even though cortisol levels in Cushing's disease are of course much higher than in a normal stress response.' In another project, Van der Wee and his team go beyond just focusing on disease and complaints, to help build an overall understanding of what keeps people healthy: 'We study biological mechanisms involved in resilience, as our contribution to what's known as "positive psychiatry".

'Research in biological psychiatry is essential to the development of new therapeutic approaches,' says Van der Wee. 'It's great to see that, after several years of standstill, there's renewed interest in developing psychiatric drugs. There are still large unmet needs in psychiatry, with many patients who don't respond adequately to regular treatment. As novel treatments reach the phase of clinical development, CHDR stands to play a vital role in the evaluation of these drugs. The coming years therefore promise to be an exciting new era not only for our collaboration, but for clinical psychopharmacology as a whole.'

‘A strong support and a key partner’

Working with CHDR

‘CHDR undertook our phase 1 study. We collaborated closely and I felt that we aligned with each other. They have been a very strong support and a very good partner throughout the process. They gave us advice, but unlike formal advisers, they worked in partnership with us, discussing the design and how to proceed. They were key partners for getting our phase 1 study completed.’

Senior Vice President,
Biotech Company *

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

Dermatology

Drug development in dermatology is expanding rapidly. Thanks to the visibility of the target organ, a compound's effects can be easily detected. CHDR offers a battery of objective tests and a wealth of immunological expertise to complement the judgement of experienced dermatologists.

A collaborative network at the leading edge of dermatology research

An increasing number of clinicians and experts from other disciplines contribute to CHDR's research in dermatology, studying innovative compounds for the treatment of various skin diseases. In addition to common conditions such as eczema and warts, a rare malignant lesion – cutaneous T-cell lymphoma – is being studied in collaboration with the Leiden University Medical Center (LUMC). Meanwhile, the CONNECTED network for clinical dermatologists is growing rapidly and yielding benefits for clinical studies.

CHDR's activities in the field of dermatology fully embody the spirit of collaboration that characterises the organisation as a whole. Research Director Dr Robert Rissmann: 'Every project we do involves a range of internal and external parties, from our own bioanalysis laboratory to the LUMC pharmacy and clinical laboratories, to additional external labs, such as a microbiome lab and academic research units. Throughout this work we are increasingly supported by our growing network of dermatologists throughout the country, active both in general hospitals and university medical centres. They are key for the recruitment of patients in general, and absolutely crucial when it comes to rare or complex diseases. And their role doesn't end there: they also contribute scientific expertise by co-writing publications, organising meetings, and so on. It's more than just a collaboration – it's a partnership, a community driven by shared values rather than transactional incentives.'

The drive that unites both the clinicians in the CONNECTED network and researchers at CHDR is to improve patients' quality of life. Both clinical practice and research play key roles in achieving this goal. Rissmann: 'CONNECTED gives dermatologists in clinical practice the opportunity to contribute to scientific research. In turn, we contribute to the training of clinicians as well as scientists, offering support for those in the earlier stages of their career. Our sense of community is enhanced by meeting face-to-face, sharing information and inspiring one another. We do so much more than just achieving specific research aims or meeting targets. Together, we can create value in all sorts of ways – for sponsors, for the academic community and ultimately, for patients.'

Joining forces

Rissmann and his colleagues increasingly collaborate with dermatology departments at the university medical centres in the proximity of CHDR: Leiden (LUMC), Rotterdam (Erasmus MC), and Amsterdam (Amsterdam UMC, a recent merger of the city's two university medical centres). These collaborations often grow organically from shared scientific interests. Rissmann: 'People who do their PhD research at CHDR often have a thesis supervisor in one of the neighbouring university medical centres. Sometimes they do part of their research there, or they participate in patient care in the outpatient clinic. This is a win-win situation for everyone involved: it gives the PhD students more opportunities to train as medical specialists, it is in the interest of the university medical centres, and it enables us to attract talented researchers.'

Community means not only benefiting from one another's knowledge, but also being able to integrate different sources of expertise in a swift and seamless manner. Rissmann: 'When questions arise, being able to just pick up the phone and chat to the head of an academic hospital department is extremely valuable. These short lines of communication really enhance our day-to-day work.'

Eczema

In 2019, CHDR conducted several studies in patients with various forms of eczema. Two studies focused on moderate to severe atopic eczema, testing the clinical efficacy and pharmacodynamic effects of a novel immunomodulating treatment. The pharmacodynamic effects were monitored by using a novel multispectral camera to measure the erythema, as well as measuring the transepidermal water loss, which gives insight into the barrier status of the skin in eczema lesions.

Recruitment proved to be a challenge in these studies. Rissmann: 'To study the novel immune modulator, we needed 16 patients with moderate to severe eczema. We managed this within eight months. For an early-phase drug trial such as this, we needed people with relatively severe eczema who are otherwise healthy enough to participate. Eczema is a systemic disease that has a significant impact on people's lives, causing considerable stress and often sleep problems.

It can therefore be difficult to find participants whose blood pressure and other characteristics meet our selection criteria. For this study, the partnership between our dermatology network and our in-house recruitment department was the key to finding enough participants.'

Validating innovative methods

Two clinical studies in 2019 conducted in collaboration with Dr Jan Nico Bouwes Bavinck at the LUMC built on earlier work on HPV-induced skin lesions. One of them, involving 80 patients, focused on the treatment of warts, while the other trial studied a similar treatment in 32 patients with actinic keratosis, a premalignant skin lesion. The latter condition is primarily caused by UV exposure, but in many actinic keratosis lesions HPV has been demonstrated, suggesting a causal contribution of the virus to the susceptibility of skin cells. Read more about these studies in the interview with Dr Bouwes Bavinck on page 70.

The vast majority of dermatology studies at CHDR are conducted on an outpatient basis, using mobile phone apps to monitor patients during the course of the trial. During visits to the Clinical Research Unit, lesions are objectively characterised using DermaToolbox, CHDR's unique battery of cutting-edge dermatological measurements. 2019 saw the publication of two scientific papers describing crucial aspects of this approach.

One of these articles shows the contribution of mobile phone apps to patient compliance and demonstrates their value for monitoring patient-reported outcomes. In this publication, results from six trials involving different HPV-induced skin lesions were evaluated. The mobile app reminded subjects when they should apply the topical therapy to the lesion, and was used to gather information about subjects' experiences using an e-diary and a numerical rating scale. Rissmann: 'We already had the strong impression that our approach was contributing to patient compliance. But when you see the results, it's quite stunning. The overall treatment adherence across these studies was 98%. The overall e-diary adherence was 93%, and the numerical rating scale adherence was also around 90%. Of course, this was a trial setting, where participants receive a financial consideration for their time. Nonetheless, these percentages are still very high.'

The other of the two publications focuses on the clinical visualisation and quantification of HPV-induced skin lesions using 3D photography. The main conclusion is that the stereophotogrammetric 3D camera system used at CHDR makes an important contribution to the objective evaluation of treatments. 'The usual approach in dermatology is to measure the lesion using callipers. That method is known to be unreliable, with a large interobserver variability. Especially in trials with a shorter duration, it's important to be able to measure subtle changes in the lesion. Our analysis shows that 3D photography provides reliable, exact and highly reproducible measurements. The system we use is handheld and portable, so it can easily be used in other studies – and potentially also in a clinical setting.'

T-cell lymphoma

In January 2019, CHDR and LUMC jointly embarked on a sponsored study to investigate the effects of a topical treatment for early-stage cutaneous T-cell lymphomas. The study consisted of a first-in-human trial in healthy volunteers, followed by a trial in 18 patients with this rare condition. 'It all went very quickly,' says Rissmann. 'We made the proposal to our sponsor in January, in April it was submitted to the medical ethics committee, in June we started testing healthy volunteers, and in September we were able to start with the first patients. By the end of 2019 we had already recruited well over half of the total number of patients we needed to include.

This rapid progress was possible thanks to our collaboration with LUMC as well as the other academic centres involved,' reflects Rissmann. 'The disorder is really rare, but the LUMC Dermatology department is one of Europe's top research centres for cutaneous lymphomas. Through this collaboration we have a unique opportunity to study this disease, allowing us to pursue questions we would be simply unable to answer our own. When we work together, we not only increase our access to patients, but we also expand our facilities and multiply our expertise.' Read more about the Dermatology group's collaboration with LUMC in the interviews with Prof. Maarten Vermeer and Dr Koen Quint on pages 68-69.

The five cornerstones of mechanistic, data-rich early-phase drug development in dermatology

In a collaborative publication appearing in the British Journal of Clinical Pharmacology, Dr Martijn van Doorn (Erasmus Medical Center, Rotterdam) and CHDR's Dr Robert Rissmann and Dr Matthijs Moerland present a blueprint for early-phase pharmacological studies in dermatology. The approach they describe is reflected in their own collaborative work. The paper defines five 'cornerstones' for this kind of research, aimed at gaining as much relevant information as possible in the first phases of clinical drug development:

1. ***Pharmacokinetics.*** Using state-of-the-art techniques such as microdialysis, open flow microperfusion and MALDI-TOF, it is possible to overcome the challenges involved in assessing the pharmacokinetic properties of a compound in the skin.
2. ***Pharmacodynamics.*** It is crucial to gain insight into the pharmacodynamic properties of the compound in the early stages of clinical drug development, using challenge models in healthy volunteers or even performing the 'first-on-human' (i.e. topical) application of the compound in patients.
3. ***Sensitive and objective clinical endpoints.*** In addition to systematic evaluation by skilled dermatologists, objective measurements should be used, such as laser speckle contrast imaging to quantify the amount of inflammation, or 3D photography.
4. ***Integrated, multimodal profiling of disease and drug effects.*** Thanks to multimodal approaches and technologies, an integrated picture of disease severity and drug effects can be put together for the individual patient. This integrated approach combines clinical evaluation with objective measurements (offered by CHDR's DermaToolbox) and omics technologies, as well as regular assessment of the patient's daily experiences using remote monitoring techniques and apps.
5. ***Landscape for trial conduct: collaborations.*** Reflecting on the examples of the UK Dermatology Clinical Trial Network (UK DTCN) and the Dutch Clinical Network for Trials in Dermatology (CONNECTED), collaboration emerges as a key ingredient for conducting trials in the current research landscape. The authors recommend single-centre execution with multi-site recruitment, as done by CHDR for many years now.

Rissmann R, Moerland M, van Doorn MBA. Blueprint for mechanistic, data-rich early phase clinical pharmacology studies in dermatology. ***British Journal of Clinical Pharmacology.*** Published online 2020.

Prof. Maarten Vermeer, professor of Clinical Dermatology and
Dr Koen Quint, dermatologist, at the Leiden University Medical Center

'A hub of expertise for clinical trials in dermatology and drug delivery'

'One of the strengths of CHDR's dermatology research is their dedication to objective biometric measurements,' says Prof. Maarten Vermeer, head of the Leiden University Medical Center (LUMC) Dermatology department. 'For example, they have techniques to measure the pharmacokinetics of a compound within the skin. This objective approach really adds value, especially in a trial setting. Some of these measurements may also prove useful in a clinical context. A key focus for us, in both research and patient care, is melanoma – especially the familial atypical multiple mole melanoma (FAMMM) syndrome. Patients with FAMMM have dozens or even hundreds of moles that may become malignant. For the objective follow-up of these patients, a digital 3D camera system can be invaluable.

'Looking ahead, I see great potential for further collaboration with CHDR and their network, such as the Leiden Academic Centre for Drug Research (LACDR). This complements the collaborative approach that already exists among basic and clinical research groups within the LUMC. And in the near future, the biomedical branch of the Netherlands Organisation for Applied Scientific Research (TNO) will come to the Leiden Bio Science Park, across the road from CHDR. Altogether, this will create a very strong concentration of expertise and facilities, all within walking distance. I see many possibilities on the horizon, both for my own field of expertise – the treatment of cutaneous lymphomas – and in a much broader context, for the development of various new treatments and the evaluation of transdermal delivery systems.'

Prof. Maarten Vermeer, professor of Clinical Dermatology and
Dr Koen Quint, dermatologist, at the Leiden University Medical Center

'Together, we're exploring new therapies for cutaneous lymphomas'

At the Leiden University Medical Center (LUMC) Dermatology department, the study and treatment of cutaneous lymphomas has been an important topic for the past two decades. The LUMC is one of the European reference centres for these rare tumours of the skin, as well as being the reference centre for Dutch patients with cutaneous lymphomas. About 60% of all Dutch patients are seen at least once in Leiden to establish the correct diagnosis. 'It's a very diverse group of tumours,' says dermatologist Prof. Maarten Vermeer. 'Their severity and clinical progression ranges from lesions that look and behave like eczema, to life-threatening conditions that require immediate referral to a haematologist for chemotherapy.' All cutaneous lymphoma patients are discussed by the Dutch Cutaneous Lymphoma Working Group, coordinated by the LUMC Dermatology and Pathology departments. 'In recent years, our scientific efforts have focused on classifying these lesions, correlating clinical manifestations with their pathology and their molecular characteristics. In parallel, we've been involved in clinical trials of various treatments for cutaneous lymphomas.'

Staff dermatologist Dr Koen Quint specialises in cutaneous lymphoma research and patient care. Together with Vermeer and CHDR's Dr Robert Rissmann, he was involved in the design of a trial at CHDR that started in 2019, in which a promising new topical treatment was evaluated. 'Both scientifically and from the perspective of clinical potential, this has been a fascinating study, and I'm really looking forward to the results,' says Quint. 'For us, organising a trial at CHDR is much simpler than in our own hospital. For example, to do the mandatory ECG at the LUMC, we need to involve our Cardiology department, whereas at CHDR everything is seamlessly integrated. They're also excellent when it comes to recruiting patients. Having CHDR taking care of all the logistical management tasks means that we doctors can focus on what we do best: providing clinical expertise and evaluating outcomes.' One outcome is already clear: the collaboration between the LUMC's dermatologists and CHDR is fruitful. Taking this partnership forward is Selinde Wind, a physician and clinical scientist conducting basic research into cutaneous lymphomas at the LUMC, who will be involved in future clinical trials at CHDR while also working towards her PhD. Vermeer: 'We're looking forward to the chance to investigate more compounds, potentially also paving the way for more collaborations with pharmaceutical companies.'

Dr Jan Nico Bouwes Bavinck, dermatologist at the Leiden University Medical Center

'Data-rich trials can help us answer a whole range of additional scientific questions'

For over three decades now, dermatologist Dr Jan Nico Bouwes Bavinck has been working to better understand the role of the immune system and the human papilloma virus (HPV) in benign and malignant tumours of skin cells. His PhD thesis concerned the risk of skin cancer in renal transplant recipients and he is still involved today in the dermatological care of organ transplant patients. According to studies conducted by Bouwes Bavinck and colleagues, immunosuppression is associated with a hundredfold increase in the risk of skin cancer, especially squamous cell carcinoma. In many of these skin cancers, strains of HPV are thought to play a role in the process of malignant degeneration.

HPV may also be involved in actinic keratosis, a premalignant condition commonly seen in older people. About one in four people over 50 years of age have actinic keratosis, most of them even presenting with several lesions. The condition is caused by ultraviolet radiation, but HPV strains may play a role. Transformation by HPV protects cells against apoptosis, meaning that skin cells with UV-induced mutations may survive and develop into cancer cells. Bouwes Bavinck: 'There are treatments for actinic keratosis, but these are quite drastic as they effectively remove part of the skin. So we're working to find something more gentle that is still effective. In 2019, together with CHDR, we evaluated whether a compound with a putative effect against HPV would be effective for the treatment of actinic keratosis.'

The study was part of a larger collaboration between CHDR and LUMC to study HPV-induced lesions, including warts, genital warts, and vulvar intraepithelial neoplasia (VIN; studied in collaboration with the Gynaecology department). Bouwes Bavinck: 'We collaborate on many levels. We help to instruct CHDR's screening physicians who need to do the dermatological evaluation of study participants, and we're involved in writing study protocols and evaluating results. In this study for example, we evaluated the use of dermatoscopy in the assessment of actinic keratosis lesions.' There is also much more insight to be gleaned from the large amounts of data generated in these clinical trials. One research physician involved in these studies has written several articles about the classification of warts, based on the large database of images gathered by CHDR. 'It's always a pleasure to collaborate with Dr Robert Rissmann and his team,' reflects Bouwes Bavinck. 'It's a symbiosis: they bring a unique set of techniques and approaches to the table, and we complement that with our expertise and access to patients. It's a real win-win situation.'

‘They did a wonderful job on a very challenging study’

Working with CHDR

‘The scientific input of the team was exceptional. They were very involved – always thinking one step ahead. They never came to us with problems, always with solutions. I was very impressed. When it came to recruitment they really excelled: they went completely above and beyond. I had never seen so many people screened! Lastly, it was fantastic how they maintained the timelines as they did. Overall, they did a wonderful job in what was a very challenging study.’

Global Medicines Development Manager, Biotech Company *

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

Internal medicine

Image-guided surgery. Cardiology Services. Endocrinology research. Gene therapy. Inborn errors of metabolism. Oncology and infectious diseases. Internal medicine is a diverse research area, where CHDR is making a vital contribution to cutting-edge developments.

Exploring new ground in the field of internal medicine

Research in internal medicine at CHDR has made vital contributions to the development of a variety of compounds and treatments. In-house Cardiology Services continue to offer vital added value for early-stage drug trials, while new approaches promise improved insights into factors influencing heart rhythm. In partnership with a diverse range of collaborators, the Internal Medicine group is eager to break new ground, applying their expertise to new approaches in oncology, infectious diseases, vascular medicine and more.

'As we've done for the past three decades, CHDR will continue to contribute to the development of therapies for a wide variety of conditions,' says Prof. Koos Burggraaf, CEO. 'With our Biomarker group and Method Development group working on the development of new tools, we can tackle almost any challenge. In addition to our ongoing efforts in fields such as endocrinology, rheumatology, cardiology and the development of fluorescent markers for image-guided surgery, we are also looking at how we can broaden our range of activities. One possibility is to leverage our approach to early-stage drug development and our expertise in immunology to contribute to modern oncology. An area of keen international interest is the development of therapies and vaccines for infectious diseases – we're also thinking about ways in which we can contribute there, in partnership with experts in those fields.'

2019 saw the conclusion of several interesting patient studies. One such study investigated the safety and effects of a gene therapy approach to rheumatoid arthritis. Other studies explored potential treatments for rotator cuff tendinopathy, a painful shoulder condition, and for non-alcoholic steatohepatitis, an increasingly common form of severe fatty liver disease associated with obesity, insulin resistance, and type 2 diabetes. In addition, two studies concerned therapies for young patients with rare diseases caused by inborn errors of metabolism.

Image-guided surgery

In the past, clinicians in the fields of internal medicine and surgery have not always seen eye to eye. However, in the 21st century, the two disciplines are becoming better connected. One promising example of cross-disciplinary integration is image-guided surgery, where fluorescent compounds are used to highlight specific structures, providing the surgeon with additional visual guidance. Fluorescent markers can be used to highlight tumours, thereby facilitating the complete removal of all cancer cells. Increasingly, researchers are also using fluorescence to highlight other structures undergoing removal, such as lymph nodes. Conversely, the markers can be used to demarcate vulnerable structures, providing an extra safeguard against damage during surgery. Burggraaf: 'We've been collaborating for many years with Dr Alex Vahrmeijer and his Image-Guided Surgery group at the Leiden University Medical Center (LUMC). It's a very fruitful collaboration. The study of these fluorescent markers has a lot in common with classical pharmacology: they need to reach their target, engage with it and remain active long enough to be of practical use to the surgeon. In many of the compounds we've already explored, we were the ones who conducted the first-in-human trials in healthy volunteers. Once the safety, tolerability and pharmacokinetics of a certain compound have been established, we then proceed to conduct patient studies at the LUMC.'

In a scientific paper published in 2019, researchers from CHDR and the LUMC describe a remarkable compound that visualises the ureters, the delicate structures that transport the urine from the kidneys to the bladder. During surgery, it can be quite a challenge to see the ureters, especially if the patient has already undergone several operations. Accidentally cutting the ureter is a severe complication that every surgeon wants to avoid. The safety of the compound was established by the team at CHDR, and the researchers went on to demonstrate that it makes the ureters fluoresce just minutes after injection. The hope is that this compound will find its way into operating theatres around the world, increasing the safety of intra-abdominal surgery.

The links between CHDR's Internal Medicine team and the LUMC Image-Guided Surgery group have also been strengthened by the many PhD students who they have jointly supervised. The collaboration is set to continue in coming years, exploring an expanding range of compounds, with different applications in image-guided surgery. On page 86, Dr Alex Vahrmeijer reflects on the collaboration with CHDR, as well as his ongoing efforts to convince surgeons to use fluorescence to improve their work.

Cardiology meets machine learning

CHDR's in-house Cardiology Services, a wide range of Good Clinical Practice (GCP)-certified diagnostic procedures for the clinical drug development process, continue to offer added value for a range of studies. Cardiovascular safety is an essential requirement for every new drug. It is of crucial importance to assess the effect of a new compound on heart rhythm, ensuring that no dangerous arrhythmias arise – such as the infamous torsade de pointes. Closely related to these clinical services is the ECG research conducted by

Senior Clinical Scientist Dr Pim Gal, in collaboration with Zwolle-based cardiologists Dr A. Elvan and Dr A. Adiyaman, and Amsterdam-based cardiologist Dr Michiel Kemme who is interviewed on page 83. Gal: 'We have a large dataset consisting of all the ECGs that have been taken as part of the screening of our volunteers. We are now mining this dataset for interesting patterns, using a machine learning approach. In these ECGs, hundreds of parameters can be defined automatically. These parameters can then be fed into a neural network, together with relevant subject parameters such as weight, age, blood pressure and haemoglobin level. Using this approach, we have derived a model which can accurately estimate a subject's age from their ECG, within a margin of 5 to 10 years. This brings into sharper focus the effects that ageing has on the heart's electrophysiology.'

The researchers found other variables influencing the ECG which may have particular relevance to clinical pharmacology, such as body temperature, blood pressure, body mass index, sex, and haemoglobin level. 'We found that a lower haemoglobin level correlates with a longer QT interval,' says Gal. 'That's something we may need to bear in mind with regard to testing for QT interval prolongation – after all, we regularly take blood from our subjects, which significantly lowers their haemoglobin level.' The results of this study were published in 2019.

Endothelial function

In addition to the studies focusing on heart rhythm, Gal and his team increasingly collaborate with Dr Matthijs Moerland and his Biomarker group, whose primary expertise is in immunology (see also page 90). There is an increasing awareness among medical professionals that atherosclerosis, the most common cardiovascular disorder, has an important inflammatory component in addition to its well-known metabolic causes. But the immune system is notoriously complex, with the result that the practical, clinical relevance of immunological measurements can be difficult to establish. Gal therefore prefers to opt for a more pragmatic approach: 'It all comes together at the endothelium, the lining of the blood vessels: the end result of those complex inflammatory cascades is a reduction of nitric oxide signalling, which disturbs the natural feedback loops regulating blood flow. Therefore we can gain a lot by having a robust way to measure endothelial function – which is why we have been developing a new method which is both sensitive and easily standardised.'

The traditional way to quantify endothelial function is to measure flow-mediated dilation (FMD): the widening of an artery as a result of increased blood flow when the endothelium releases nitric oxide (NO). 'The FMD procedure is complex, difficult to standardise and notoriously difficult to execute in a reproducible manner, so we looked for alternatives,' says Gal. 'We now have a much more straightforward procedure, which is also more sensitive to changes in NO production. We measure the blood flow in the femoral artery using Doppler ultrasound. The subject sits on a chair with one leg extended and elevated. When the knee is flexed passively just once, it triggers a reflex which usually serves to increase blood supply to the muscles as we start walking. If the endothelium is healthy, you see a significant increase in blood flow that lasts for about two minutes. If endothelial function is reduced – for example, after a meal rich in sugar and fats – it's immediately apparent.' In elderly subjects, the response is substantially reduced and in patients suffering from heart failure, there is hardly any response at all. The team now uses this test to evaluate compounds acting on endothelial function, whether directly or through immunological pathways.

Studying infections

'There is a growing interest in the prevention and treatment of viral infections, and we are busy working on a safe way to study them in healthy volunteers,' says Associate Director Dr Ingrid de Visser-Kamerling. 'Thanks to our collaboration with Dr Meta Roestenberg at the LUMC, we hope to soon have a reliable model to study respiratory syncytial virus (RSV). We are also involved in a consortium for the study of influenza.' Both influenza and RSV will be studied by infecting healthy volunteers, an approach that Roestenberg is already using at the LUMC to study malaria. The collaboration between CHDR and Roestenberg will also extend to the field of malaria studies, as explained by Dr Roestenberg in the interview on page 84.

Roestenberg has a wealth of experience designing safe studies in infectious diseases, and has also studied a range of ethical and practical issues implicated in this kind of research. However, the study of RSV and influenza comes with a new challenge that is not present in malaria research: these viruses can be transmitted from one human to another, while the malaria parasite depends on mosquitoes for transmission. 'The effect of this is that, while malaria studies can be done on an outpatient basis, volunteers in RSV or influenza trials must remain entirely isolated until they are no longer contagious,' says De Visser. 'Nonetheless, since RSV and influenza are level 2 pathogens, they don't require the most extensive type of biosafety facilities – for example, there's no need for negative pressure rooms. This means that with some straightforward adaptations, it would be possible to equip our Clinical Research Unit for the study of these viruses.'

In healthy adults, the RSV virus is relatively harmless, causing a fairly innocuous upper respiratory tract infection – the common cold. In young children, elderly people and immunocompromised patients, however, the infection can be far more dangerous and even fatal. Currently, there is no treatment for RSV infection, and no vaccine to prevent it. Globally, RSV infections are an important cause of child mortality, especially in developing countries. 'In 2019, I attended the 3rd IABS meeting on Human Challenge Trials in Vaccine Development in Oxford. I was struck by how the field is developing, as well as the need for RSV infection models,' says De Visser. 'We believe that CHDR, along with its collaborators, could really add value to the development of preventative or curative treatments for this type of infection.'

CHDR has a strong track record in the study of immunology, complementing a wealth of

pharmacological expertise and decades of experience in conducting clinical trials. Thanks in particular to the work of Dr Matthijs Moerland and his Biomarker group in this area, the organisation is well-positioned to conduct immunological studies in RSV. ‘We can already learn a lot from simply studying the immune responses in the blood of RSV-infected volunteers. In the early stages of an infection, even before the virus actually infects us, the innate immune response is of crucial importance. Once the infection is manifest, innate and adaptive immunity together drive the body’s effort to overcome the virus. It will be very interesting to study those phases closely, with a view to identifying potential drug targets,’ says De Visser. ‘A relatively innocent virus such as RSV can serve as a model for studying treatments that boost innate immunity – treatments which could eventually be used to fight more dangerous viruses, such as the novel coronavirus. I see great potential in our collaboration with the LUMC, for the future of CHDR and for the improvement of care for patients with infectious diseases.’

Improving the treatment of two orphan diseases

Two interesting projects began in 2019, with the goal of improving the wellbeing of young patients suffering from two rare orphan diseases: cystinosis and the ARID1B syndrome (also known as Coffin-Siris syndrome). The cystinosis project concerned the testing of a new formulation of an existing drug, aiming to establish whether this formulation has improved pharmacokinetic properties.
Associate Director Dr Ingrid de Visser-Kamerling: ‘Cystinosis is a storage disease in which cystine accumulates in the cells, causing damage to the kidneys and the cornea. Damage can be delayed by the drug cysteamine. Unfortunately, cysteamine has a short half-life and needs to be given frequently, even in the middle of the night, adding to the burden on children and their parents. We’re currently investigating whether the new formulation has more favourable pharmacokinetics, allowing more time between doses. This would significantly ease the burden on cystinosis patients and their parents, at a reasonable price.’

Meanwhile, Coffin-Siris (or ARID1B) syndrome is rare genetic disorder that causes developmental delays and cognitive deficits, in addition to a characteristic appearance. Associate Director Dr Rob Zuiker: ‘Most Dutch patients with this syndrome are treated at the Leiden University Medical Center (LUMC).

In 2017, a preclinical study showed that in a knock-out mouse model, a benzodiazepine drug had positive effects on recognition and social memory, and reduced anxiety-like behaviour which is common with this syndrome. So Prof. Adam Cohen proposed to investigate the effects of this drug in patients suffering from Coffin-Siris syndrome, financed by our R&D Fund.’
In 2019, a team at CHDR including Dr Matthijs Kruizinga undertook a preliminary study to explore the use of NeuroCart with Coffin-Siris patients. The researchers found that, while the patients refused to wear an EEG cap, they were nonetheless willing and able to engage with several NeuroCart tests – including the adaptive tracker, visual analogue scales and a subset of memory tasks. ‘Our next step will be to use the same NeuroCart tests to objectively measure the effects of the benzodiazepine treatment. Using a placebo-controlled multi-dose setup, we will also gather data from these patients outside the Clinical Unit, by asking their parents or caregivers about their behaviour at home,’ says Zuiker. ‘Our close link with the physicians who treat Coffin-Siris patients in the Netherlands means that it’s entirely feasible to include more than half of all Dutch Coffin-Siris patients in this study. This is a unique project: not many organisations are in a position to undertake this work, and so we see it as our duty to fill that gap.’

Dr Michiel Kemme, staff cardiologist at Amsterdam University Medical Center

'I enjoy being able to contribute to CHDR's work'

'I'm glad I stayed in touch with CHDR after my PhD in 2003,' says Dr Michiel Kemme, staff cardiologist at Amsterdam University Medical Center and part-time consultant to CHDR Cardiology Services. From 1997 to 2002, he was employed at CHDR, conducting research into endothelial function and leading several studies with patients and healthy volunteers. He went on to train as a cardiologist at the Leiden University Medical Center, and followed this with a fellowship in electrophysiology. In 2008, he joined Amsterdam University Medical Center. 'In all those years, when I was a resident and even after I came to Amsterdam, I visited CHDR regularly, collaborating on scientific papers and helping out by reviewing ECGs. Then, in 2014, Prof. Koos Burggraaf told me about his plans for Cardiology Services. The core concept was that CHDR would analyse the 24-hour ECG registrations – what we call "Holters" – in-house, instead of outsourcing them. To complement this, sponsors would be offered a package of other cardiology-related services. With this in place, CHDR is now able to handle most routine analyses – even more so since my colleague Dr Pim Gal joined their staff. But whenever they need me to provide my expertise, I'm more than happy to help out.'

The Holter registration is crucial in early-stage clinical drug development, to monitor the effects of a compound on cardiac electrophysiology. 'The most important feature to monitor is the length of the QT interval in the ECG. If the compound is associated with a prolongation of the QT interval, there is an increased risk of a dangerous ventricular arrhythmia and sudden death,' says Kemme. 'That's why it's important to check for this phenomenon early in clinical drug development, to make sure that a drug is safe and won't fail at a later stage of development due to this complication.' On the other hand, it is important to minimise the chance of excluding promising new drugs that are, in fact, safe. To this end, Kemme has collaborated with Burggraaf and Gal in recent years on efforts to find the optimal way to study the QT interval in the context of early-phase studies.

'I enjoy being able to contribute to Cardiology Services at CHDR, but what really elevates the collaboration for me is that I can be part of their scientific research. Last year, for example, we published four papers based on an analysis of hundreds of ECGs in healthy volunteers. As you know, every subject is screened before participating in a study. This yields a huge database that we can use to study the effects of risk factors such as age, blood pressure and weight on the ECG of healthy people. With rich data like this, we can better understand the gradual process of cardiovascular decline in ageing and the roles of the various risk factors.

'Another CHDR study I was involved in concerned a new drug to treat atrial fibrillation. New medications for the treatment of arrhythmias are rare, so this was a great opportunity. More medications for arrhythmias would be a real asset in cardiology practice. Although nowadays we can treat many arrhythmias with catheter interventions, for some cases – such as when patients are too frail – it would be good to have a pharmacological alternative to treat the problem.'

Dr Meta Roestenberg, infectious disease specialist at the Leiden University Medical Center

'Together, we can help in the global fight against infectious diseases'

'Our extensive collaboration with CHDR is rooted in an equal and complementary partnership,' says Dr Meta Roestenberg, specialist in infectious diseases at the Leiden University Medical Center (LUMC). Roestenberg's research has a particular focus on malaria and other poverty-related infectious diseases. 'My colleagues and I have spent some years developing an approach whereby we can study malaria and other parasitic infections by infecting healthy volunteers. We do this on an outpatient basis, with the subjects visiting our laboratory once a day for a thorough check-up,' says Roestenberg. 'With malaria, the dynamics of the infection are well-known. For the first seven days, the parasites develop in the liver. There aren't any parasites in the bloodstream, and subjects don't present with any symptoms. Then, once the parasites start emerging into the bloodstream, the subject receives a curative treatment.' To infect the subjects, Roestenberg uses GMP-produced wild-type *Plasmodium falciparum* parasites. Rapid treatment is key to ensuring subjects' safety. In addition, subjects only receive a small number of parasites – enough to demonstrate the effects of a drug or vaccine, without causing a full-blown malaria infection.

Alongside ongoing work on parasitic infections, Roestenberg and CHDR plan to expand their collaboration to include work on viral infections, such as influenza and the respiratory syncytial virus (RSV). 'Of course, special measures will be required to make sure the viruses don't spread to the outside world or infect the staff. For CHDR, this is novel territory, which calls for a very close collaboration. We will be on site at least once a day to make sure everything is going smoothly.'

While Roestenberg and CHDR's Dr Ingrid de Visser were collaborating on the development of an RSV infection model together with Rotterdam-based company Viroclinics, Roestenberg was approached by a pharmaceutical sponsor who wanted to test a new anti-malaria compound. As well as using Roestenberg's infection model to study the compound's efficacy for treating malaria, the company also needed data on the pharmacokinetics of the compound. Roestenberg: 'Our malaria studies normally run on an outpatient basis. However, to investigate the pharmacokinetics, we need to take blood samples at regular intervals during the first 36 hours after administering the drug. So, of course, I asked Ingrid if we could do it at CHDR, and we prepared the study together.'

According to Roestenberg, her own approach has much in common with CHDR's philosophy. 'I like their rational approach to drug development, tackling the most difficult questions first in order to make the process more efficient. The earlier you can get a basic understanding of whether your product works, the better. The same is true of our infection models: with our method for studying infectious diseases in healthy volunteers, we can show already at an early stage of development whether a vaccine or a treatment is potentially effective.'

In studying RSV and influenza, Roestenberg remains true to her core research interest: poverty-related diseases. 'An infection that is already problematic for a rich country with a robust healthcare infrastructure can really wreak havoc in a country where the healthcare system is more vulnerable. For example, RSV can cause problems for small children in Western countries. But when we look at developing countries, we see that the burden of this disease is far greater. So a vaccine could make a huge difference. The same is true for influenza,' says Roestenberg. 'It's clear that a better understanding of these infections – and accompanying advances in treatments and vaccines – will contribute to better healthcare worldwide. Thanks to the strong synergy between CHDR and our team at the LUMC, we are poised to play our part in the process.'

Dr Alexander Vahrmeijer, Image-Guided Surgery group at the Leiden University Medical Center

'We're pioneering new approaches and spreading the word among surgeons'

'In our ongoing collaboration in the field of image-guided surgery, we're exploring a variety of fluorescent compounds together with Prof. Koos Burggraaf and his team,' says Dr Alexander Vahrmeijer, from the Department of Surgery at the Leiden University Medical Center (LUMC). 'Some of these compounds have been developed by companies, others are made in the LUMC's own GMP-compliant facility. So far, we've investigated a wide range of compounds for an increasing number of indications.

'Our collaborative work extends to several different applications of image-guided surgery. We use antibodies labelled with a fluorescent marker to detect cancer cells, ensuring complete tumour removal with minimal damage to healthy tissues. Additionally, we explore the application of fluorescence to highlight structures that need to remain intact during surgery, such as nerves or the ureters. We also use image-guided techniques to evaluate tissue oxygenation, to determine its viability. In 2019, we tested several new compounds, including one aimed at detecting prostate cancer,' says Vahrmeijer. 'An interesting new development is the use of the same antibody in both PET scans and image-guided surgery. This makes it possible to visualise a tumour during surgery in a way that reflects the preoperative PET images – in other words, enabling a one-to-one relationship with the images that have been used to plan the surgical procedure.' Another innovative approach that is currently being studied involves spraying a compound on the surgical field to visualise tumours or other structures. This topical administration avoids systemic exposure and reduces the chance that the patient will experience side effects.

Vahrmeijer and his team are pioneers in their field, which also means that they face the challenge of convincing their colleagues of the value of image-guided surgery. This has proven to be more difficult than it might seem, as the necessary investments in camera systems will only be made if there is convincing evidence that the technique improves the quality of surgery. This requires large clinical trials, which are generally costly. 'If just one or two of these compounds were to become mainstream, it would be much easier to finance trials,' says Vahrmeijer. 'For that reason, we're preparing a multicentre regional trial in 1,000 patients undergoing colorectal cancer surgery, focusing on so-called anastomotic leakage.' The term anastomosis refers to the connection made between the two remaining parts of the colon, to re-establish continuity after the removal of the tumour. In approximately 6–15% of patients, depending on tumour localisation, this connection does not hold. The result of this is anastomotic leakage, which can be a severe complication requiring additional surgery. 'Using the dye indocyanine green (ICG), we hope to be able to see the viability of the ends to be joined, thereby ensuring the optimal healing of the anastomosis. Our aim is to reduce the number of patients suffering from an anastomotic leakage by at least 50%. It's great that our colleagues in nearby general hospitals are willing to participate in this trial. Together, we should be able to enrol those 1,000 patients in a relatively short time. And the nice thing about ICG is that it's inexpensive – so if it works, we can keep using it. We really hope that the approach with ICG will take us a step closer to wider acceptance of image-guided surgery. In the meantime, we'll continue to collaborate with CHDR to explore new compounds and indications. There is plenty still to do, but together we make a great team.'

Biomarkers and Laboratory

How to measure a drug's effects in immunology, cardiology and vascular medicine – that's the challenge CHDR's Biomarker group is always eager to take on, supported by a state-of-the art Bioanalysis laboratory.

Bridging disciplines: immunology, cardiology and the gut microbiome

Early-phase drug development bridges preclinical and clinical research. At CHDR, this translational role is most evident in the work of the Biomarker group. Traditionally, the team has focused on the immune response, but now plans to include cardiovascular biomarkers. Alongside ongoing projects in both immunology and cardiology, a new research project studying the gut microbiome promises to bring these two disciplines together.

In recent years, Dr Matthijs Moerland and the Biomarker group have validated a series of procedures to study the effects of compounds on various immune reactions in healthy volunteers. Using *ex vivo* blood tests, *in vivo* skin tests and even *in vivo* experiments, they can show the effects of anti-inflammatory compounds on the innate immune response. Increasingly, they also study the T-cell and B-cell compartments of the adaptive immune response. In addition to these ongoing studies, Moerland has been planning an organisational change: 'We are collaborating more and more with our colleagues who study cardiology and the endothelium, and in the coming year, they will join our research group. As you know, CHDR has a long tradition of cardiovascular research, thanks to the work of our current CEO Prof. Koos Burggraaf and our Senior Clinical Scientist Dr Pim Gal. Immunology plays an increasingly important role in cardiology and vascular medicine. Atherosclerosis can be regarded as a disturbed interaction between the immune system and metabolism, leading to vascular inflammation. So we can both benefit from a closer collaboration.'

Microbiome

Rapid growth of knowledge about the gut microbiome has recently begun to yield promising treatments for various diseases. Although this field is still in early stages of development, Moerland and his colleagues are eager to explore what it has to offer. 'In principle, it is very likely that we can influence immune reactions and other physiological parameters through the gut microbiome. But this approach is also challenging for many reasons. To begin with, the vast differences in gut microbiome between humans and animals mean that preclinical data from animal studies are of limited value. On top of this, there are large differences between individual humans, and we only have limited data on how individuals' gut microbiomes change over time.'

Studying the gut microbiome means breaking new ground, but Moerland is confident that his team is up to the challenge. In recent years, researchers at CHDR have already studied the skin microbiome and its interaction with the immune system. Moerland and his colleagues also have a variety of challenge tests at their disposal to study specific immunological effects of interventions in the gut microbiome. Their approach is similar to the study of novel immunomodulating compounds with a direct effect on immune reactions. For the last three years, for example, the team has been using a vaccination with a neoantigen to study the antigen-specific adaptive immune response, while developing an investigational compound to modulate this response. The neoantigen in question is the KLH antigen, derived from a limpet that lives in the Pacific Ocean. In this approach, healthy volunteers are vaccinated with the KLH antigen, and the immune response to this specific antigen is then monitored. An effective immunomodulator will have a measurable effect on this response.

Moerland: 'One of our new sponsors is developing bacterial strains that interact specifically with immune cells in the intestine, in order to influence certain populations of circulating immune cells. Some of their products aim to stimulate the immune response, while others have an anti-inflammatory effect. It's difficult to test the effect of such bacteria in healthy people, but the KLH neoantigen vaccination now provides us with a way to do so. The KLH model is becoming increasingly important for CHDR, and is being further perfected and characterised as part of our own R&D programme. It holds particular promise for the early clinical development of immunosuppressive agents, and maybe even for immunotherapeutic compounds against cancer and other conditions.'

Vascular effects

CHDR is now also a member of a consortium with Royal DSM and TNO (the Netherlands Organisation for Applied Scientific Research), looking at the effects of dietary fibre on the microbiome. Here, too, the ultimate aim is to bring about systemic health improvements, especially in the cardiovascular system. Moerland: 'We're very excited about this collaboration, because it allows us to study a range of different aspects of the gut microbiome. To begin with, we hope to learn more about natural inter- and intra-individual variation

in the composition of the gut microbiome. The placebo group, who will receive no dietary fibre, will therefore provide us with an all-important baseline, yielding insights that are just as compelling as those from the intervention group.'

Studying interventions that derive their potential effect from the gut microbiome requires a different approach from typical drug development studies, because the effects arise more slowly. 'When we study small molecules, we can usually measure an effect after a single administration, if we have the appropriate readout. Fibre or bacteria, however, must be administered for a few days or weeks before we can expect any demonstrable systemic effects,' notes Moerland. 'The matter is more complex still when you consider that the gut microbiome shows great variability between individuals, not least due to differences in diet.'

In the consortium study, the systemic effects of the dietary fibre intervention will be measured using a standard meal which is rich in fat, protein and carbohydrates. Such a meal causes several temporary changes in the subject's metabolism, inflammatory status and vascular responses. Moerland: 'Studying the effects of this meal on the vasculature will also help us to establish whether we can use this approach as a challenge test in our cardiovascular research. If we want to do a first-in-man study with a compound that may improve endothelial function, we need to be able to demonstrate pharmacological effects in healthy volunteers. So we are on the hunt for challenge tests that temporarily affect endothelial function. The mixed meal with protein, fat and glucose holds potential here.' Learn more about CHDR's collaboration with TNO in the interview with Dr Femke Hoevenaars on page 97.

To measure subtle vascular effects, the team also needs to establish a sufficiently sensitive readout. CHDR has extensive experience in using laser speckle contrast imaging, which is less operator dependent and less invasive than conventional Doppler measurements. 'Another approach, which Pim Gal is now exploring, is to use a small camera under the tongue to take direct measurements of the diameter of the sublingual blood vessels,' says Moerland. 'Once we have a robust challenge, we will also be able to select the best imaging technique.'

Improving existing models

'We are constantly refining our tools to be able to learn more from first-in-human studies,' says Moerland. 'With our earlier challenge tests using intradermal bacterial lipopolysaccharide (LPS) to trigger the innate immune response, we have demonstrated that we can quantify and visualise the effects of immunomodulatory compounds on that response. To prepare for sponsored studies in that area, we are now quantifying the effects of conventional immunomodulators such as corticosteroids. In 2020, we will start a self-financed study comparing the pro-inflammatory effects of intradermal LPS and imiquimod, and the response to different doses of corticosteroids.' The amount of inflammation will be extensively studied using the various DermaToolbox techniques to visualise the skin, in addition to skin biopsies and suction blisters to measure immune cells and cytokines.

The team will also return to this LPS challenge model to look again at specific cell subsets and physiological mechanisms. Moerland: 'Among other things, we want to study the activation of the inflammasome by LPS. We're also planning to evaluate the effect of LPS and corticosteroids on the neutrophil in greater detail, looking at cellular function and NET formation.' NETs – neutrophil extracellular traps – are fibres consisting of DNA and proteins, formed by neutrophils as they turn themselves inside out in the capillaries of the skin or the kidney. NETs can bind pathogens and cytokines and induce a local inflammatory reaction. Some inflammatory and autoimmune diseases are characterised by an exaggerated NET response. 'There are compounds under development to suppress the NET response. Once these compounds are ready for clinical development, we want to have the models to be able to study them,' says Moerland.

> 'We are constantly refining our tools to be able to learn more from first-in-human studies'

In their efforts to improve existing models and approaches, the team can again count on the support of a rich network of collaborators. Read more about this dynamic exchange of expertise in the interviews with Dr Erik Lubberts from the Erasmus Medical Center (page 98) and Dr Jeffrey Bajramovic of the Biomedical Primate Research Centre (page 96).

Investigating neurodegenerative diseases in the bioanalysis lab

CHDR's bioanalysis laboratory, also headed by Dr Matthijs Moerland, offers complex high-tech measurements that play a vital role in clinical studies carried out across the organisation's various areas of expertise. The lab has become increasingly important for research into neurodegenerative diseases, in particular through conducting precision measurements of cellular energy balances. Moerland: 'mTOR is becoming increasingly important as a target for new drugs. This major signalling molecule is an important central point in the cell, which monitors the energy balance between the cell and its environment and then translates this into cell behaviour – whether the cell proliferates, whether the mitochondria have to work faster or slower, and so forth. We are now developing all kinds of cell-based methodologies in the laboratory to measure the activity of mTOR and related pathways.'

Equipped with these techniques, CHDR will be in a leading position to conduct studies with various compounds aimed at combating neurodegeneration. In many of these disorders, there is a disturbed energy balance in the immune cells in the brain (neuroglia). These cells become less vital, produce less ATP and become more vulnerable to cell death and other degenerative processes. It is likely that the energy-sensing pathways in cellular metabolism play an essential role in these processes. Moerland: 'The methods we're developing focus on measuring these metabolic pathways in circulating immune cells, as a proxy for activity of a drug in the microglia. If we are able to demonstrate in circulating immune cells that a compound is effective in the pathways it targets, we are one step closer to demonstrating the ultimate desired pharmacological effect.'

Dr Jeffrey Bajramovic, head of the Alternatives Unit, Biomedical Primate Research Centre

'With complementary expertise, we can explore shared interests'

The Biomedical Primate Research Centre (BPRC) is one of the largest centres in Europe keeping primates for scientific research. 'At BPRC, we do preclinical research ranging from drug discovery to translational studies,' says Dr Jeffrey Bajramovic, who leads BPRC's efforts to develop alternatives for animal studies. In 2019, he published a paper in collaboration with Dr Matthijs Moerland and his colleagues on adverse effects of biopharmaceuticals caused by undetected impurities. The article, based on earlier collaborative research, describes several causes of adverse immunostimulation by endotoxins and other contaminants in biopharmaceuticals. 'Even drugs that have been approved via the usual tests may contain impurities that can cause fever, sometimes even leading to severe problems,' says Bajramovic. 'We have several sensitive tests in our lab that are able to identify these contaminants.'

Although the long-term goal of the Alternatives Unit is to eliminate the need for animal studies, in the short term the tests and models developed in the Unit are primarily aimed at refining preclinical studies and gleaning more information from them. Bajramovic: 'Using data from RNA sequencing and cell-based tests, we can devise animal experiments with more precision, based on mechanistic insights. Maybe, in some cases, we could even skip the animal model and go straight to human subjects, using techniques such as microdosing. An interesting angle to explore is how such an approach can be implemented while maintaining subject safety as the utmost priority.

'Matthijs Moerland and I have many scientific interests in common,' notes Bajramovic. 'For example, we are both interested in natural variations in the innate immune response. Received wisdom has it that humans have highly similar innate immune responses, but we have demonstrated that there is in fact considerable variation, both in humans and primates.' Moerland and Bajramovic also share an interest in the big picture of the drug development process, in particular the value of preclinical models for predicting later outcomes. Bajramovic: 'There is a saying in the industry that a bad model is better than no model. Nonetheless, this shouldn't mean being satisfied with models that don't perform well. It's important that we evaluate how well a given model predicts the success or failure of a drug in later phases of development – or, if a model fails, trying to understand why. Basic biology can provide valuable pointers here. For example, rodents and primates differ in their innate immune response to viruses, something which must be borne in mind when using rodent experiments to predict the success of an antiviral agent. All in all, I believe there is much to be gained from reverse translational analysis. Of course, this is only one of many areas where a joint effort can be beneficial. With our shared interests but diverse expertise, I see many possibilities for future work with CHDR.'

Dr Femke Hoevenaars, Netherlands Organisation for Applied Scientific Research (TNO)

'There's still much to discover by studying the gut microbiome'

TNO, the Netherlands Organisation for Applied Scientific Research, takes a dynamic approach to health. The Healthy Living unit investigates resilience as an index of health. Resilience is defined as the ability of the organism to return to homeostasis after exposure to a stressor. 'We refer to this as phenotypical flexibility. We give test subjects a drink that is very rich in fat, protein and carbohydrates, and then measure the amplitude and duration of various changes in their physiology,' says Dr Femke Hoevenaars, who works at TNO investigating nutritional physiology and metabolism. 'Using this approach, we have been able to stratify a group according to age. In addition, we have demonstrated a markedly different response in patients with type 2 diabetes. This confirms that our test has a clear relevance to health,' says Hoevenaars.

The high-calorie standard meal challenge used in the tests influences the immune system towards a more pro-inflammatory state. Recent results show that this pro-inflammatory effect is stronger in subjects following a diet of white bread and refined flour, compared to those who follow a diet based on wholemeal bread and flour. Hoevenaars: 'We assume that this effect is partly due to changes in the composition and function of the gut microbiome, but we need to study this more explicitly. Our current collaboration focuses on that.'

Most of TNO's research takes place in the context of public-private partnerships, so a project was set up in collaboration with Royal DSM and CHDR. The plan is to enrol 64 subjects in this study in 2020. In this randomised controlled crossover trial, the intervention group will either receive a daily dose of a specific dietary fibre supplement produced by DSM, or a placebo control supplement. All subjects will visit CHDR's Clinical Research Unit at the beginning of each intervention period, and again after 12 weeks, to be tested using the high-calorie meal challenge. In addition to analysing the microbiome in the subject's stool samples, TNO researchers will study the effects of the investigational dietary fibre supplement on the microbiome in these samples using *in vitro* assays. Hoevenaars: 'TNO is a large research organisation, and we have experts in many different fields. One of the exciting things about working at TNO is that, no matter how wild your ideas, there's always someone you can discuss them with.'

Microbiome research is a relatively new area, and there are still many unknowns. Hoevenaars: 'For us, an important step would be to study the effects of fibre on the gut microbiome, as well as the relationship between the microbiome and phenotypical flexibility. DSM is interested in innovative measurements of health, which they can use to better understand and improve the health impact of dietary fibre and other food components. Collaboration with CHDR offers us not only the facilities to conduct the study, but also the interaction with other scientists who are interested in the immunological and microvascular effects of this high-calorie meal challenge. Whatever the outcome of this study, it promises to yield valuable insights for everyone involved.'

Dr Erik Lubberts, immunologist at Erasmus Medical Center, Rotterdam

'Our scientific discussions really enhance the collaboration'

'In 2009, my colleagues and I published our animal model for the study of psoriasis plaque formation, using imiquimod on the skin of mice to induce a lesion that is similar to psoriasis,' says Dr Erik Lubberts, immunologist at the Erasmus Medical Center in Rotterdam. 'Our model can be used to study the role of several cytokines such as IL-17 and IL-23, and it has been widely adopted. In 2018, we became involved in CHDR's research through Errol Prens, our professor in Immunodermatology. Dermatologists at Erasmus MC had already established a collaboration with CHDR. When I got involved, Dr Matthijs Moerland and his team were studying immune reactions in the skin, using imiquimod and LPS to trigger an inflammatory response.

'In recent years, we have regularly contributed to these studies, aimed at gaining a deeper understanding of the innate immune response and finding ways to measure the effects of immunomodulators in healthy volunteers. Matthijs and his team were already using suction blisters to study various inflammation markers. Additionally, we analysed skin biopsies, using microscopic tissue evaluation to look at the immune cells. Sometimes, we used additional markers to visualise specific subsets of immune cells. We also analysed the mRNAs of a set of genes. For each experiment, Matthijs sent us a list of target genes that he wanted us to analyse, to understand their role in the inflammatory response.

'In addition to my research activities around skin inflammation, I'm also engaged in rheumatology research. It's interesting to see the similarities and differences between the various immune-mediated inflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis, and psoriasis. Studying skin reactions is of course a very useful approach for evaluating the effects of a potential treatment. In some cases, the effects on cutaneous inflammations predict what a compound will do in other inflammations – for example, in the joints or in the gut. Of course, there are always exceptions. Anti-IL 17, for example, is quite effective in reducing psoriatic lesions, and it may also work in the joints in psoriatic arthritis, but it has hardly any effect in rheumatoid arthritis. We still don't fully understand why.

'What I cherish about the collaboration with Matthijs is our scientific discussions, the chance to explore and examine the data from different points of view. We each have our own specific background, but when we combine our expertise, the gain in knowledge is not purely additive: the interaction itself opens up new perspectives. Being able to see the big picture in this way can really add value to our individual lines of research.'

‘Not just a phase 1 unit, but a partner too’

Working with CHDR

‘We worked with CHDR on our development programme. CHDR was more than just a contractor or a phase 1 unit for us – they were a partner, too. Many phase 1 units simply follow the protocol you give them, but CHDR takes a thoughtful and questioning approach. I appreciate their critical perspective: rather than simply agreeing, they take an evaluative stance and come up with alternative suggestions where appropriate. They have invested as much into our programme as we have, something which sets them apart from other organisations.’

Medical Director,
Biotech Company *

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

Method development

Technology plays a crucial role in CHDR's data-rich approach to early-phase drug development. The Method Development group adapts and validates innovative measures, tailored to the needs of clients. Rich datasets yield deep insights thanks to machine learning approaches and specially-developed algorithms.

Cutting-edge solutions to the challenges of early-phase drug development

The Method Development group is tasked with developing and validating novel measurements, as well as designing algorithms to analyse the data these measurements yield. The group's work in 2019 contributed to improved methods for studying a range of disease areas, with a particular focus on pain and neurodegenerative disorders. Objective, high tech approaches – such as CHDR's MORE remote monitoring platform – give rise to increasingly large datasets, calling for innovative machine learning solutions.

'It has always been our philosophy to learn as much as we can from early-stage drug trials, and doing so requires the highest standards of data quality and reliability,' says CMO/CSO Dr Geert Jan Groeneveld. 'That's why we see the development and improvement of measurements as such an important area for investment. These modern, data-rich approaches are also generating ever-larger data sets, and we need talented people to develop and validate the algorithms necessary for effective analysis. The work of our Method Development group is paramount not only for tackling current challenges, but also for keeping pace with the rapid technological developments taking place across the industry.'

The group, led by Dr Robert-Jan Doll, consists of dedicated professionals from a variety of backgrounds. 'We're a dynamic group with diverse expertise – from technical physicians, to data scientists, and engineers. That makes for interesting discussions,' says Doll. 'What we have in common, though, is that we're all very solution-focused: it's our job to provide practical solutions to the challenges of early-stage drug development, and we're all keen to play our part in delivering on that.'

PainCart® developments

In 2019, the group was involved in several new developments at CHDR. Among these are ongoing projects in CNS and pain research, including efforts to improve and diversify the pain models used in the PainCart test battery. Doll: 'Some of these new models deal with factors that may influence pain perception on various levels of the nervous system. We're currently exploring the use of virtual reality in pain research, to understand the role of visual cues. We've conducted studies using an augmented reality approach, where subjects see virtual effects overlaid on real-time images of their own body. They see a visual overlay on a specific area of their body – for example, on one of their legs – depicting physical damage or injury. Meanwhile, a painful stimulus is applied to that same area. We're particularly interested in how their pain responses are modulated by the presence or absence of these visual cues.' An illustration of this approach can be seen on page 32.

Two other recent additions to the PainCart are pressure algometry and laser-evoked potentials (LEP), both of which were the subject of validation studies in 2019. In pressure algometry, a device is used to apply and measure pressure on a small surface on the body, to determine the threshold pressure at which the stimulus is experienced as painful. Meanwhile, LEP is a pain model that offers an objective measurement to complement a subject's behavioural or verbal responses. In this model, the electrical activity in the brain is measured (EEG) while the subject receives a painful stimulus consisting of a brief laser pulse on a small patch of skin. The subject is also asked to rate the pain on a visual analogue scale, making it possible to study the relationship between subjective experience and objective measurement. As of 2019, the PainCart now offers the possibility to tailor the LEP pulse strength per subject. LEP can be used separately or in combination with other models, such as increased pain sensitivity (hyperalgesia) induced by capsaicin, the substance that gives chilli peppers their characteristic heat.

Neurodegenerative disorders

In the field of CNS research, an important mission of the Method Development group is to expand the set of tools for studying neurodegenerative disorders such as Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). A new method for studying brain excitability – transcranial magnetic stimulation in combination with EEG recording (TMS-EEG) – has been validated in various conditions (see page 37). TMS-EEG is one of the

fields in which CHDR collaborates with researchers from the University of Twente, who feature in the interview on page 42. Doll: 'My colleagues are also working on methods to study the excitability of the peripheral nerves and muscle fibres, using threshold tracking and muscle velocity recovery cycles. Used separately or together, these methods provide sensitive measures of motor function. With this in hand, we're better equipped to study novel treatments for neurodegenerative disorders such as ALS.'

CHDR's involvement in PD research is growing year on year, and the development of new methods plays an important role in that work. 'To be able to measure the effects of a compound after a relatively short period of time, it's important to have sensitive measures for various symptoms of the disease,' says Doll. 'As part of this, we're working on a better setup to quantify finger tapping, a test that assesses subtle motor control. The old setup used two arcade-style buttons with accompanying lights, and the subject's task was to tap each button when its corresponding light switched on. However, in practice, this wasn't sensitive enough to assess the effect of medication on symptom severity.' The group has now developed a touchscreen version of the task, which provides many advantages over the old button-press setup. Doll: 'The touchscreen version allows for the measurement of many more parameters, such as the spatial accuracy of the patient's movements. We are validating this new approach and correlating it with the gold standard in Parkinson research, the Unified Parkinson's Disease Rating Scale (UPDRS).'

There have also been improvements to the NeuroCart test battery, one of CHDR's key tools in the study of CNS functioning. In 2019, the group developed a portable version one of the tests – the so-called adaptive tracker test, which measures visuomotor coordination and vigilance. In this test, the subject uses a joystick to move a small dot so that it stays within a continuously moving circle on a computer screen. A portable version of this test means that it can be applied in settings outside the Clinical Research Unit, such as in the subject's home, or at other research or healthcare centres.

Big data: time series and machine learning

Many new methods at CHDR generate large datasets, and the challenge facing the Method Development group is to make sense of these complex, multifaceted measurements. In some cases, the data is generated in the form of a constant flow of information, which needs to be funnelled into a small set of informative biomarkers. Much of the group's work, therefore, concerns the development of algorithms to perform these key processes. Doll: 'Basically, we develop two types of algorithms: algorithms which use sets of biomarkers to predict outcomes or classify groups, and algorithms that convert extensive time-series data into single biomarkers. The data we work with are varied – in one project we might work with output from our driving simulator and on-the-road test car, while in another project it could be something as specific as the angle of finger joints during a finger-tapping task administered to PD patients.'

Common forms of time-series data are EEG and ECG recordings. In these datasets, frequency can also be a point of interest. Doll: 'One study conducted at CHDR in 2019 involved a drug that was suspected to cause an increase in heart rate. The subjects, who took either the medication or placebo, were monitored for a period of two weeks using the MORE platform in combination with a smartwatch that continuously measured their heart rate. Researchers from our group designed an algorithm that could reduce this wealth of time-series data into a small set of biomarkers. With such an algorithm, we have the possibility to demonstrate the effect of medication on heart rate.'

Machine learning approaches are pivotal for finding patterns in large datasets. A key example of the power of machine learning is CHDR's work developing methods to assess drug effects on driving behaviour. The classical method, developed decades ago, relies on the use of just one parameter: the deviation of the car from the white line in the middle of the road. Clearly, a combination of measurements could provide far more detailed information about the influence of medication on safety while driving. Therefore, CHDR now works with a driving simulator from Green Dino, and an on-the-road test car fitted with an array of devices measuring a variety of relevant parameters. However, the issue facing the researchers is that the datasets yielded by this approach are vast. Therefore, they use machine learning approaches to glean insights from this rich array of measurements. To validate the approach for use in drug trials, researchers in the Method Development group are currently exploring how driving behaviour is affected by different states, such as being sleep deprived, or under the influence of (low doses of) alcohol or benzodiazepine medication. The aim is to use these machine learning approaches to come up with drug-specific profiles of driving behaviour.

The MORE remote monitoring platform also yields an immense amount of data, but here again, the rewards in store are significant. In particular, remote monitoring approaches hold much promise for improving paediatric studies, as described by Dr Gertjan Driessen on page 116. Recently, MORE has been deployed in paediatric care settings to assess the duration of infants' crying, and to determine the amount of coughing in children with asthma. Doll: 'The researchers on that project wanted a way to be able to identify these sounds automatically. Using long audio recordings of children in paediatric care wards, my colleagues were able to develop an algorithm that can automatically and instantaneously detect crying or coughing. What's exciting is that this approach has potential beyond the research setting: it could find application in paediatric healthcare.'

Large datasets are not only generated by novel technology, however. There is, in fact, a wealth of data already being generated in the course of everyday operations at the organisation – and these datasets, too, can yield new insights through machine learning. One such example is the ECG data recorded during the screening of subjects. By applying a machine learning approach, CHDR researchers developed an algorithm that is able to determine the age of a subject based on the ECG, precise to within 10 years. (see also page 78).

A future application of machine learning again involves the study of Parkinson's disease. A large PD cohort study will soon begin at the Leiden University Medical Center, led by Prof. Bob van Hilten, which promises to yield rich datasets for further study of the disease (see also page 40). The Method Development group hopes to use these datasets to develop algorithms that can predict disease progression, and in 2019, they already began formulating ways to meet that challenge. Groeneveld: 'It's fascinating to see how the Method Development group finds ways to address questions that could not be answered in a classical paradigm. Their contributions have already enriched our approach to early-phase clinical drug development, and their work is set to play a vital part in our future success.'

'The work of the Method Development group is set to play a vital part in our future success'

Innovation Services

Drug development is constantly evolving. That's why CHDR Innovation Services (InnoS™) aims to innovate consulting for drug development, combining fresh perspectives with expert networks. Following successful validation studies, the MORE® remote monitoring platform is now ready to be deployed.

Innovating with the power of expert networks

CHDR has always sought to innovate the processes involved in developing new therapies. Prof. Adam Cohen, Research Director of Innovation Services (InnoS™), is now preparing to take this mission to the next level, by advancing innovative approaches across the industry. With specialist networks throughout the Netherlands and beyond, InnoS can call on a rich variety of expertise and facilities to support the needs of modern drug development.

'Modern drug development is an increasingly complex, multidimensional challenge,' says Cohen. 'The traditional consultant – the single expert who tells the rest what to do – will soon be obsolete. What we need is a more collaborative approach, bringing experienced consultants together with specialists who have the necessary in-depth expertise in a particular area.' This idea lies at the heart of InnoS™, CHDR's youngest division, which Cohen has been developing since he stepped down as CHDR's CEO. InnoS offers consulting services, interim CSOs or CMOs and other resources to biotech companies, pharmaceutical companies, investors, scientific entrepreneurs, governments, and regulatory bodies.

Beyond sequential drug development

Throughout Cohen's career, he has taken a critical stance towards the classical approach in drug development. Traditionally, drug development forms a linear, sequential process, defined by the criteria of the market authorities. Cohen, on the other hand, believes a study should not merely aim to fulfil regulatory demands. An effective, efficient approach to drug development must be question-driven, rather than being dictated by the predetermined linear sequence. This philosophy has given rise to the question-based drug development (QBD) approach as an alternative to the traditional sequence of phases 1 to 4. QBD has now been ingrained in CHDR's approach to clinical drug development for almost two decades.

Where QBD disrupts the traditional linear sequence, InnoS takes things to the next level with the concept of concurrent engineering. This approach, which originated in engineering industries such as aerospace and car manufacturing, seeks efficiency and success through non-sequential design. 'If you design a new product in sequential stages, there's a big chance of missing something early on that will turn out to be a serious flaw at a later stage. Ultimately, sequential approaches risk failure due to issues that could, in fact, have been foreseen,' says Cohen. With concurrent engineering, on the other hand, experts from all stages of the process are involved right from the start. This way, criteria for success or failure at any point in the development can be determined with all parts of the process in mind. 'An example of concurrent engineering in the drug development context is bringing clinicians and clinical pharmacologists on board already at the preclinical stages,' says Cohen. 'It's fundamentally a collaborative approach, where experts are invited to communicate with each other throughout the development process – not just at the stage when their specific expertise is the focus.'

National networks

Cohen sees the Netherlands as a potential key player in international drug development. 'We have a tremendous concentration of expertise in a relatively small geographical area. Our primary care system is very well organised, and our university medical centres deliver high-quality research output in both preclinical and clinical disciplines. So we have everything at our disposal to conduct information-rich clinical trials – the kind of trials that are essential in this age of precision medicine. The only challenge I see for the Netherlands relates to issues of bureaucratic control, and the amount of paperwork involved in large-scale clinical trials and advanced therapy medicinal products. However, with a concerted nationwide effort, this is something that can certainly be improved.'

For InnoS, the high concentration of expertise in the Netherlands is already proving to be a major asset. 'For almost any problem I can think of, I can find an internationally renowned expert within an hour's drive – and most of them are people I know personally,' says Cohen. 'Of course, our network doesn't stop at the borders of the Netherlands, but sometimes it's convenient to physically be at the same table.' This rich network also makes it possible for InnoS to reach out to multiple people for input in the same field of expertise. 'This not only avoids placing too much burden on any one individual, but also circumvents the rigidity inherent in relying on a single expert,' says Cohen. Building InnoS, that approach will be key: to provide a team of experts to match the needs of each client and the development of each specific therapy.

Technology and wellbeing

Another major driver of CHDR's success over the last three decades is a commitment to methodological innovation. This mindset has led to the development of the NeuroCart, PainCart, DermaToolbox and

the rapidly growing set of immunological challenge tests and other biomarkers. In recent years, new tools have been emerging that take advantage of the latest developments in technology and the ubiquity of smartphones. The Method Development group is the team tasked with translating these advances into practical applications for studies at CHDR (see page 102). Recently, various projects have explored the great potential of the MORE remote monitoring platform.

Remote monitoring offers unique possibilities for the frequent measurement of drug effects in a naturalistic setting, while people are going about their day-to-day lives. This is especially important in those fields where there are relatively few objective biomarkers, such as psychiatry, or where hospital visits are a great burden, such as for children or elderly participants. 'Psychiatry and paediatrics are challenging fields for clinical drug research. In psychiatry, we've had to rely until now on retrospective questionnaires. These are notoriously unreliable, especially if someone is suffering from a condition such as a mood disorder or anxiety – conditions which are known to colour participants' memories. Now we can gather objective data about a participant's activity levels and social behaviour, and ask them to self-evaluate at regular intervals to avoid memory bias,' says Cohen. 'In paediatrics, meanwhile, the challenges for research relate more to the burden we place on children and parents, and the fact that we can't afford to cause any unnecessary discomfort. Remote monitoring radically opens up the possibilities for gathering data with minimal burden on the child or the parents.'

This Annual Report features a range of examples of the MORE platform in action. A study to validate MORE for measuring symptoms in major depressive disorder, in collaboration with the mental health organisation Transparant, is described on page 48 and 54. The validation of MORE in paediatric patients is the main theme of the interview with Dr Gertjan Driessen on page 116. Paediatric research also features in the interview with Dr Timo de Haan on page 118, describing a method to gather data on blood levels of drugs in young children while minimising discomfort.

MORE progress

Now that the MORE platform has been validated for a number of conditions, it can be applied in biomedical research. The first task is to integrate MORE as a component of the Trial@home approach, enriching the possibilities for gathering data from participants who are not staying at the Clinical Research Unit. Additionally, CHDR plans to offer the capabilities of MORE as a service to other research organisations and academic institutions. Meanwhile, the Method Development group is actively engaged in the next challenge: what to do with the huge amounts of data generated by remote monitoring and other data-rich methods. 'We used to have far too little data in clinical medicine. Our standard method of gathering data was to ask our patients how they were doing. Most of our patients, being fairly polite, would simply say "fine", and we would conscientiously write that in our dossier,' says Cohen. 'Now, with innovations like remote monitoring and sensor technology, it's the opposite: we're almost overwhelmed with data!' However, keeping pace with information-rich technologies, recent years have seen the rise of sophisticated approaches for leveraging big data, such as machine learning. 'Thanks to the work of our talented team of data scientists, we're discovering the many insights that this wealth of data has to offer,' says Cohen. 'These data-rich approaches have the potential to revolutionise drug development, paving the way for more precise and personalised healthcare in the future.'

'Data-rich approaches pave the way for more precise and personalised healthcare in the future'

Dr Gertjan Driessen, paediatrician at Juliana Children's Hospital, The Hague

'I see great potential for remote monitoring in paediatrics'

'Many people see the promise of remote monitoring for paediatric research and healthcare,' says paediatrician Dr Gertjan Driessen. 'But very few groups are actually collecting baseline data to validate remote monitoring procedures in paediatrics. CHDR is conducting such a validation study in our hospital using their MORE remote monitoring platform, and I'm really excited to be involved.' Juliana Children's Hospital in The Hague, which treats a spectrum of paediatric disorders, is unique in the Netherlands in that it is the only children's hospital that is not part of a university hospital. However, for a range of specific disorders such as cystic fibrosis, the hospital does deliver specialised care on a level comparable to university centres. Driessen: 'That means we see many children with routine needs, as well as those patients who need highly specialised care. I think that's an advantage from a research perspective.

'A few years ago, I got in touch with Prof. Adam Cohen to discuss the possibilities for doing drug trials in paediatrics,' says Driessen. 'As we all know, it's not easy to perform trials in children, because of the stringent ethical requirements prohibiting anything that's an extra burden for the child. On the other hand, the result is that we use medicines in paediatrics that haven't been specifically tested in children – which you could also argue is unethical.' The MORE platform represents a potential solution for this dilemma. It offers the possibility to gather data remotely from participants at home, placing minimal burden on the children and their parents. 'We started a collaboration with Adam Cohen and his team, with the initial aim of validating MORE in various populations of paediatric patients. Over the last few years, CHDR's Matthijs Kruizinga has been working hard in our hospital gathering all the data, and we're now looking forward to see what comes out of the analysis,' says Driessen. 'I've been really impressed by the smooth organisation and data management in this study. And of course, we really value the investment: we couldn't have financed this validation study ourselves. If the analysis demonstrates the value of remote monitoring – and I'm convinced that it will – we'll be in a prime position to acquire funding for future studies using this approach.'

> 'Parents and children are enthusiastic about using wearable technology to monitor symptoms'

The validation study was conducted in a group of 175 healthy children in various age categories, as well as in hundreds of paediatric patients suffering from acute lung problems, sickle cell anaemia, obesity, asthma, cystic fibrosis or fatigue. Data were gathered both in a clinical setting and in an outpatient setting. Two additional studies were also carried out with the Juliana Children's Hospital, to validate apps for the objective measurement of crying in infants and coughing in young children, respectively. Driessen himself specialises in paediatric infectious diseases and immunology. 'When diagnosing and treating children, especially babies and toddlers, we always face the challenge that our patients can't completely describe their complaints. To add to that, there's the well-known problem of recall bias: it's hard for parents or patients to remember when exactly a complaint started, or when a symptom resolved. That's why remote monitoring has the potential to add so much to our repertoire of research tools. We may even find ways to use it to enhance day-to-day healthcare in the future.'

Even before the results of the validation study are in, much has already been learned. It has become clear that the majority of parents are willing to participate, and that the equipment is effective for most age groups – however, there are a few exceptions. 'In infants and very young children, the smartwatch that we used to measure variables such as heart rate and movement didn't fit well on their wrist. This is a challenge that a designer needs to solve. But overall, parents and most children were enthusiastic about using this piece of tech to monitor their symptoms. In the coming years we're looking forward to collaborating further with CHDR, to use MORE to assess therapeutic effects of interventions in children.'

Dr Timo de Haan, neonatologist paediatrician at Emma Children's Hospital, Amsterdam

'Non-invasive measurements could revolutionise paediatric research'

'For our patients in the neonatal intensive care unit, a personalised approach to treatment is essential, because of the enormous variability in this age group,' says paediatrician Dr Timo de Haan. 'However, we're up against a scarcity of data and scientific findings to base our clinical decisions on, because the burden that research would place on these patients – for instance, through extra blood sampling – would in many cases be ruled out as unethical.' In light of this dilemma, CHDR has sought a way to provide crucial data while minimising the burden on neonates: using saliva samples and mathematical models to estimate drug levels in the blood. 'Such a non-invasive approach could revolutionise paediatric drug research,' says De Haan.

'A few years ago, I was contacted by Prof. Adam Cohen, who has a great affinity with paediatrics, to explore the possibilities for a collaborative study. Together, we wrote a scientific protocol to pursue innovative therapeutic drug monitoring (TDM) approaches in neonatal medicine. In our intensive care unit, we have a large population of premature and full-term newborn patients who receive many different medications. We use TDM for a number of these drugs, to check that the blood levels are neither too high nor too low. What this means is that, for some drugs, there is a gold standard already which could easily be used to validate the novel approach using saliva.'

The researchers began a pilot study to determine the optimal way to collect saliva, which took place in the neonatal ICU of the Emma Children's Hospital in Amsterdam, part of the Amsterdam University Medical Center. 'It turned out that a simple cotton swab worked fine, making it a pretty straightforward, non-invasive procedure. Most babies have an abundance of saliva, and they're constantly trying to put things in their mouths anyway, so it's no burden at all for them.'

The study is focused on comparing the levels of the antibiotic gentamicin in saliva with the levels in blood samples. Following saliva collection, the swab is sent to the in-house pharmacy, which has a dedicated lab to determine blood levels of various medicines. To detect the minute quantities of gentamicin in the saliva samples, clinical pharmacologist Prof. Ron Mathôt and his team use LC-MS, a combination of liquid chromatography and mass spectrometry. At CHDR, data from the saliva samples and the blood samples are entered into mathematical models, to assess the correlation between blood levels and saliva levels. 'It's all been going smoothly so far, including the logistics. By the end of 2019, we had included almost the full number of participants in the study already,' says De Haan.

The results from this study will be used to further develop the saliva sampling method for drug development studies in children. Saliva sampling can be useful in various contexts, including in conjunction with CHDR's Trial@home approach, to non-invasively determine a compound's blood level at specific moments in time. And of course, if the validation experiments show it to be a useful technique, saliva sampling will be used in further studies at the Emma Children's Hospital. De Haan: 'The collaboration we have with CHDR is unique. When we leverage our combined expertise, we can improve pharmacotherapy for these vulnerable patients. This can have an impact not only in our own clinic but worldwide. I'm looking forward to seeing where this partnership will take us.'

'By leveraging our combined expertise, we can improve pharmacotherapy for neonatal ICU patients'

HRM and Finance

To the outside world they might be invisible, but their contribution is invaluable: CHDR's Human Resource Management and Finance departments. Their smooth collaboration enables growth, while caring for a unique company culture.

Growing together as an organisation

Following recent growth, 2019 was an important time for consolidating and reinforcing the services that support core processes, including human resource management (HRM), administrative infrastructure and facilities. Operational needs across HRM and Finance have become more streamlined, thanks to a new integrated IT system. Meanwhile, the organisation continued to invest in its dedicated personnel, as well as taking active steps to maintain and nurture the dynamic company culture that has contributed so much to CHDR's success over the years.

'The organisation has recently gone through a period of rapid growth, and during that time the primary processes of the organisation naturally received the most attention,' says Bart Mooy, Finance Director. 'We were running more studies, so we hired many new researchers, nurses, and data scientists to support those activities. The focus now is on expanding and increasing our support services, to consolidate this growth. As we do so, we're also busy making sure that we have the necessary systems in place to equip us for continued success.'

Important developments have been taking place in human resource management (HRM). This department is the responsibility of Yvette Akkermans, who succeeded previous HR head Margreet ten Kate and interim HR manager Cindy Barry-Schoten. Since joining CHDR in July 2019, Akkermans has already contributed to several crucial changes in HR policy and practice across the organisation. 'During the past year, we've been very active in all areas of human resource management,' says Akkermans. 'This includes the traditional themes of recruitment, such as career paths, training, and personal development, as well as the implementation of our new Enterprise Resource Planning system, AFAS.'

Developing professionals

To ensure continued growth for the organisation, it is vital to stimulate the professional growth of employees. In 2019, the HRM department's efforts in this area included mapping out paths for career development within the organisation. Akkermans: 'For the research staff, that meant formalising career paths in the senior clinical research programme. For employees who are undertaking doctoral research, this gives them the reassurance that they can continue to grow here after they've obtained their PhD. And for those that decide to pursue their career elsewhere, they now know that there will still be opportunities for professional development if they want to return to us in the future.'

Besides scientific personnel, operational staff formed another key HRM focus in 2019. 'The labour market in the Netherlands is changing rapidly. It used to be relatively easy to recruit enough nurses, research assistants and other operational staff, but it's becoming more of a challenge. So we're now taking a more active approach to recruitment. We're spreading the word through print and social media, and making podcasts and videos so that potential recruits can get to know us. In the region around Leiden, we're using all the marketing tools at our disposal, including billboards and posters. In 2019 we also attended the Nursing Experience, a two-day fair for nursing professionals, which generated a new wave of interest. We've received a number of CVs and some candidates have even come for a tour of our facility.' For nurses who are looking for a change from the standard routines of the clinical setting, working at CHDR promises interesting new challenges and a dynamic work environment. Akkermans: 'Nurses have a different range of care tasks here, with an emphasis on medical and technical procedures and accuracy. The nursing team at CHDR is a great community, and there are plenty of opportunities for professional development too.'

Meeting staffing needs across the organisation involves more than just increasing the number of staff. It is crucial to be able to deploy personnel flexibly, to respond to changing staffing requirements for various studies. To meet these needs, CHDR has a large pool of flexible workers. Mooy: 'Although these are temporary workers, they're vitally important to our operations. We work hard to include them into our culture, and share with them our values and our emphasis on professionalism.' Temporary work at CHDR provides great opportunities for medical students and those embarking on a career in biomedical research. 'What we find is that many of these students are keen to come and work here in a different function after they've graduated. This underscores the importance, from a recruitment perspective, of investing in our temporary workforce.'

Integrated approach

In the second half of 2019, Akkermans and Mooy collaborated closely to coordinate the implementation of a new software package integrating several applications relating to HRM and Finance. Mooy: 'Over the years, we had found a range of solutions for different automation tasks in our respective domains. However, this meant we'd ended up with a sort of patchwork. So, in 2018, we started looking for a system that could provide a smoother integration across all these functions. Once we had made our choice, the next thing was to prepare ourselves for implementation.'

On 1 January 2020, the organisation switched to an integrated Enterprise Resource Planning package, provided by AFAS software. Akkermans: 'This software integrates different systems relating to both staffing and finances, including timesheets and payroll. It's a significant transition for us and we'll still be working over the next few months to finalise the implementation. But overall it's gone smoothly, thanks to the efforts of our software provider and the coaching we had from our implementation consultant.' Mooy: 'A consultant is essential for a process like this, but we're definitely mindful of relying too much on external consulting. In the end, it's our people who will be the ones using the system, so we've put a lot of emphasis on training them. We've also been active participants in designing the system, and we'll continue to work on tailoring it to our needs.'

Personal development

'CHDR is a knowledge-intensive organisation, so professional training is essential for maintaining the high quality of our work,' says Akkermans. 'Staff members appreciate the opportunity to acquire new skills and update their expertise.' Examples of this include the clinical pharmacology training for project leaders, and the training programme organised for operational staff by Breederode, a vocational college specialising in healthcare (see page 128).

'We also wanted to provide our employees with the opportunity to develop skills that benefit their personal development and wellbeing in a broader sense. With that in mind, we recently conducted a pilot with an online learning platform called GoodHabitz. This platform offers a range of different training opportunities, from soft skills like personal effectiveness, to practical skills such as Office 365 and business English.' Following this successful pilot, GoodHabitz is now available to all CHDR staff members.

Inclusive growth

'Our goal? To be the best employer in the Leiden Bio Science Park!' says Akkermans. 'The first step towards that goal is to open a dialogue with our employees and hear what they have to say. We want to find out what it is they value about CHDR as an employer. Defining our strengths will help us to continue to position ourselves as an attractive employer for the best talent out there.'

Another important project on the horizon for the HRM team is the move of several administrative departments from the main facility to another building within the Leiden Bio Science Park. The growing number of studies called for an expansion of testing facilities, so in 2019, the decision was made to find additional premises in order to free up more space for the Clinical Research Unit. Fortunately, a suitable location was found within sight and walking distance of the main facility. The plan is to have around 50 staff members working these new offices from mid-2020 (see also page 11).

Relocating personnel can be a logistical challenge, but Akkermans and Mooy are taking it in their stride. 'The new offices are just 300 metres away from here, and the main resources required there will be desks and computers. Our ICT structure is now cloud-based, meaning that staff can transition between the workspaces seamlessly,' says Mooy. 'The only real challenge I see here is to maintain the community feeling that defines the culture of CHDR. This move means that, including our Screening Unit, we'll be spread across three locations. It's important that this doesn't diminish anyone's sense of belonging to the CHDR community.' Akkermans agrees wholeheartedly: 'CHDR's unique character goes back to the time when it was a small company where everyone knew each other personally. Through this time of growth, we're determined to preserve that character, which so many of us cherish about working here. To do that we need to work together, to talk and listen to each other. Besides our open dialogue with staff, the Works Council is actively collaborating with us on this. There's also an active staff association, which does a great job organising social gatherings like drinks and barbecues. To be successful, though, it's crucial that we bring all levels of the organisation on board: from encouraging managers to reach out to staff in person rather than email, to making sure the cafeteria is working smoothly so that people can easily connect over lunch.'

Healthy finances

The culture of CHDR owes much to the organisation's status as a not-for-profit foundation without shareholders. Finance Director Mooy: 'Compared with profit-driven firms, there is much more intrinsic motivation at CHDR: staff know that their efforts add value that goes far beyond the bottom line. Nonetheless, like any organisation, financial health is of fundamental importance. A healthy financial position is vital to ensure continuity and growth, and it's what allows us to fund cutting edge in-house R&D.

'A growing number of personnel also means we are the source of livelihood for an increasing number of people. As an organisation with a nurturing culture, we believe that when staff are financially secure they can better focus on fulfilling their potential, whatever their role,' says Mooy. Mooy's own role has recently diversified, and now includes overseeing internal services, catering, office space and facilities. 'Working at CHDR means working with people who are exceptionally dedicated – to the success of scientific research, to the wellbeing of study participants, to the improvement of patient care and to delivering sponsors the best service possible. It feels good to be part of that.'

Piet de Boer, Confidential Adviser at Winston & Partners

'I'm here to support employees and empower them to resolve problems'

CHDR is an organisation with an open culture and strong sense of community. 'Nonetheless, even in the best of circumstances, problems can still arise that impact staff members and their working relationships with each other,' says Piet de Boer. De Boer works as confidential adviser for CHDR, as well as various other organisations, on behalf of the consultancy firm Winston & Partners. 'If an employee has a problem and wants to talk about it, I'm at their disposal. My role is to support them and empower them to find solutions. Sometimes, it's enough to just listen, to be a sounding board. Additionally, I can give advice on how to deal with a situation. If that doesn't solve the problem, and the employee wants me to become involved, I can step in and help them to discuss the matter with the employer, or to escalate the matter further where needed. If necessary, I will take steps to ensure that a thorough investigation is being conducted. But however things proceed, it's always the employee who is in charge. I have a duty of confidentiality and, except in extreme situations such as serious crimes, I never take action on my own. The path to a solution is always in the employee's own hands, supported by my guidance and advice.'

It is common practice nowadays for companies and organisations in the Netherlands to have a confidential adviser who offers support for staff members facing such issues as harassment (including sexual harassment), extreme demands by their employer (such as pressure to work overtime or take unnecessary risks), or being witness to inappropriate behaviour of others. Confidential advisers are essential for the implementation of policies concerning integrity and whistleblower protection, as well as complaints procedures. 'For employees who are considering filing a complaint or acting as a whistleblower, it can be a challenging time. In many cases, they have experienced or witnessed something that has shaken their trust at a fundamental level. The first thing I aim to do is to restore their trust, by establishing a safe environment in which we can unpack the situation and consider the options.' Besides De Boer, who is CHDR's primary confidential adviser, his colleague Maaike Mentink is available for those who prefer to consult a female adviser.

In order to be effective, it is of course important that every employee is aware of the confidential adviser and knows how to get in touch. De Boer: 'In this line of work, there's a strange paradox: if no one calls me, does that mean that everything is fine, or does it mean that people are suffering in silence because they don't know how to reach out to me?' At CHDR, De Boer improves his visibility by posting informative columns on the staff intranet about topics such as discrimination or sexual harassment. To make sure he is a familiar face, he also joins staff social gatherings now and again.

'Every employee needs to know that, if they're facing a difficult situation, there are several options available to them. We can talk on the phone, I can come to CHDR, or we can meet off-site. Often, the first step – summoning the courage to get in touch – is the most difficult one. The more visible and accessible I can be, the more I can contribute to making CHDR a safe and nurturing working environment.'

'The path to a solution is always in the hands of the employee, supported by my guidance and advice'

Challenging training brings rewards

In collaboration with Breederode, a vocational healthcare training college based in Rotterdam, CHDR has been able to offer staff nurses and other operational personnel an intensive six-day course, covering aspects of Good Clinical Practice (GCP) procedures and relevant skills. Emilie Jonxis, manager of the Clinical Research Unit: 'Breederode was an ideal partner to bring on board for this training because they had already given a similar course for research nurses in hospitals. They adapted that course to fit our needs. Initially it was provided just for our nurses, but soon others wanted to join too – such as the medical assistants from our Screening Unit, lab technicians, and other operational staff. This turned out to be a great idea: these different groups also got to know each other better and learned about each other's jobs. I think everyone went away with an increased sense of mutual understanding. So it ended up being not just an educational experience, but a community building event too.'

In 2019, the course was run four times. Each time, it concluded with an exam and a certificate for every participant who passed. Jonxis: 'At first, some participants saw it as something light, but it soon became clear that the course was in fact quite challenging – and rewarding, too.' The plan is to run the course several more times in the future. 'The instructors from Breederode were impressed by the level of expertise our staff already had, and they found it to be an enjoyable experience. We're all looking forward to the next session.'

Better synergy through sharing

Team Up is the name of a monthly event at CHDR with two key aims: to share knowledge about a specific subject, and to offer opportunities to meet colleagues from different departments. 'As the organisation grows, these occasions become increasingly important,' says Emilie Jonxis, manager of the Clinical Research Unit, who organises Team Up. 'Every meeting includes a talk on a subject that is of interest to CHDR staff – whether that's a general topic such as European privacy regulations, or a specialised topic such as a specific treatment featuring in CHDR's current research.'

In addition to Team Up, a so-called 'pizza night' takes place several times a year: an informal event where results of recent studies are discussed – accompanied, of course, by pizza. 'Staff who are involved in carrying out a study are often curious to know the outcome. However, we found that people didn't always have the chance to find out the results of studies they had worked on. And so that's how pizza nights started! These events are always well attended: it's great to see how engaged people are in their work here.'

CHDR nurses get new uniform
In 2019, all nurses and medical assistants at CHDR were given a new uniform, consisting of a jacket to be worn over their own clothes. This new workwear helps study participants to easily recognise the nurses, as well as contributing to overall hygiene.

Dr Jules Heuberger, Senior Clinical Scientist and chair of the Works Council

'We keep the channels of communication open'

'The Works Council and the Executive Board have a common goal: a healthy working environment where everyone can prosper,' says Dr Jules Heuberger, Senior Clinical Scientist and, in 2019, chair of the Works Council. 'This means that we're not confronting each other, but rather seeking common ground and working towards consensus. If a mismatch does arise between the plans of the management and the interests of our colleagues, we try to bridge the gap, through formal meetings and informal discussions. Even more importantly, we're there to communicate any structural problems to the management, so that we can find solutions together.'

A recent example of such an issue is the increase in workload resulting from the growth in the number and complexity of studies. Heuberger: 'We raised this issue with the Board back in early 2019, and they clarified the measures they were taking to recruit more staff. We kept it on the Works Council agenda for several months, making sure to regularly check in with colleagues throughout the organisation regarding their perception of workload. That way, we were able to monitor the improvements and communicate any remaining issues to the Board.'

Another recent theme raised by the growth of the organisation has been the pressure on building space and the quest for sustainable solutions. The Works Council took an active role in discussing the plans to relocate some staff to another building, paying close attention to how these plans would personally impact the employees. 'Together with our HR department and the Board, we considered these plans in great detail. We discussed how the plans would be communicated to the staff, the provisional timeline for the move, and what further requirements would arise from having an additional location,' says Heuberger. 'One of our main concerns is to be able to maintain cohesion even when staff are divided across three locations. CHDR has always been a dynamic, open organisation, and as we grow, everyone is keen to make sure that our unique company culture flourishes along with us.'

> 'The Works Council and the Board have a common goal: a healthy working environment where everyone can prosper'

There have also been some important ICT developments: as well as the organisation-wide transition to a cloud infrastructure, 2019 saw the introduction of an integrated Enterprise Resource Planning system. 'The Works Council was involved in preparing for the implementation of this new system, which concerns HR management, salary administration, registration of hours and so forth. We gave input on a range of practical issues and even had a say in the choice of provider. The new system promises some major improvements, particularly in that it provides better transparency for employees,' says Heuberger.

'Transitions like this are of course major operations. Whenever there are high-level changes like this, we are there to monitor the potential impact on different groups of employees and to provide a channel of communication between staff members and the Board.'

The Works Council consists of nine members from different parts of the organisation, who have diverse backgrounds. 'Each of us brings a unique combination of experience and expertise to the table. Beyond that, it's important for the composition of the Works Council to mirror that of the organisation, so that everyone feels represented and gets heard,' says Heuberger. As a Senior Clinical Scientist, Heuberger is also involved in developing the future strategy of CHDR. 'At first, I was concerned that the duties of my job might conflict with my activities on the Works Council. In practice, though, the two positions go well together: whichever role I'm in, I'm working for the best interests of CHDR and our stakeholders.'

New hires

To meet the needs of the growing organisation, many professionals joined CHDR in 2019, and existing staff members began new phases of their careers. In the following pages, a few of them share their stories.

'I love how committed people are to their work here'

Yvette Akkermans, Human Resources Director

Yvette Akkermans joined CHDR in July 2019 as HR Director. Previously, she worked for eight years as HR Director at the Merck Sharp & Dohme packaging plant in Haarlem, the Netherlands. 'I like the fact that I can stay involved in this industry, but from a completely different perspective,' says Akkermans. 'During these first months at CHDR, I've been moved by the dedication and the high degree of professionalism among the staff, throughout the organisation.'

Akkermans enjoys her new job: 'CHDR is a pleasant and diverse organisation. There's obviously a strong scientific side, with a lot of bright minds, but the operations side that complements this is truly dynamic too, with employees who are totally committed to keeping things running smoothly. These two groups have great appreciation for each other, and together they form a vibrant community.'

'I enjoy using my expertise to improve data management'

Niha Bambroo, senior programmer

'Thanks to my previous clinical data programming experience at pharmaceutical companies and contract research organisations, I'm in a good position to help implement CDISC-SDTM data standards here at CHDR,' says Niha Bambroo, member of CHDR's data programming team. SDTM stands for Study Data Tabulation Model, which defines a standard structure for trial data, developed by the Clinical Data Interchange Standards Consortium, or CDISC. It is increasingly the case that market authorities demand that all data in the dossier of a new compound are in this format. Clinical data at CHDR are collected using the Promasys protocol management system, but the Promasys system does not automatically generate SDTM-compatible datasets. 'A key part of my work has been writing the necessary programs to translate the data into an SDTM format,' says Bambroo. 'We are increasingly able to do things in-house, without having to rely on external parties.'

Before moving to the Netherlands in 2016, Bambroo worked in Bangalore, India as a statistical analysis consultant, first at a consultancy firm and then at a contract research organisation. The five years she spent working at that CRO enabled her to hone her skills in data analysis and SDTM standards. Her position at CHDR is her second since moving to the Netherlands. 'It's exciting to be part of such an enthusiastic, international team,' says Bambroo. 'I enjoy contributing to the group effort, using my expertise to help streamline CHDR's data management processes.'

'Pharmacometric models give us powerful insights into the data we collect'

Dr Michiel van Esdonk, pharmacometrician

When he joined the organisation in 2019, pharmacometrician Dr Michiel van Esdonk had already been a regular at CHDR for several years. During his PhD, he divided his time between CHDR and the Leiden Academic Centre for Drug Research (LACDR), culminating in his dissertation entitled *The quantification of growth hormone secretion – Application of model-informed drug development in acromegaly.* His PhD supervisors were CHDR's CEO Prof. Koos Burggraaf and LACDR's Prof. Piet Hein van der Graaf, who holds a chair in Systems Pharmacology. Van Esdonk: 'CHDR did a study with a compound that repressed growth hormone secretion. For my PhD research, I developed mathematical models to quantify the inhibition of growth hormone secretion. The aim of this was to learn more about the clinical pharmacological properties of this compound, and to simulate the next step to facilitate better forward planning.' His current role as pharmacometrician involves similar tasks: 'We use mathematical models to integrate all available data in a single analysis to explore possible study scenarios and support decision making. Before a study is conducted, we can incorporate information from existing literature into a model, which then informs our choices with regard to study design or dose selection. Afterwards, we can assist in the analysis of the data collected, and explore a concentration-effect relationship or perform clinical trial simulations for subsequent phase 2 trials.'

Van Esdonk is also involved in educating his colleagues about pharmacometric modelling, as well as pharmacokinetic and pharmacodynamic concepts. 'At CHDR, many Clinical Scientists are training to become clinical pharmacologists. It's important for them to acquire an understanding of pharmacokinetics, pharmacodynamics, and modelling techniques. The better informed they are, the better they can understand and interpret the results of the clinical trials they're conducting.' Every two weeks, Van Esdonk can be found back at LACDR: 'We're currently working to strengthen the collaboration between CHDR and LACDR. Our expertise and scientific interests complement each other, and both sides stand to benefit from closer partnership. And for me, of course, it's a great chance to maintain connections with my former colleagues.'

'It's so important to have good colleagues'

Teodóra Bán, ICT project manager

'I joined CHDR in September 2019, and I really like it here,' says ICT project manager Teodóra Bán. Currently, she is involved in implementing the organisation's new authorisation management software, SmartAIM. 'Until now, CHDR has been working with authorisation records, which is a bit outdated. The new system will speed up the process of verifying identities and checking authorisations. It's an interesting project, and I'm looking forward to getting it up and running. First, we have to implement and validate the system, and then it will be expanded to include all CHDR users.'

Bán, who was born and raised in Hungary, has been living in the Netherlands for over 10 years. 'After gaining my MBA from the University of Amsterdam, I worked for several companies, mostly within the pharmaceutical industry. I was a Master Data and Business Specialist for four years at Hospira, which was bought by Pfizer and later sold to ICU Medical.' Before coming to CHDR, Bán was working at Astellas, which is just around the corner from CHDR. 'I didn't have to come far for my job interview!' she says, laughing. 'CHDR is a great place, and it's certainly different from the production facilities where I used to work. What's more, the people here are great too – it's so important to have good colleagues.'

'As one team, we can be more efficient'

Dr Kirsten Bergmann, head of the Statistics and Pharmacometrics group

'When I joined CHDR in 2018 as a pharmacometrician, Statistics and Pharmacometrics were separate groups. However, it soon became clear it would be more efficient if the two groups were merged,' says Dr Kirsten Bergmann. 'We were already collaborating closely – both groups were working with data, after all.' In 2019, Bergmann became head of the new, integrated Statistics and Pharmacometrics (SPx) group. 'We kicked off the year with a strategy meeting to discuss how we could best work together as a unified team. Given that our work is so intertwined with that of the rest of the organisation, we also involved members of other departments in that meeting. We identified some key areas for change, such as the process of formulating statistical analysis plans, and procedures relating to statistical analysis reporting.'

Bergmann has a background in applied physics and applied mathematics. She is a graduate of the Technical University of Denmark, where she also obtained her PhD in 2010 with a thesis on nonlinear stochastic modelling of antimicrobial resistance in bacterial populations. In recent years, she has worked as a modelling and simulation scientist at a number of companies, including Abbott, Astellas, and LAP&P, which was founded by Leiden pharmacologist and former chairman of CHDR's Scientific Advisory Board, Prof. Meindert Danhof. 'My experiences in those roles have proven valuable for my current job in a number of ways. At Astellas, for example, my manager was closely involved in setting the standards for concentration-QTc analysis – one of the core activities of CHDR Cardiology Services,' says Bergmann. 'Now, at CHDR, I'm busy overseeing the standardisation and streamlining of our activities in both statistics and pharmacometrics. In addition to our day-to-day activities, we're paying close attention to transparency and quality control, areas which are becoming increasingly important.'

'Open dialogue will help ensure the wider success of remote monitoring'

Dr Vasilis Exadaktylos, product manager of Trial@home

'We're currently considering what services we can offer to sponsors – and, eventually, external partners – who want to harness the power of remote monitoring,' says Vasilis Exadaktylos, who is in charge of Trial@home and the MORE remote monitoring platform. 'In recent years, CHDR has pioneered the development and application of remote monitoring. The approach has been validated in various target groups and digital endpoints have been developed to quantify specific processes, such as crying in infants or behavioural changes in depression patients. We are now using these approaches in drug trials, while also continuing to develop new digital endpoints for other processes. What's more, we're now in a position to start offering the benefits of MORE to clients and external researchers.'

Exadaktylos studied electrical engineering in Greece, where he was born, and gained his PhD from Lancaster University in the United Kingdom. From 2007 to 2016 he held a postdoctoral position at KU Leuven, Belgium, where he focused on the analysis of measurements from a variety of biological systems, and in the few years before joining CHDR, he was part of a spin-off company applying this expertise to measure stress in the workplace. 'I've been involved in a range of interesting projects over the years – from developing a method to assess the physical condition of athletes, to measuring parameters correlated with mental states such as sleepiness and stress,' says Exadaktylos.

'There are many similarities between my work in Belgium and what I'm doing now for CHDR. But of course, there's one big difference: when devices are to be used in clinical research, there are far stricter regulations to deal with than when we are oriented towards the consumer market,' says Exadaktylos. 'I'm glad that regulatory authorities such as the EMA and FDA welcome open dialogue. Remote monitoring represents new ground, so it's important that researchers and authorities can communicate well – this way, we can ensure a better alignment between practice and regulations. As scientists, criticism and evaluation are pivotal components of everything we do, so we in turn welcome input from the authorities that can help us improve our approach.'

'The things I'm learning here will make me a better psychiatrist in the future'

Koshar Safai Pour, Clinical Scientist

After graduating as a physician, Koshar Safai Pour had various options to consider, but his overall ambition was clear: to become a psychiatrist. His scientific internship in the Psychiatry department of the Leiden University Medical Center (LUMC) – which won him a poster prize at the spring conference of the Dutch Psychiatric Society – had focused on ketamine as a therapy for patients with treatment-resistant major depression. 'A good friend of mine told me about a job opening at CHDR, where I could do research and obtain my PhD, but also train to be a clinical pharmacologist,' says Safai Pour. 'I think clinical pharmacology is really valuable in psychiatry. When I did my internship at the LUMC, I was particularly intrigued by what we learned from CHDR's Dr Gabriël Jacobs. His thorough knowledge of pharmacology made a strong impression on me.'

Safai Pour applied for the job at CHDR, and was hired in December 2019. 'I'm now part of Gabriël Jacobs' team. I'll be a project leader for studies in psychiatry, and maybe some other studies as well. It's early days of course, but I'm really glad to be here. There are so many interesting projects going on. The MORE platform, for example – gathering objective data on movement, sleep and social interactions – that's a major step forward compared to the subjective data that clinicians still have to rely on. I hope that in the future, such objective measures will be part of psychiatric care as well. There are already algorithms based on objective measures that can predict when somebody suffering from bipolar disorder will have another manic phase. In the future, these approaches could help reduce the number of hospitalisations.

'CHDR is a very nice place to work. I feel that the organisation really cares about its staff. And there is a very good social atmosphere too,' Safai Pour continues. 'Compared to an academic department, it's much less hierarchical. It's quite common that a Research Director joins you for lunch and has a genuine interest in hearing about your work day. For me, that's really valuable. Having nice social interactions at work adds so much enjoyment to the job.'

'It's a vibrant organisation with smart, dedicated people'

Dr Ard Vink, Director of Clinical Operations

'As Director of Clinical Operations, I'm responsible for all the activities taking place from the start of clinical protocol development to the finalisation of the clinical study report,' says Dr Ard Vink. Before joining CHDR in December 2019, Vink had worked for almost two decades in clinical operations within CROs and pharmaceutical companies. 'I finished my master's in Biology at Leiden University in 1989. Thirty years later, coming back to Leiden to join CHDR, I feel like I've come full circle,' says Vink, whose international career has included roles in Houston, Düsseldorf, Breda, Vienna, Graz and Rostock. 'I feel at home at CHDR. It's a vibrant organisation with lots of smart, dedicated people and an open culture. I was happy when the opportunity arose to join CHDR's Management Team,' says Vink. 'My focus for 2020, and the years to come, will be operational excellence: when our goal is to be the best team we can be, we enable growth and flexibility, meeting and exceeding the requirements of our clients.'

‘Every participant has a different story to tell’

Sanneke de Vreugd, nurse in the Clinical Research Unit

‘I officially joined CHDR on 1st March 2019, but I already knew the organisation well,’ says nurse Sanneke de Vreugd. ‘Through an agency, I had been working on and off at CHDR since 2017. Finally I had the chance to join the organisation where I enjoyed working the most.’ After completing her nursing training, De Vreugd worked in a nursing home for several years, mostly with patients suffering from severe dementia. Deciding it was time for a change, she tried her hand at various hospital nursing jobs. ‘Working in a hospital didn’t really suit me, so I went and joined the nursing agency. Through them, I worked not only at CHDR, but also for a home care organisation, and in the care of people with mental disabilities. In the end, it was CHDR where I felt most at home,’ says De Vreugd. ‘My experience working with different groups of patients is useful in my current job, such as in studies with Alzheimer’s and Parkinson’s patients. I find patient studies rewarding, because patients often have a personal story to tell about their reasons for participation. But it’s also fun working with young healthy volunteers. That’s the power of our team, and also what keeps me engaged: we can take on any study, in any target group or research area.’

According to De Vreugd, working as a nurse at CHDR is quite different from working in healthcare. ‘When I worked in nursing homes and hospitals, we would always work ahead – so we’d have plenty of buffer time when things didn’t go as expected. In a clinical study, however, the timing is rigid: everything needs to be done at precisely the right moment, no earlier and no later. In my first few weeks here, I found it challenging to adapt to the different way of working. But after a while it grew on me, and I started to become more involved in the studies I was working on,’ says De Vreugd. ‘To any nurses considering working at CHDR, I would say this: be prepared to allow time for the benefits of the job to reveal themselves. It’s worked out well for me.’

‘The new organisational structure meets the needs of our growing organisation’

Margreet Rienstra, Compliance Director

Margreet Rienstra originally joined CHDR 20 years ago, as a nurse. Following a two-year interval in which she worked elsewhere as research coordinator and pursued additional training, she returned to CHDR in 2006 to take up the role of Quality Assurance Manager. In this role, she oversaw the team responsible for all internal and external quality audits. In 2019, she was appointed Compliance Director and joined the Management Team. ‘The recent structural changes that have taken place are positive, and better meet the needs of our growing organisation. Together with my Management Team colleagues, I enjoy the opportunity to contribute on policy matters and support the work of the Board.’

As Compliance Director, Rienstra remains responsible for the Quality Assurance team and is an important contact for sponsors regarding quality matters, including audits. In addition, she now advises the Board on all quality and compliance matters affecting the organisation. ‘For instance, if a change in regulations regarding clinical trials is announced, I advise the Board on the potential impact on CHDR and what’s needed to prepare the organisation for these changes. Where applicable, I also seek input from my colleagues in QA, in the Management Team, or elsewhere in the organisation. My job also calls for me to take the initiative to offer advice where I see the need,’ says Rienstra. ‘So in some ways, my work is the same as it used to be, but my new role brings increased responsibility and formal authority. This shift also enables the Board to delegate more tasks and responsibilities to the Management Team.’

Quality Assurance and Compliance involves enforcing and upholding strict rules and regulations. This may seem like a challenge, but according to Rienstra, much of the time it comes down to common sense. ‘All the regulations, whether set out in law or issued by regulatory agencies, boil down to two principles: the safety of study participants and the reliability of research data – in that order of importance,’ says Rienstra. ‘Both of those are already core values of CHDR. In fact, there have been several instances in the past where we found that we were already compliant with regulations before they were issued. So even if a new regulation requires some extra effort, the fact that we already align so closely with these values means that it’s usually fairly straightforward to bring the organisation on board.’

Education

Besides cutting-edge research, education is another important way CHDR contributes to the quality of drug development and pharmacological care. CHDR's staff provide modern, student-centred university teaching, and contribute to continuing education for professionals at all career stages.

Reaping the rewards of innovative education

Education is a vital part of CHDR's work, and a cornerstone of many collaborations. The organisation contributes to a variety of educational activities, spearheading online pharmacology education for students around the world as well as offering diverse learning opportunities closer to home. In 2019, the didactic innovations introduced in recent years continued to bear fruit, maximising and deepening students' engagement with complex material.

'Contributing to education is really enjoyable,' says Dr Jeroen van Smeden, Education Director at CHDR. 'And when I see how keen my colleagues are to be involved in teaching activities, I know it's not just me who feels that way. Just today, one of our Senior Clinical Scientists came over to me during lunch, excited to share some new ideas for a course he's about to give.' Van Smeden and his colleagues are always looking for novel ways to communicate knowledge and engage students. The core philosophy behind many of these innovations is that the time in the classroom is valuable, and should be devoted to deep engagement with the material, rather than a traditional one-way transfer of knowledge. Van Smeden: 'An example of this approach is the way I teach medical students about NSAID painkillers. First, I send out a short case description of a patient who has difficulty walking because of pain in his hips from coxarthritis. I ask the students to come up with suggestions about the optimal treatment before the next lecture. At the next lecture, I begin by putting all their ideas up on the big screen and getting the students to discuss and debate them as a group. What you then see is that, as the lecture continues further into the details of NSAIDs, students remain better engaged because they are already invested in the topic.'

Rational prescribing

Teaching medical students at the Leiden University Medical Center (LUMC) is an important part of CHDR's educational duties. Van Smeden and his colleagues regularly give classes alongside staff from various LUMC departments. 'These days, there is much more focus on pharmacotherapy education than in the past. Students learn to explicitly reflect on the steps that lead from a diagnosis to a choice of treatment, using the World Health Organisation's six-step process of rational prescribing. I think that's a really positive development. In the past, the attention paid to pharmacotherapy was minimal, especially compared to the vast amount of time devoted to things like memorising tiny details of anatomy. The important thing to realise is that, where pharmacotherapy is concerned, you can't just rely on looking things up in guidelines. You have to learn how to weigh up different factors affecting the choice of treatment for each individual. For example, many patients are already being treated for various conditions, so if you just applied the guidelines blindly you could end up with dangerous drug interactions.'

The six-step framework provides students with a systematic way to go from a definition of the patient's problem to a choice of therapy, including attention to patient education, monitoring and treatment evaluation. Van Smeden: 'The first step teaches students to be critical of standard solutions and consider each problem in context. For example, in the case of someone who already has a life expectancy of only a few months, a newly-diagnosed prostate carcinoma probably doesn't need to receive curative treatment.'

A thorough education in pharmacodynamics and pharmacokinetics remains indispensable for future doctors learning how to prescribe medicines. 'Every year, there are patients who are hospitalised or even die because their doctor switched them to another drug without considering the half-life of the first drug, or as a result of toxic drug interactions that could have been avoided. The opioid crisis is another example of how important it is to have sufficient pharmacology education. If doctors had properly understood these drugs, they wouldn't have bought into the misleading information that some pharma companies were spreading about their products. If a company claims that a certain opioid is not addictive, but you know that it works on the same receptor and has no substantial difference in pharmacokinetics from addictive opioids, you're obviously going to start questioning what you're being told.'

The six-step approach, too, can benefit from modern and engaging didactic methods to keep students involved. Van Smeden: 'We find that using a case-based presentation helps to bring the topic to life. In this approach, we present the students with the diagnostic findings and lab results of a real patient, who is currently being treated by one of the clinician teachers. The class is divided into small groups to discuss the treatment options and decide what to say to the patient, using the six-step approach. The next stage is for the groups to evaluate each other's choices — by critically evaluating their classmates' ideas, they also learn to challenge their own thinking. In the following lecture, the clinician will be there with the patient, to discuss the choices that were ultimately made in the consultation room. Applying the six-step approach to a real-life situation like this enables students to understand its value, as well as giving them the opportunity to try applying this abstract framework to a real-world scenario.

‘Overall, we aim to equip the students with a broad and nuanced perspective on treatment approaches. This better prepares them for when they start prescribing treatment themselves, which may be at quite an early stage in their career – most prescriptions in hospitals are written by doctors who are still training or have just completed their specialisation. In addition, when new interns or residents have already developed a questioning mindset, they can help to stimulate positive developments in healthcare provision.’

The renewed Teaching Resource Centre

In recent years, much effort has been invested into an upgrade of the Teaching Resource Centre (TRC), an online resource for teaching pharmacology that is used by medical students and their teachers all over the globe. The TRC was originally developed in the 1990s, and in 2018 it began undergoing a complete overhaul. The renewed platform is now more dynamic and interactive. Particular attention has been paid to the visual design, with a special design team working in close collaboration with CHDR and the Paul Janssen Futurelab to create an attractive and precise graphical presentation of the educational material. Just like the original version, the new TRC can be accessed free of charge, meaning that this high-quality training is available to medical students and professionals around the world. Van Smeden is proud of what the TRC team has achieved: ‘It looks great, and we’re getting positive feedback from all over the globe. We see it as our contribution to the quality of pharmacology education worldwide: when doctors everywhere are better informed about pharmacology, we all stand to benefit.’ The redesign of the TRC has also given the team the chance to further enhance the resource with useful new features. ‘Thanks to a grant from Leiden University, we are now able to optimise both the performance and the content. We’re exploring the possibility of adding an interactive pharmacokinetics module, to complement texts on pharmacokinetics that are already part of the resource. Pharmacokinetics is quite an abstract subject, but one that is nonetheless vital for clinicians to grasp. With an interactive module, the content comes alive and learning follows naturally. For example, we’re in the process of creating an environment where you can play around with pharmacological variables, such as the distribution volume or the elimination rate of a drug, and see what the effect is on the other variables. Our Senior Clinical Scientist Rik Stuurman and our pharmacometrician Michiel van Esdonk (see page 136) are working on this, together with our graphic designer Folkert van Meurs. That’s also a great advantage of the new platform: we can easily add more interactive elements as we go forward, meaning that the TRC always stays at the forefront of pharmacology education.’

International collaboration

The TRC is also a pivotal part of the growing collaboration with the British Pharmacological Society (BPS). ‘Education is one of the main strategic priorities of the BPS, so we’re proud to collaborate with them in this area,’ says Van Smeden. ‘They have a tremendous amount of expertise in various aspects of clinical pharmacology and education, but they don’t have a platform like the TRC. We were glad to welcome them at the launch of the new TRC, and we’re currently discussing the specifics of how our collaboration will take shape.’ An editorial board has been established at CHDR to coordinate the TRC collaboration, and it is hoped that BPS members and other contributors will join this board in due course. Van Smeden: ‘The board is tasked with setting priorities and allocating tasks to experts in specific subjects. It will also be interesting to consider international differences – for example, differences in which groups of compounds are preferred for treating a specific symptom.’

> ‘We are passionate about contributing to the education of physicians and pharmacologists, both at a national and a global level’

This international perspective is reflected in the shared goal of CHDR and the BPS to contribute to the education of physicians and pharmacologists worldwide, particularly in developing countries. Where medical education and infrastructure is less developed, the TRC can be a valuable source of training for medical students and physicians alike. This goal is achievable thanks to the huge global network of the BPS, which allows the specific issues and needs of international users to be identified and fed back into the development of the TRC, resulting in an education platform with truly global relevance. Read more about this collaboration from the BPS perspective in the interview with Dr David James on page 151.

Closer to home, the collaboration with the BPS may also feed into CHDR’s other educational activities, perhaps even leading to changes in how Dutch students are assessed. ‘The BPS has developed a test, the Prescribing Skills Assessment, which could in the future offer a new way to assess how our students have assimilated the material,’ says Van Smeden. ‘In the Netherlands, we’re already in the process of introducing an assessment that tests knowledge in the areas that account for most of the hospitalisations resulting from medication errors.’ This test is designed to be stringent, but with good reason. ‘Students need to score at least 85% correct just to pass the test. They find this quite strict, but they need to realise how indispensable this knowledge is for clinical practice. A score of 85% may seem high, but it suggests that you’re still prone to making mistakes in 15% of cases. In a clinical context that would have serious consequences.’

Student-centred education

CHDR is involved in the education of students from a range of disciplines besides medicine. An example of this is the final course in the BSc Bio-Pharmaceutical Sciences programme at Leiden University, which aims to recapitulate the whole process of developing a new treatment. Van Smeden: ‘This course used to be a traditional-style lecture series covering all the steps in the process – from target

finding, preclinical work and clinical development, through to market introduction and pharmacovigilance. Then, two years ago, we redesigned the whole course from scratch with a much more student-centred approach. Now, students in this course have to write the protocols for the clinical trials themselves, and review them as if they were in a medical ethics committee. This not only helps them to comprehend the process as a whole, but also gives them the chance to experience the dilemmas involved first-hand.' Read more about this redesign in the interview with Prof. Erik Danen and Prof. Miranda van Eck on page 152.

There are also students from a variety of disciplines doing their internships at CHDR, participating in research projects that may lead to an idea for PhD research, or yield other career opportunities. And of course, the educational activities go beyond just courses for university students. CHDR collaborates with the LUMC in offering clinical pharmacology training, and with the Paul Janssen Futurelab in educating the international biotech entrepreneurs of the future. To promote the diversity and breadth of in-house expertise, CHDR also offers a range of opportunities for its own staff to grow further in their own fields. Van Smeden: 'Last year, we organised a PK/PD course that was very well received. We've got an excellent PK/PD modelling team, and by educating our project leaders in this area, we can help them improve their communication with the modellers and collaborate more effectively.'

Blended learning

The future is bright for education at CHDR, with many innovative ideas waiting to take shape. Van Smeden: 'We continue to invest in a combination of online and face-to-face education, and we see a lot of potential in so-called "hybrid" or "blended" learning. We're planning to equip our auditorium with recording capabilities to be able to produce video lectures. Eventually we hope to work towards a blended model, where students use video lectures and the TRC to study in advance, before coming to the class for a workshop-style teaching session where we explore the topic in depth together. I've already started to see the benefits of this "flipped classroom" approach in our current course offerings. I'm looking forward to expanding it further, creating a more enriching and rewarding learning experience for both students and teachers.'

Dr David James, Executive Director of Strategic Innovation at the British Pharmacological Society

'We share a dedication to improving pharmacological education'

'Education is essential to our activities as the UK's primary learned society in the field of pharmacology,' says Dr David James, Executive Director of Strategic Innovation at the British Pharmacological Society. 'A key goal for us is to ensure that all our educational materials are as comprehensive and up-to-date as possible – whether it's pharmacology training for university students, or courses for continuing professional development in healthcare. This increasingly calls for the development of online learning resources and assessments alongside more traditional classroom approaches. CHDR's Teaching Resource Centre (TRC) is a perfect companion for both face-to-face and online learning activities. What's particularly valuable about the TRC is that it teaches about mechanisms of action in a way that makes the material really accessible for the learner. The fact that anyone can access it free of charge makes it a global resource, enriching education not only for our own students but for people all over the world, including in developing countries. It's clear that BPS and CHDR share a dedication to serving the global pharmacological community, and this common ground provides a strong foundation on which to grow our collaboration.

'In fact, the relationship between BPS and CHDR goes back a long way,' says James. 'Until 2019, CHDR's founder Prof. Adam Cohen was the editor-in-chief of the British Journal of Clinical Pharmacology, which is one of our journals. We're pleased to now be embarking on an active collaboration with CHDR in the field of education. The upgraded TRC has been a milestone achievement, and the task for us now is to figure out how we can best integrate it into our own educational activities. We are exploring the possibilities, partly through our strategic alliance with the European Laboratory Research & Innovation Group (ELRIG). One of our first courses to involve the TRC will be a newly-developed curriculum on PK/PD modelling for trainees in the pharmaceutical industry. And of course, there will be many more opportunities to come.'

Prof. Erik Danen and Prof. Miranda van Eck, Leiden Academic Centre for Drug Research

'CHDR's passion for education is inspiring'

The Leiden Academic Centre for Drug Research (LACDR) is Leiden University's centre of excellence for multidisciplinary research on drug discovery and development. Like CHDR, LACDR began as the brainchild of Prof. Douwe Breimer, the head of Leiden University's Pharmacology department in the 1980s. Back then, budget cuts threatened to put an end to all pharmacology research at the university. However, Breimer succeeded in negotiating a compromise: Leiden University would no longer train pharmacists, but would maintain a research programme and an educational programme training future pharmacology researchers. This was the foundation of LACDR. A few years later, Breimer established a unit for conducting early clinical drug development, which then grew into CHDR. The two establishments have had a close connection ever since, especially in the field of education.

'CHDR plays an essential role in the final course of our BSc programme: Developing Modern Therapies,' says Prof. Erik Danen, director of the BSc programme Bio-Pharmaceutical Sciences. 'This course covers the fundamental aspects of drug discovery, from development through to commercialisation. With CHDR's depth of expertise regarding the testing of new medicines in humans, they are the ideal people to take the lead on this course. And here at LACDR, we have a lot of expertise on the preclinical part – so we complement each other well.' Danen's colleague, Prof. Miranda van Eck, is the former Director of Education at LACDR and current director of the MSc programmes. Van Eck: 'The Developing Modern Therapies course used to be a series of lectures, but now we have a blended approach combining online self-study and classroom discussion, with lots of active involvement from the students. CHDR's Dr Jeroen van Smeden and I were awarded an innovation grant from the university to redevelop the course. Jeroen used to work here at LACDR, and I knew he was very eager to implement a new approach. In 2018, the first cohort of students started the new course, and the evaluations came back very positive.' Danen: 'The course consolidates everything students have learnt in the preceding years, and augments this knowledge with practical themes, such as clinical trial protocol development and medical ethics committee assessment.'

The course on therapy development is only one of several contributions that CHDR makes to education at LACDR. CEO Prof. Koos Burggraaf, who holds a chair in Translational Drug Development at LACDR, teaches a course for MSc students called A Clinical Pharmacologist Approach to Type 2 Diabetes. Besides class-based instruction, CHDR also offers students the chance to experience the world of clinical drug research first-hand. Danen: 'Students can do their final BSc internship at CHDR, spending ten weeks being involved in research and writing a paper. It's a very popular internship, because there are always a lot of interesting projects going on at CHDR. MSc students can undertake more intensive internships at CHDR, lasting six or even nine months. This longer timeframe allows them to engage more deeply with the science behind a project, and they can even work on a research question of their own.'

Alongside their educational duties, Van Eck and Danen are actively involved in scientific research. Van Eck studies the mechanisms behind atherosclerosis, looking for therapeutic targets. Danen studies cancer cells in tissue culture and other models, seeking to understand the behaviour of these cells and identify drug targets. Van Eck: 'It can be challenging to combine responsibilities in both education and research, but I really enjoy the variety. In my eight years as Director of Education, I saw the numbers of BSc students increase significantly – from 150 to over 300 per year. It's a challenge that's also turned out to be a blessing: it has forced us to innovate, implementing new teaching strategies to be able to offer personalised, tailored learning experiences in spite of those huge student numbers. Our partnership with CHDR has played a key role in our success. I'm always inspired by their passion for education and their creativity in meeting challenges. They've demonstrated this not only in our collaboration, but elsewhere too, such as in the updated Teaching Resource Centre. When Jeroen van Smeden left us to take up the position of Director of Education at CHDR, we at LACDR were sorry to see him go. But he told me that in his new role at CHDR he would be able to do more for our students – and he was right.'

‘Friendly and approachable’

Working with CHDR

‘I’m most satisfied with the way they thought together with us about the setup and conduct of the study, and that we collaborated on the quality of the study. Their level of involvement is above average for a CRO – they definitely exceeded my expectations. Our clinical department is quite small, so the external input they provided was really welcome. The team were approachable and accessible: even between the scheduled weekly calls, we could always reach them. Overall, it was an equal and friendly collaboration.’

Clinical Research Scientist,
Biotech Company *

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

Scientific output

Publication highlights

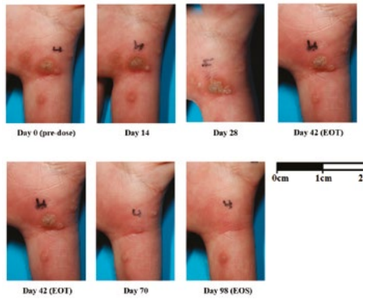
Contributing to scientific progress is an important part of CHDR's mission. To give the readers of this Annual Report a taste of the diversity, impact and scope of the growing scientific output, the following pages highlight six key publications from 2019. Several research areas are represented: dermatology, pain research, image-guided surgery, immunology and psychiatry. Among these is also a book chapter which reflects on the future of clinical research, looking beyond the gold standard of the randomised controlled trial. Links to these publications, and many more, can be found in CHDR's online publication library.

A randomised controlled proof-of-concept trial of digoxin and furosemide in adults with cutaneous warts

BJD

Rijsbergen M, Niemeyer-van der Kolk T, Hogendoorn G, Kouwenhoven S, Lemoine C, Klaassen ES, de Koning M, Beck S, Bouwes Bavinck JN, Feiss G, Burggraaf J, Rissmann R. *Br J Dermatol*. 2019; 180(5):1058-1068.

This innovative paper presents novel approaches to the proof-of-concept of a topical treatment for cutaneous warts. A unique feature of the study design is the implementation of 3D photography and a participant e-diary. This publication is one example of the numerous studies performed at CHDR in collaboration with the Leiden University Medical Center.



Photographic assessment of a treated wart in the digoxin + furosemide group (EOS: end of study).

Topical ionic contraviral therapy (ICVT) with digoxin and furosemide inhibits the potassium influx on which DNA viruses rely for replication. Therefore, ICVT was hypothesised to be a potential novel treatment for cutaneous warts. To assess the clinical efficacy, safety and tolerability of ICVT in adults with cutaneous warts. The secondary objective was to gain insight into the underlying working mechanism of ICVT. Treatment with ICVT was assessed for efficacy, safety and tolerability in a single-centre, randomised, double-blind, placebo-controlled phase IIA trial. Eighty adult patients with at least two cutaneous warts (plantar or common) were randomised to one of four treatments: digoxin + furosemide (0.125%), digoxin (0.125%), furosemide (0.125%) or placebo. The gel was administered once daily for 42 consecutive days. Predefined statistical analysis was performed with a mixed-model ANCOVA. The trial was registered at ClinicalTrials.gov with number NCT02333643. Wart size and human papillomavirus (HPV) load reduction was achieved in all active treatment groups. A statistically significant reduction in wart diameter of all treated warts was shown in the digoxin + furosemide treatment group vs. placebo (-3.0 mm, 95% confidence interval -4.9 to -1.1, P = 0.002). There was a statistically significant reduction in the HPV load of all treated warts in the digoxin + furosemide group vs. placebo (-94%, 95% confidence interval -100 to -19, P = 0.03). With wart size reduction, histologically and immunohistochemically defined viral characteristics disappeared from partial and total responding warts. This study demonstrates the proof-of-concept for the efficacy of topical ICVT in adults with cutaneous warts.

The future of clinical trial design: The transition from hard endpoints to value-based endpoints

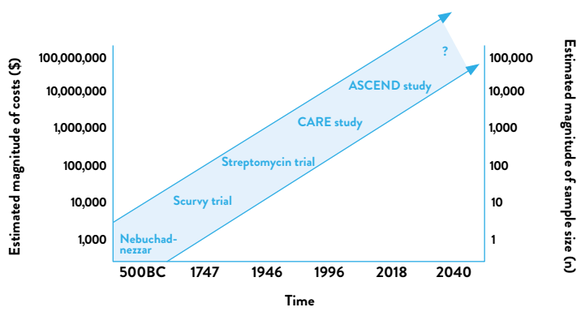
Handbook of Experimental Pharmacology

Kruizinga MD, Stuurman FE, Groeneveld GJ, Cohen AF. *Handb Exp Pharmacol.* 2019; 260:371-397.

Value-based clinical trials of the future promise to generate high-quality evidence in the form of real-life data. This book chapter advocates for an innovative approach to trial design, with a strong focus on the benefits for future drug research.

Clinical trials have been conducted since 500 BC. Currently, the methodological gold standard is the randomised controlled clinical trial, introduced by Austin Bradford Hill. This standard has produced enormous amounts of high-quality evidence, resulting in evidence-based clinical guidelines for physicians. However, the current trial paradigm needs to evolve because of the ongoing decrease of the incidence of hard endpoints and spiralling trial costs. While new trial designs, such as adaptive clinical trials, may lead to an increase in efficiency and decrease in costs, we propose a shift towards value-based trial design: a paradigm that mirrors value-based thinking in business and health care. **Value-based clinical trials will use technology to focus more on symptoms and endpoints that patients care about, will incorporate fewer research centres, and will measure a state or consequence of disease at home or at work.** Furthermore, they will measure the subjective experience of subjects in relation to other objective measurements. Ideally, the endpoints are suitable for individual assessment of the effect of an intervention. The value-based clinical trial of the future will have a low burden for participants, allowing for the inclusion of neglected populations such as children and the elderly, will be data-rich due to a high frequency of measurements, and can be conducted with technology that is already available.

The exponential increase in funds and sample sizes needed to conduct a clinical trial.



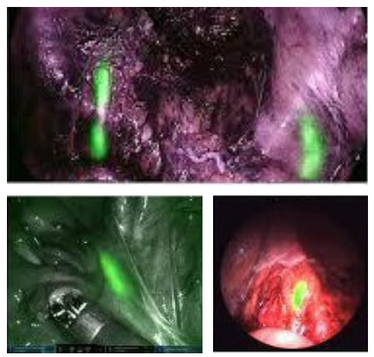
A zwitterionic near-infrared fluorophore for real-time ureter identification during laparoscopic abdominopelvic surgery

nature COMMUNICATIONS

de Valk KS, Handgraaf HJ, Deken MM, Sibinga Mulder BG, Valentijn AR, Terwisscha van Scheltinga AG, Kuil J, van Esdonk MJ, Vuijk J, Bevers RF, Peeters KC, Holman FA, Frangioni JV, Burggraaf J, Vahrmeijer AL. *Nat Commun.* 2019; 10(1):3118.

This high-impact paper demonstrates the rapid and efficient clinical translation of a new chemical class into a promising compound. This work illustrates multidisciplinary teamwork, using an adaptive design including both healthy volunteers and patients.

Iatrogenic injury of the ureters is a feared complication of abdominal surgery. Zwitterionic near-infrared fluorophores are molecules with geometrically-balanced, electrically-neutral surface charge, which leads to renal-exclusive clearance and ultralow non-specific background binding. Such molecules could solve the ureter mapping problem by providing real-time anatomic and functional imaging, even through intact peritoneum. Here we present the first-in-human experience of this chemical class, as well as the efficacy study in patients undergoing laparoscopic abdominopelvic surgery. The zwitterionic near-infrared fluorophore ZW800-1 is safe, has pharmacokinetic properties consistent with an ideal blood pool agent, and rapid elimination into urine after a single low-dose intravenous injection. Visualisation of structure and function of the ureters starts within minutes after ZW800-1 injection and lasts several hours. Zwitterionic near-infrared fluorophores add value during laparoscopic abdominopelvic surgeries and could potentially decrease iatrogenic urethral injury. Moreover, ZW800-1 is engineered for one-step covalent conjugatability, creating possibilities for developing novel targeted ligands.



High sensitivity detection of ZW800-1 near-infrared (NIR) fluorescence in patients using three different commercial imaging systems. Invisible NIR fluorescence of ZW800-1 is pseudo-coloured in green and overlaid in real-time onto the anatomical images.

Immunomonitoring of tacrolimus in healthy volunteers: The first step from PK- to PD-based therapeutic drug monitoring?

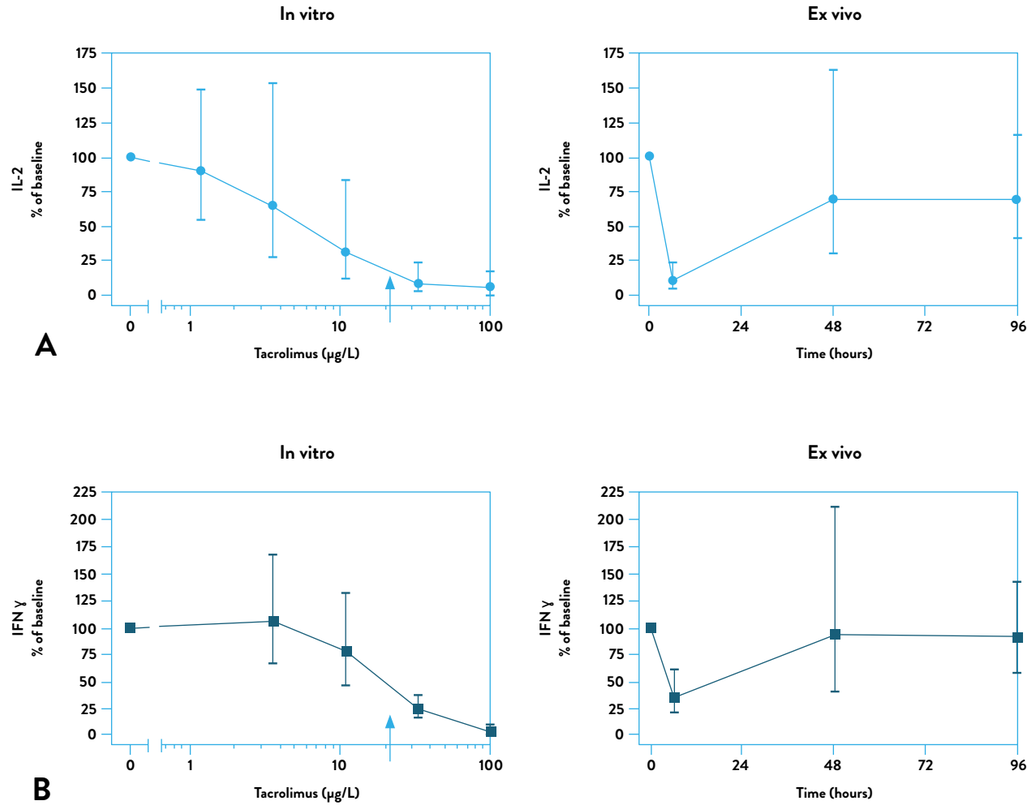
International Journal of *Molecular Sciences*

In 't Veld AE, Grievink HW, Saghari M, Stuurman FE, de Kam ML, de Vries APJ, de Winter BCM, Burggraaf J, Cohen AF, Moerland M. *Int J Mol Sci*. 2019; 20(19):e4710.

This publication demonstrates the development of a widely applicable readout measure to measure the immunosuppressive effect of tacrolimus on the T cell. It marks a paradigm shift from pharmacokinetic-based to pharmacodynamic-based therapeutic drug monitoring in transplant recipients using tacrolimus.

Therapeutic drug monitoring is routinely performed to maintain optimal tacrolimus concentrations in kidney transplant recipients. Nonetheless, toxicity and rejection still occur within an acceptable concentration range. To have a better understanding of the relationship between tacrolimus dose, tacrolimus concentration, and its effect on the target cell, we developed functional immune tests for the quantification of the tacrolimus effect. Twelve healthy volunteers received a single dose of tacrolimus, after which intracellular and whole blood tacrolimus concentrations were measured and were related to T-cell functionality. A significant correlation was found between tacrolimus concentrations in T cells and whole blood concentrations ($r = 0.71$, $p = 0.009$), while no correlation was found between tacrolimus concentrations in peripheral blood mononuclear cells (PBMCs) and whole blood ($r = 0.35$, $p = 0.27$). Phytohaemagglutinin (PHA) induced the production of IL-2 and IFNγ, as well as the inhibition of CD71 and CD154 expression on T cells at 1.5 h post-dose, when maximum tacrolimus levels were observed. Moreover, the in vitro tacrolimus effect of the mentioned markers corresponded with the ex vivo effect after dosing. **In conclusion, our results showed that intracellular tacrolimus concentrations mimic whole blood concentrations, and that PHA-induced cytokine production (IL-2 and IFNγ) and activation marker expression (CD71 and CD154) are suitable readout measures to measure the immunosuppressive effect of tacrolimus on the T cell.**

In vitro and ex vivo tacrolimus effect on cytokine production. (A) IL-2 production (top graphs) and (B) IFNγ production (bottom graphs) in phytohaemagglutinin (PHA)-stimulated whole blood. In vitro tacrolimus effect: pre-dose cytokine production after incubation with decreasing doses of tacrolimus. Ex vivo tacrolimus effect: cytokine production after dosing. Cytokine production is calculated as percentage of baseline and is displayed as mean ±SD.



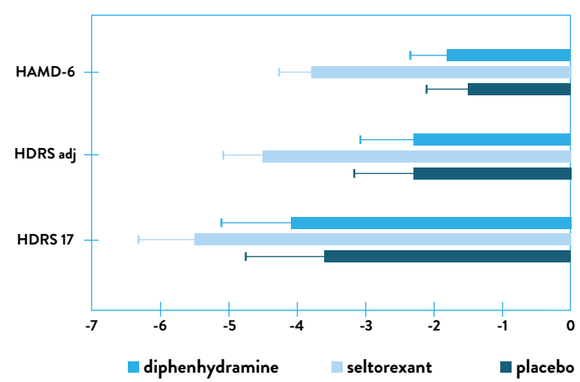
The selective orexin-2 antagonist seltorexant (JNJ-42847922/MIN-202) shows antidepressant and sleep-promoting effects in patients with major depressive disorder

Translational Psychiatry

Recourt K, de Boer P, Zuiker R, Luthringer R, Kent J, van der Ark P, van Hove I, van Gerven JMA, Jacobs G, van Nueten L. *Translational Psychiatry* 2019; 9(1):216.

This high-impact publication illustrates the benefit of combining subjective rating scales and electrophysiological measures to characterise the pharmacodynamic effects of a novel compound in an early-phase depression study.

The orexins/hypocretins are stimulatory neuropeptides that regulate wakefulness, arousal and food intake. Prior preclinical work in rodents had suggested anti-arousal effects mediated by orexin (OXR) antagonism. Although the basis of hyperarousal symptoms in major depression (MDD) is unknown, we hypothesised that these might be related to an inability to downregulate central OXR activity. In this exploratory phase 1b study, we investigated the effects of night-time arousal suppression on sleep and depressive symptoms using seltorexant, a central nervous system penetrant and selective human orexin-2 receptor (OX2R) antagonist. Both medicated and antidepressant-naive patients with non-treatment-resistant MDD in a current major depressive episode of moderate severity were enrolled. The sedative histamine-1 receptor antagonist diphenhydramine was applied as comparator drug. Symptoms of depression were evaluated using the 17-item Hamilton Depression Rating Scale (HDRS17). To establish the specificity of the antidepressant effect, the HDRS17 was adjusted for sleep items by excluding the three insomnia questions from the total score. In addition, the effect on the six core items of depression (HAMD6), being depressed mood, guilt, work and interests, psychomotor retardation, psychic anxiety, and general somatics, was evaluated. Furthermore, polysomnography (PSG) was performed to explore a relationship between changes in sleep parameters and depressive symptoms, and electroencephalogram (EEG) power spectra were calculated. Compared to placebo, seltorexant did not significantly affect PSG parameters. However, baseline total sleep time (TST) and latency to persistent sleep (LPS) correlated with seltorexant effects on these parameters, suggesting that insomnia symptoms did improve in patients who entered the study with disturbed sleep. The HDRS17 total score did not differ between either seltorexant 20 mg or diphenhydramine 25 mg compared to placebo. Yet both the sleep-adjusted HDRS17 score and the core symptoms of depression (HAMD6) were statistically significantly reduced by seltorexant but not diphenhydramine, compared to placebo. This effect was evident by day 10 of treatment and was maintained with continued treatment up to 28 days. Power spectral analysis of the overnight sleep EEG showed that the antidepressant effect of seltorexant coincided with an overall increase in (left posterior) EEG power and a relative increase in delta- and decrease in theta-, alpha- and beta power during stage 2 sleep, compared to placebo. Since delta power has previously been shown to be relatively decreased in patients with MDD compared to controls, seltorexant-induced increase in EEG delta power may contribute to its antidepressant efficacy. OX2R antagonism with seltorexant therefore reduced non-insomnia-related symptoms of depression and increased delta power during stage 2 sleep in the absence of overt changes of PSG parameters, while diphenhydramine did not demonstrate any effects. Together, these findings warrant a study in a larger sample of MDD patients stratified for the presence of sleep disturbance.



Change from baseline to Day 11 [mean ± SE]

Analgesic potential of PF-06372865, an alpha2/alpha3/alpha5 subtype-selective $GABA_A$ partial agonist, in humans

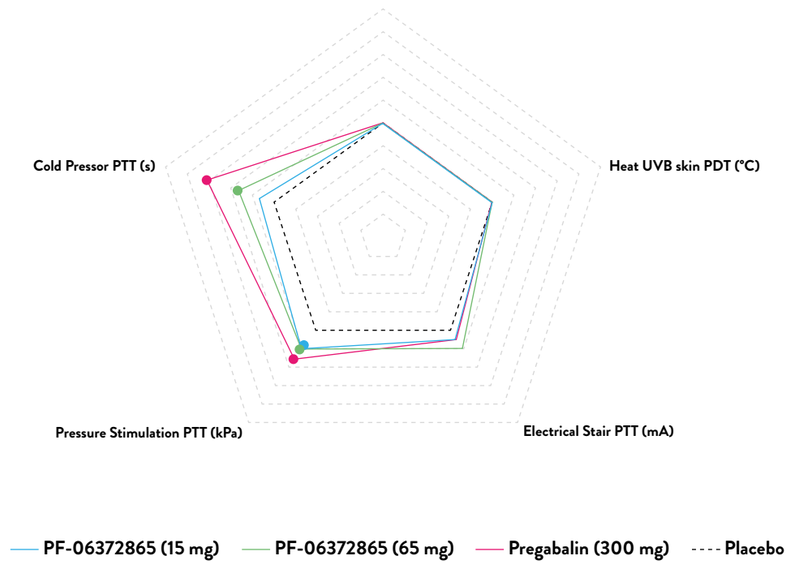
BJA
British Journal of Anaesthesia

van Amerongen G, Siebenga PS, Gurrell R, Dua P, Whitlock M, Gorman D, Okkerse P, Hay JL, Butt RP, Groeneveld GJ. *Br J Anaesth*. 2019; 123(2):e194-e203.

This publication establishes the role of the PainCart® test battery as a tool in the development of analgesics with novel mechanisms of action, for the treatment of various pain states including neuropathic pain.

This study investigated the analgesic effects of two doses (15 and 65 mg) of PF-06372865, a novel α2/α3/α5 gamma-aminobutyric acid A ($GABA_A$) subunit selective partial positive allosteric modulator (PAM), compared with placebo and pregabalin (300 mg) as a positive control. We performed a randomised placebo-controlled crossover study (NCT02238717) in 20 healthy subjects, using a battery of pain tasks (electrical, pressure, heat, cold and inflammatory pain, including a paradigm of conditioned pain modulation). Pharmacodynamic measurements were performed at baseline and up to 10 h after dose. A dose of 15 mg PF-06372865 increased pain tolerance thresholds (PTTs) for pressure pain at a ratio of 1.11 (90% confidence interval [CI]: 1.02, 1.22) compared with placebo. A dose of 65 mg PF-06372865 led to an increase in PTT for the cold pressor at a ratio of 1.17 (90% CI: 1.03, 1.32), and pressure pain task: 1.11 (90% CI: 1.01, 1.21). Pregabalin showed an increase in PTT for pressure pain at a ratio of 1.15 (95% CI: 1.06, 1.26) and cold pressor task: 1.31 (90% CI: 1.16, 1.48). **We conclude that PF-06372865 has analgesic potential at doses that do not induce significant sedation or other intolerable adverse events limiting its clinical use.** In addition, the present study established the potential role for this battery of pain tasks as a tool in the development of analgesics with a novel mechanism of action, for the treatment of various pain states including neuropathic pain and to establish proof-of-concept.

Spider plot summary of pharmacodynamic response profile for pain test battery normalised to placebo. Dashed placebo line represents a value of 1 to which other treatment effects are normalised. Distal from the centre beyond the placebo line indicates least square mean PTT/PDT greater than placebo; towards the centre and within the placebo line indicates least square mean PTT/PDT lower than placebo. A closed circle (●) indicates met pre-specified decision criteria relative to placebo for treatment on pain task. PDT, pain detection threshold; PTT, pain tolerance threshold.



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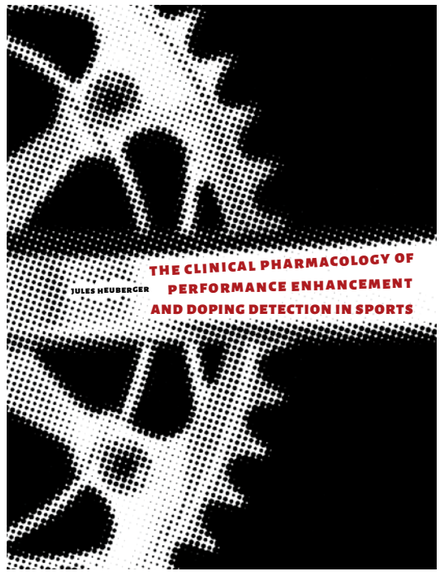

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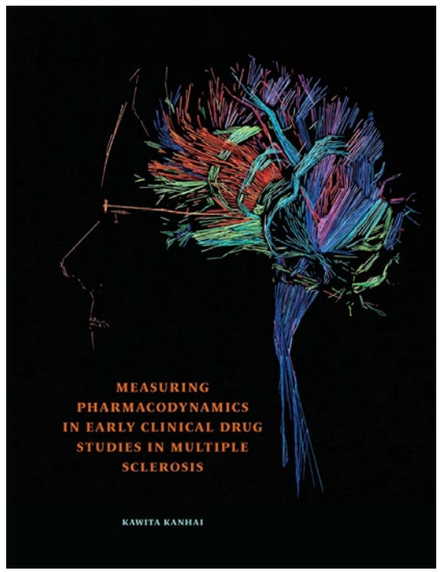

Kawita Kanhai

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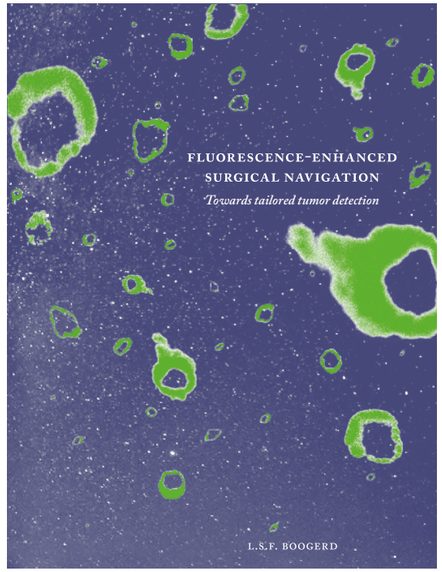

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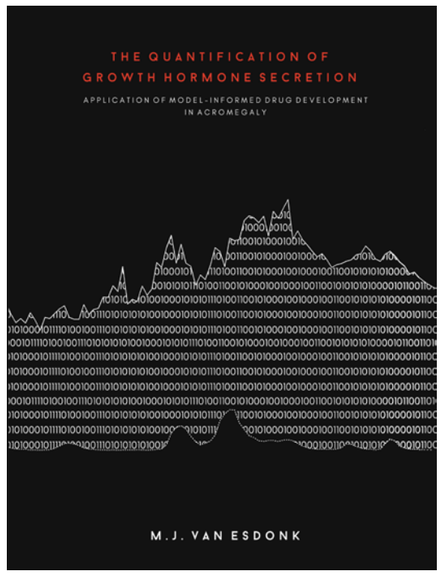

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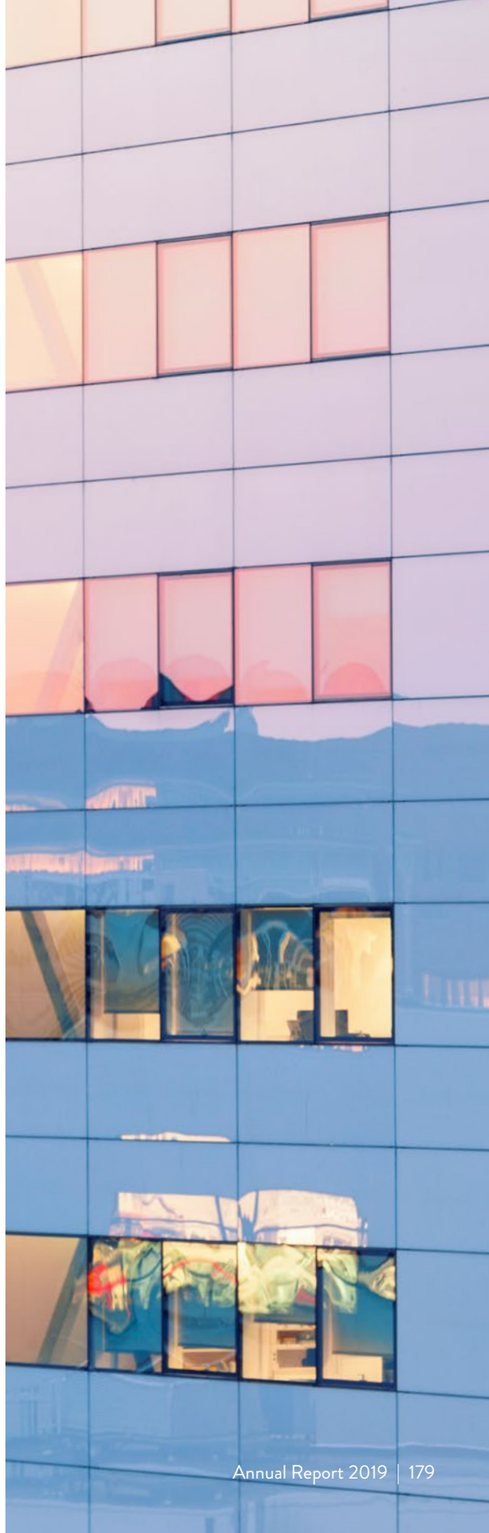

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