CHDR
Centre for Human Drug Research

Annual Report 2020

Foreword

As the Dutch saying goes, 'in times of need, you get to know your friends better'. The past year has certainly been a time of need – a time of crisis, even – for many individuals and organisations around the world. At CHDR, we too have met with our fair share of challenges during 2020. The silver lining is that, like the saying, we have got to know our friends even better: by pulling together in these times of need, we have reinforced the friendships and collaborations, both internal and external, that are vital to our success. Our clients, our scientific partners, our suppliers and our extensive professional networks have all contributed to the way we overcame the challenges posed by the COVID-19 pandemic. Our clients in particular showed great understanding for our decision to temporarily halt all our clinical activities to guarantee the safety of study participants and staff. We are also especially grateful for the commitment, the flexibility and the professionalism demonstrated by our staff in this extraordinary year.

Even though the pandemic prompted the temporary closure of our Clinical Research Unit, we were far from idle over this period. Staff across the organisation found creative and productive ways to make use of the unexpected downtime. From the moment that it was reasonable and safe to restart clinical activities, we continued our work developing new methods and biomarkers and resumed clinical trials. We were also glad to play a role in the global fight against the pandemic, by participating in multi-centre vaccine and therapy studies, and by working closely with our colleagues at the Leiden University Medical Center.

As you will read in the following pages, we have many positives to look back on this year, amid all the challenges. Although the pandemic led to financial losses in 2020, we have continued to grow as an organisation, continuing to explore new methods and expand both the capacity of our unit and the scope of our research. We hope that in the course of 2021, the global community will overcome the most severe impacts of the COVID-19 pandemic – an effort in which we will continue to play our part. In the coming year, we also look forward to the chance to shift our focus back to the many other unmet therapeutic needs that have been overshadowed by the pandemic. Now that we know our friends so much better, we are in an even stronger position to contribute to a brighter future for patients and healthcare workers across the globe.

Leiden, June 2021

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

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The year in perspective

Facing adversity and seizing opportunities

2020 has been a year of surprises and challenges for every organisation, and CHDR is no exception. The COVID-19 pandemic and the necessary measures to stop the spread of the virus inevitably had a negative impact on operations and turnover. Nonetheless, it has also been a year of solidarity, where success has hinged more than ever on the spirit of collaboration shared between CHDR and its partners. Thanks to the agility and dedication of everyone involved, it was possible to make continued progress towards long-term goals, enabling the expansion of both clinical capacity and scientific reach. The Executive Board reflects on a year that brought both adversity and opportunity.

CEO Prof. Koos Burggraaf

CMO / CSO Prof. Geert Jan Groeneveld

‘During the COVID-19 crisis, we have come to appreciate more than ever the dedication of both our staff and our external partners,’ says CEO Prof. Koos Burggraaf. ‘Our clients and our academic collaborators have been very supportive – and of course, we have tried to support them too wherever possible. Our staff have worked extremely hard, often in unusual circumstances, to meet the many new challenges that emerged.’ Prof. Geert Jan Groeneveld, Chief Medical Officer / Chief Scientific Officer: ‘Everyone involved has shown a remarkable ability to adapt – not just on one occasion, but constantly throughout the year. There were uncertainties on many levels, including personal health risks, changing guidelines from the authorities, and last-minute alterations to operational planning. And despite all these setbacks, we remain on a path towards further growth.’

Communication

On 27 February 2020, the Netherlands saw its first diagnosis of COVID-19. More cases soon emerged, and in the first weeks of March, the Dutch government began to issue regulations to prevent the spread of the virus, including scaling down all non-COVID-19 related clinical research. On 15 March, a nationwide ban on starting new clinical studies came into force. A few days earlier, CHDR had already decided to suspend operations and facilitate staff to begin working from home. Groeneveld: ‘We took it upon ourselves to act pre-emptively for the safety of our subjects and our staff. We were also keenly aware of the situation in ICUs throughout the country and did not want to run the risk, however small, of increasing the burden on the Leiden University Medical Center (LUMC) in the case of an emergency at our unit.’

‘Everyone involved has shown a remarkable ability to adapt’

‘We worked closely with the LUMC throughout the crisis, coordinating our response and supporting their efforts to care for COVID-19 patients,’ says Burggraaf. ‘We contributed our infusion pumps and personal protective equipment for use at the LUMC, and when the opportunity arose to participate in collaborative COVID-19 studies, our clinical and data management staff were eager to lend a helping hand.’ Read more about studies involving the antiviral drug remdesivir and a COVID-19 vaccine on pages 62 and 124.

Especially in those first months of the pandemic, there were many unknowns. The Board immediately recognised the importance of clear communication in navigating these uncharted waters. Groeneveld: ‘We made sure to keep our clients and stakeholders informed about local developments in the Netherlands, issuing a bulletin whenever our Prime Minister gave a press conference. And we had regular meetings with all

our staff – virtual meetings, of course – to inform and support them. As part of this, we strived to ensure that staff had sufficient opportunity to ask questions and raise any issues.'

Impact

At the end of May 2020, CHDR received permission from the Dutch Health and Youth Care Inspectorate (HYCI) to resume operations. Within two weeks, the first trial participants were welcomed back, under a strict safety protocol. 'The various measures required to ensure the safety of subjects and staff meant that only half of the clinical capacity could be used,' says Burggraaf. 'For everyone involved, it was a challenge to get a handle on all the adjustments to operating procedures that were required.'

> 'We have all grown a great deal through our experiences this year'

The shutdown of the unit and the subsequent temporary reduction in capacity made its impact felt beyond just the domain of clinical operations, of course. 'For those staff pursuing research programmes, particularly PhD students, one of the key impacts of the operational shutdown was that it was not possible to collect new data,' says Groeneveld. 'Luckily, most of our scientists had existing data from previous studies to analyse and write up for publication. 2020 was a record year in terms of scientific output, so the time was certainly well spent! Of course, this would not have been possible without extra support from their supervisors and colleagues, in particular our Statistics and Pharmacometrics group.' Read more about the Statistics and Pharmacometrics group on page 94.

Inevitably, the unusual circumstances had consequences for the organisation as a whole, including the financial situation. Burggraaf: 'It was clear from the beginning that the pandemic would affect our revenue in 2020, so we made contingency plans. When we proposed to our staff that they forfeit their expected salary increases to avoid layoffs, they were overwhelmingly in agreement with the plan. I was really moved by that solidarity, that unity.'

Long-term strategy

'The events of 2020, both within CHDR and across the industry, have reaffirmed our vision of the future,' says Burggraaf. 'The pandemic has shown how important it is to anticipate future developments, and to have a broad portfolio centred on our core strength: delivering science-based proof of pharmacology. We are still confident we can reach our 2025 strategic goals.' These goals are laid down in CHDR's long-term strategy, which was formulated early in 2020. 'We see that there is an increasing demand for our services, which blend operational excellence with scientific insight,' says Groeneveld. 'We are keen to grow to meet this demand. As part of this, we are adding two new therapeutic areas to our portfolio: (immuno-)oncology and infectious diseases. We feel we have valuable contributions to make to current market developments in both these areas, building on our scientific expertise, particularly in the field of immunology.'

These two new therapeutic areas were immediately impacted by the pandemic, albeit in different ways. For the Infectious Diseases group, which centres on a collaborative partnership between CHDR and the LUMC, the focus shifted abruptly towards therapy and vaccine development for COVID-19. Meanwhile, the more long-term strategic developments in both therapeutic areas needed to be postponed – in particular, research with compounds affecting the immune system was suspended for several months until a clearer picture emerged about the interaction of such compounds with SARS-CoV-2.

'These are temporary setbacks, however – we are still on track with our long-term strategy,' says Groeneveld. 'In fact, we have all grown a great deal through our experiences in this challenging year, which I have no doubt will be to our advantage in the long run.' Indeed, despite the adverse circumstances of the pandemic, 2020 saw interesting developments across all the established therapeutic areas at CHDR. All areas have seen increased demand for clinical studies, from Neurology and Pain (see page 30) and Internal Medicine (page 56) to Dermatology (page 48) and Psychiatry (page 40). At the heart of many new developments in these areas is the innovative work of the Method Development group (see page 84) and the Research & Development lab (page 68). New avenues of investigation are also given space to grow: in addition to the new therapeutic areas of Immuno-oncology and Infectious Diseases (page 62), the Immunology-Cardiovascular research group (page 76) has now gained a distinct presence alongside the Research & Development lab.

Building for the future

To accommodate operational growth, increased CRU capacity is of course essential. Even during the pandemic, CHDR continued with the implementation of planned changes to the main facility, moving several departments to a nearby office building to make space for an expansion of the CRU. 'The newly converted clinical research space will be ready for use from the first half of 2021 – so whenever we can return to full capacity, we will be off to a flying start,' says Burggraaf. 2020 also saw the appointment of Bart van der Kroef as Director of Technology, a valuable addition to CHDR's Management Team. This represents another important step in enhancing the long-term sustainability of the organisation, as Burggraaf explains: 'Bart's appointment as Director of Technology marks the completion of a major restructuring process within the organisation. With a focus on scalability, the new organisational structure is designed to accommodate the continued growth of CHDR in the years to come.'

In realising the organisation's long-term strategic ambitions, CHDR will continue to draw on an extensive network of commercial and academic collaborations. 'Our collaborations are crucial to our success in all key

aspects of our work: from our clinical research and our work developing new methods and biomarkers, to our educational activities. We have networks that extend across the globe, but we make sure to never lose sight of our close collaborations with nearby universities. The recent appointments of Geert Jan Groeneveld as professor of Clinical Neuropharmacology at the LUMC and Robert Rissmann as professor of Translational Dermatology at the Leiden Academic Centre for Drug Research (part of Leiden University) will open the doors to yet more dynamic collaborative ventures in the future,' says Burggraaf. 'And, particularly as we look back on this difficult year, we cherish the ongoing collaboration with our many clients across the pharmaceutical and biotech industries. We look forward to brighter times ahead, as we work together towards a better future for patients worldwide.'

Geert Jan Groeneveld appointed extraordinary professor of Clinical Neuropharmacology

In October 2020, CMO/CSO Geert Jan Groeneveld was appointed extraordinary professor of Clinical Neuropharmacology at the Leiden University Medical Center (LUMC). 'I'm honoured by this professorship, and excited about the opportunities in store,' says Groeneveld. 'This appointment reflects the strong collaboration we have with the LUMC. I already had an appointment at the LUMC Anaesthesiology department for some time, and in recent years I have been collaborating closely with anaesthesiologist Prof. Albert Dahan who has a dedicated respiratory lab there. Together, we will continue to study respiratory depression caused by opioid overdose. In fact, the collaboration between the LUMC and CHDR is set to grow not only in neurology and pain research, but also in many other fields.'

Groeneveld is particularly looking forward to supervising and teaching new PhD students. 'Now that I'm a professor, our senior staff members will also have the opportunity to act as official co-supervisors, not only gaining valuable experience but also being awarded the visibility they deserve for their input. Our field attracts many PhD students – there are currently 16 working under our supervision,' says Groeneveld. 'As CHDR continues to grow, my primary duty as CMO/CSO demands an ever greater part of my focus. So these co-supervisors play an increasingly integral role in providing the day-to-day supervision for PhD students in Neurology and Pain.'

Prof. Marianne de Visser, member of the Supervisory Board

'Strategic developments continued even in this challenging year'

The Supervisory Board had front-row seats during the many challenges and achievements of 2020. Supervisory Board member Prof. Marianne de Visser shares her impressions of this unusual year. 'We were kept up-to-date on a regular basis and were pleased to see the organisation continue to grow despite the difficult circumstances. The Executive Board has been very open and transparent towards all stakeholders,' says De Visser. 'They held regular update meetings with the staff and Works Council, and with clients and other partners. Trial participants were well-informed, too, which is very important – if I were to participate in a clinical trial, I'd appreciate being informed about the measures in place to deal with infection risk.

'I have much respect for the way the directors dealt with all the difficult decisions they had to make. While always putting the safety of trial participants and staff first, they strived to attend to the needs of clients and maintain their networks. CHDR's staff, too, have done a stellar job in keeping everything going. Not only did they manage to perform many clinical studies despite the limited capacity, but they even managed to work towards the organisation's strategic goals: the expansion of the Clinical Research Unit went ahead as planned and steps were taken to add two new therapeutic areas.'

Collaborations

Early in 2020, before COVID-19 hit, the Supervisory Board gave the green light for CHDR's five-year strategic plan. De Visser: 'We had lively discussions with the directors, encouraging them to set an ambitious growth-oriented agenda. We were sceptical at first about the need for adding infectious diseases as a new therapeutic area – but of course, the events of 2020 proved that it is very relevant indeed. We are now even more confident that the current vision of the directors will help CHDR thrive in the coming years.

'Adding new therapeutic areas such as immuno-oncology and infectious diseases involves coalition-building. One of the foundations of CHDR's approach is their strong connection to academic research, through which they are able to nurture vital collaborations with academic groups. Besides the long-standing relationship with the neighbouring Leiden University Medical Center (LUMC), CHDR works together with several other universities across the Netherlands, cultivating a broad scientific network. These developments have continued in 2020: the collaboration with the LUMC, in particular, has been further strengthened by the joint effort to combat the COVID-19 pandemic, including participating in clinical trials to study the treatment and prevention of the infection.'

Critical distance

De Visser joined CHDR's Supervisory Board in 2019, three years after her official retirement as a clinical neurologist at the Amsterdam University Medical Center. 'I'm still involved in research activities, including supervising PhD students, but I'm no longer treating patients,' she says. 'I sit on the board of several organisations, including the Supervisory Board of the Utrecht University Medical Center. I'm glad to be able to contribute in this way, using my experience in governance and in matters of quality and safety.

'Although my particular scientific interests lie in the study of neuromuscular diseases, it's not my job to discuss specific studies or be involved in operational choices at CHDR. On the contrary: as the Supervisory Board, it's our philosophy to keep a critical distance and oversee the strategy and running of the organisation as a whole,' says De Visser. 'We have been impressed by the resilience and dedication of both the Board and the staff in this difficult year.'

Looking back on three decades of innovative thinking

After more than 33 years, Prof. Adam Cohen is retiring from the organisation he founded and led through its first three decades. Here, we look back at the achievements and contributions of an original thinker who fostered innovation while remaining true to his origins in academic research.

Much has changed in the three decades of CHDR's existence. The organisation has grown from a four-bed unit housed in a temporary building close to the Leiden University Medical Center (LUMC) to a state-of-the-art contract research organisation with a dedicated, purpose-built facility. At heart, however, much has stayed the same: CHDR still is a foundation which aims to bring data-rich, scientific insight to early phase clinical drug development. And, while the scale and scope of the organisation have evolved, the original CHDR spirit remains: intrinsic motivation, interdisciplinary collaboration and a drive to pursue research of the highest quality. It is in these characteristics that Cohen's original vision is still palpable.

Research roots

Back in 1986, Prof. Douwe Breimer, professor of Pharmacology at Leiden University, set about establishing a small independent clinical pharmacology unit. Breimer called upon Cohen, his former PhD student, to run this new organisation, which would be known as the Centre for Human Drug Research. At this time, Cohen had just finished his PhD thesis, conducting research at the Wellcome Research Laboratories in Beckenham, UK. At Wellcome, Cohen had absorbed a science-driven approach to drug development, using state-of-the-art technology to quantify drug effects even in the first administration of novel drugs to humans. The Wellcome approach aligned with the vision of Prof. Breimer. 'The transition from preclinical research to the first-in-human testing of a new compound is an extremely exciting step from a scientific point of view,' explained Breimer in a 2017 interview. 'For the Leiden Institute of Bio-Pharmaceutical Sciences, early-stage clinical drug development was simply a logical extension of the work that we were doing in animals and our computer-based PK/PD models.'

The influence of Cohen's early days at the Wellcome Laboratories can still be found at CHDR. The NeuroCart®, CHDR's unique test battery to investigate CNS effects, contains several tests that already were in use in the Beckenham facility when Cohen worked on the development of novel drugs such as the antiepileptic lamotrigine. Cohen's British connection is also evident in the collaboration between CHDR's Education department and the British Pharmacological Society (BPS). For many years, Cohen was Editor-in-Chief of the British Journal of Clinical Pharmacology, the flagship scientific publication of the BPS. CHDR staff have always attended the annual BPS meeting in London every December, with Cohen keen to show his colleagues around the British capital he knows so well.

Steady growth

Cohen, both a physician and a pharmacist, proved to be the ideal choice to lead the fledgling organisation. Most clinical pharmacology research at Leiden University moved to CHDR. The safety of subjects and the integrity of data were central issues from the beginning. Under Cohen's leadership, the organisation moved towards an increasingly systematic and professional approach to clinical drug development. CHDR also started the development of Promasys, the software system which to this day registers all data.

Around this time, the organisation's staff increased to around 20 employees. Some of these pioneers are still staff members at CHDR, including current CEO Prof. Koos Burggraaf and neurologist Prof. Joop van Gerven, who currently serves as chairman of the Netherlands' central medical ethics committee (CCMO). The organisation's unique approach to early phase clinical drug development began to attract the attention of increasing numbers of clients, and operations soon outgrew the small temporary building where CHDR was located. Set on a path of growth, Cohen and his staff started to think about building a new facility. The first plans for that facility date from 1991, but due to local politics it would take four years before the organisation moved to its newly-built unit in the Leiden Bio Science Park. Meanwhile, in 1993, Cohen was appointed professor of Clinical Pharmacology at Leiden University.

In 2003, CHDR's building was extended to increase capacity by 50%. Meanwhile, the organisation continued to expand, not only in the number and complexity of studies but also in the number of therapeutic areas. In 2009, neurologist Prof. Geert Jan Groeneveld joined CHDR as a Research Director,

bringing to the organisation his expertise in the field of neurodegenerative disorders and pain research. During this time, CHDR's educational activities were professionalised, first by US-educated pharmacist Dr Kari Franson and then by Prof. Robert Rissmann, who initially joined CHDR as Education Manager. Dr Matthijs Moerland, who joined CHDR as a Senior Clinical Scientist in 2007, laid the foundations for CHDR's innovative work in the development of novel biomarkers. With the organisation prospering, plans were again drawn up for a new purpose-built facility, on a plot of land close by in the Leiden Bio Science Park. In 2013, the organisation moved into the facility where it is today. This innovative, custom-built unit was designed around CHDR's key processes, incorporating a state-of-the-art Clinical Research Unit with modern and comfortable subject accommodation, complemented by office areas and spaces for meeting, learning and collaboration. The organisation has not stopped growing, of course – in recent years, this facility has been supplemented by a dedicated screening centre and, in 2020, the CRU was expanded to again increase clinical capacity.

Original thinker

The growth of the organisation is one way of describing the success of Cohen's leadership, but the story of CHDR is about much more than just expansion. It is also about vision and innovation: cornerstones that were laid down by Cohen, and which still form the foundation today. As Breimer put it: 'His independent thinking, his innovative approaches, his perseverance, his flair, and his vision have contributed greatly to CHDR's strong growth and development. Adam has also managed to remain true to CHDR's mission, developing the business side while maintaining their strong commitment to science through education and research.' As amply demonstrated by this Annual Report, CHDR continues to operate on these principles, delivering high quality services to clients, developing new methods through cutting-edge research, and investing in a diverse range of educational activities.

Thanks to Cohen, innovative thinking is woven into CHDR's organisational culture. Years before 'disruptive innovation' became a hot topic in business theory, Cohen and his colleagues challenged their friends in the industry to rethink how things were done. Cohen's preference for original and sometimes even contrarian thinking formed the genesis of many of CHDR's unique characteristics. A good example is his critique of the classical, sequential approach to drug development with its well-known 'phases': preclinical, phase I, phase II, phase III, and so forth. This sequential approach, which is ingrained in the organisational structure of many pharmaceutical companies, has several disadvantages. Firstly, the sequential approach does not challenge researchers to define and address specific scientific questions. This criticism gave rise to question-based drug development (QBD), an approach first worked out in detail in the thesis of Cohen's PhD student Dr Saco de Visser. De Visser described the drug development process as a systematic quest to answer a set of questions, such as 'Does the compound reach the target?' and 'Does the compound cause its intended pharmacological and/or functional effect(s)?'.

QBD is in many ways an expression of CHDR's raison d'être: to address questions that relate to the underlying science, rather than simply performing phase I or phase IIa trials. Secondly, a purely linear, sequential approach does not reflect the complexity of today's therapy development, in which it is often necessary to go back to earlier phases. Taking inspiration from other industries that had dealt with the same problem, Cohen advocated for a 'concurrent design' approach to drug development, where all stages of the process are considered right from the start.

Another example of the innovative vision Cohen fostered at CHDR is the use of portable technology and remote data collection in drug development. With almost everyone these days carrying a powerful computation and communication device in their pocket, there are diverse possibilities for gathering data and interacting with subjects while they are going about their daily lives. This paves the way for a more naturalistic approach to clinical trials. Cohen's vision is crystallised in CHDR's Trial@home remote monitoring platform, which has grown from its inception six years ago to become part and parcel of CHDR's services.

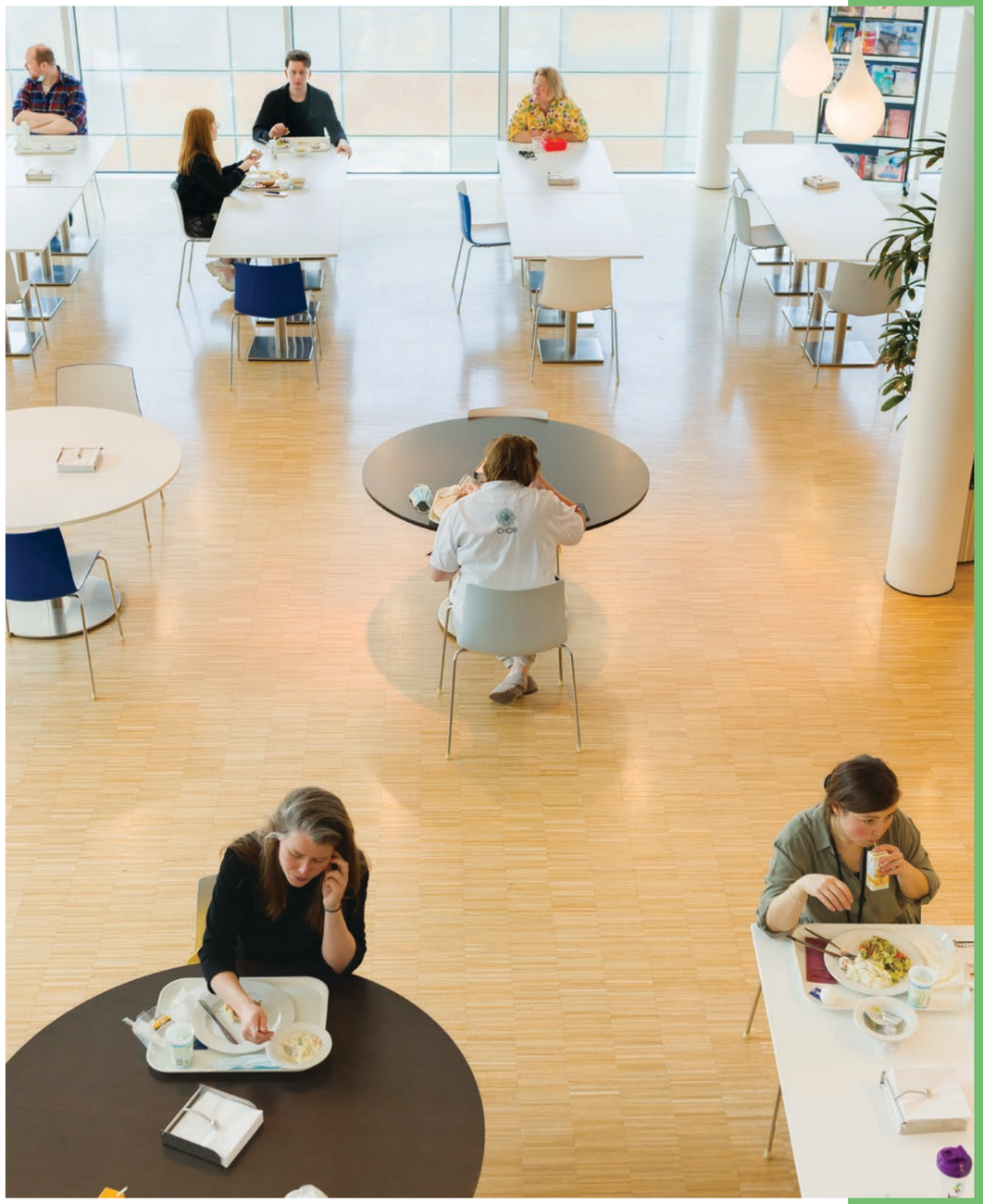
In a playful nod to CHDR's role as a disruptor, the dinosaur has become an in-house motif that refers to the importance of innovating and adapting. The dinosaur, once a hugely successful biological design, failed to adapt to the drastic ecological changes after a meteor hit the earth. The fate of the dinosaur was first used as a metaphor to discuss the radical changes in the pharmaceutical industry at a series of so-called 'dinosaur meetings', held to mark CHDR's 15th anniversary in 2002 at Naturalis, Leiden's museum of natural history. The 30th anniversary celebrations in 2017 were again held at Naturalis, in the presence of Trix, one of the world's most complete Tyrannosaur specimens.

Farewell

In 2018, Cohen stepped down as CEO and gave his farewell lecture at Leiden University. In that lecture, he reflected on the past decades in pharmacology and drug development and argued for a more integrative approach to novel therapies, including medical devices and advanced therapy medicinal products. Since stepping down as CEO, Cohen has devoted his energy to consultancy activities.

In 2020, Cohen decided it was time to retire. His innovative spirit will remain part of CHDR's DNA, while the network of long-term relationships he helped build, across academia and industry, will continue to play an important role for the organisation.

The Board and everyone at CHDR would like to express their best wishes to Adam and his family on the occasion of his retirement.



2020 at a glance

2020 in numbers

50
studies

>37,000
volunteers available

29
contracts signed

>21,000
patients available

71
articles published*

21
nationalities

4
clinical pharmacology graduates

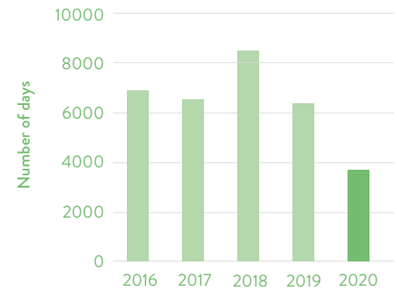
13%
turnover of clinical research staff

4
PhDs graduated

17%
growth in personnel

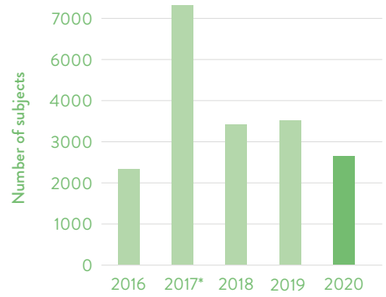
**22% increase compared to 2019*

CRU OCCUPANCY



Our purpose-built clinical research unit offers a dedicated first-in-human unit and private, hotel-style accommodation for study volunteers. Thanks to the unit's innovative design, we can intensively monitor subjects without compromising on comfort.

SUBJECTS SCREENED



**includes approximately 4000 patients with Parkinson's disease*

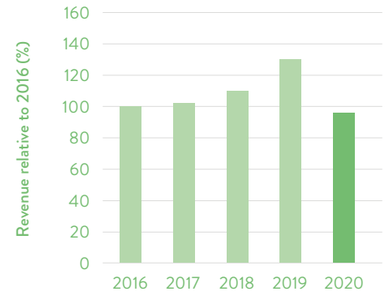
Screening at CHDR is carried out by skilled physicians in a dedicated facility next to Leiden's central train station, within easy reach for participants from the densely populated Randstad region.

OVERALL CLIENT SATISFACTION

8.5/10

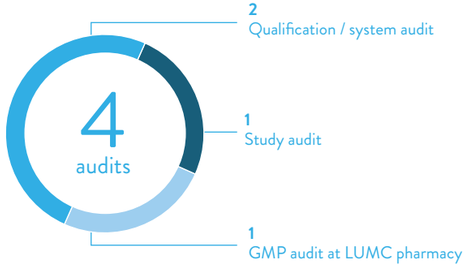
Combining scientific and operational excellence, we're driven not only to meet our clients' needs, but to also think proactively and provide added scientific value. Jump to pages 28, 82, 92, 126 and 152 to read what our clients appreciated about working with us in 2020.

CONTRACT REVENUE

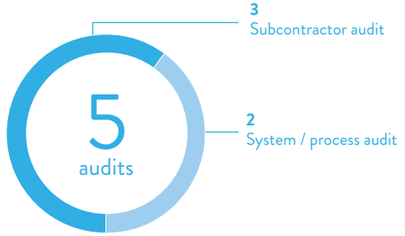


Although 2020 was a challenging year financially, CHDR's status as a foundation added to our financial resilience, while allowing us to continue supporting vital R&D. Read more from our Finance Director on page 136.

EXTERNAL AUDITS

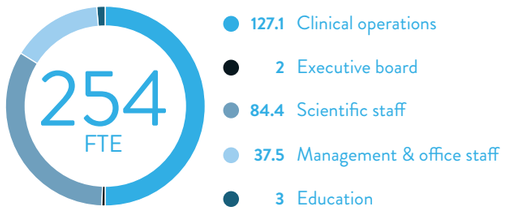


INTERNAL AUDITS

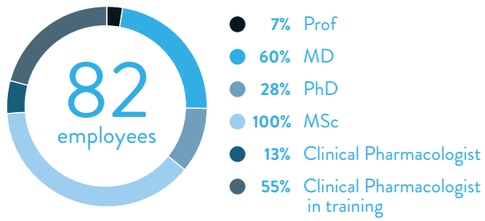


With on-site visits restricted by the pandemic, many internal and external audits were conducted remotely in 2020, leveraging the possibilities offered by digital technology. Read more about QA and Compliance during COVID-19 on page 146.

EMPLOYEES BY DEPARTMENT

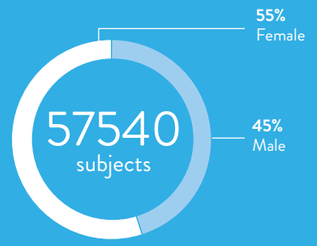


CLINICAL RESEARCH STAFF

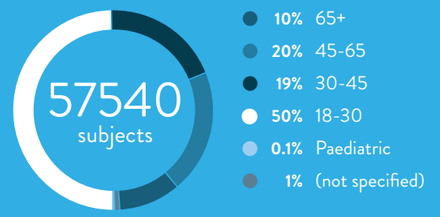


Many new faces joined the organisation during 2020. With a mission to promote education and cultivate talent, CHDR strives to offer staff in all departments opportunities for professional and personal development. Read more about Human Resources at CHDR on page 128.

SUBJECTS BY GENDER

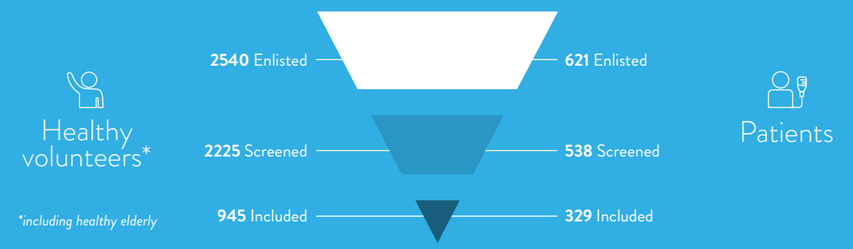


SUBJECTS BY AGE



The whole lifespan – from young healthy volunteers to the elderly – is represented in CHDR's participant database. With an innovative, strategic approach, CHDR's Recruitment department rises to the challenges of recruiting healthy volunteers and patients for a wide variety of study requirements.

SUBJECTS RECRUITED



CHDR's recruiters take a proactive, social approach to study recruitment, exploiting the possibilities offered by social media, print advertisements, in-person events and more. During 2020, pandemic restrictions meant finding creative new ways to reach out to potential subjects. Read more on page 118.

TYPES OF STUDY

PK/PD	30%
Multiple ascending dose	16%
Single ascending dose	13%
First-in-human	11%
Proof-of-concept	7%
Exploratory	9%
Food effect	6%
Biocomparison	2%
Biomarker	3%
Method development	2%
Drug-drug interaction	1%
Ethanol interaction	1%

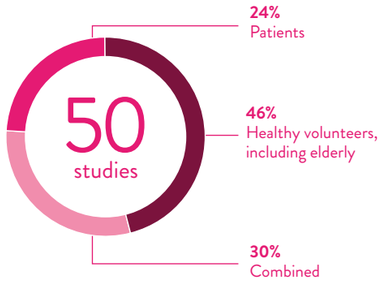
The CHDR perspective on early-phase drug development is defined by the quest for both safety and insight. This integrated approach can be seen across the many types of study we perform, from classical SAD and MAD trials to studies exploring and validating novel methodologies.

TYPES OF PATIENTS

Parkinson's disease	30%
Atopic dermatitis	15%
COVID-19	7%
FSHD	7%
Actinic keratosis	4%
Amyotrophic lateral sclerosis	4%
Atopic diathesis	4%
Cutaneous T-cell lymphoma	4%
Cutaneous warts	4%
Episodic migraine	4%
Facial seborrhoeic dermatitis	4%
Huntington's disease	4%
Myasthenia gravis	4%
Osteoarthritis	4%
Prostate cancer	4%

Research at CHDR spans an ever-expanding variety of patient groups. Our patient studies are supported by thriving networks of clinicians in various fields, including dermatology, mental healthcare, neurology and more.

STUDIES WITH SUBJECTS



From first-in-human safety studies in healthy volunteers to studies in patient populations, we offer the means to gain a comprehensive picture of a compound's properties early on in the development process.

STUDIES PER RESEARCH AREA

Neurology	32%
Dermatology	24%
Immunology & inflammation	6%
Infectious diseases	10%
Pain	10%
Musculoskeletal	8%
Psychiatry	4%
Cardiovascular	2%
Endocrinology	2%
Imaging	2%

Studies at CHDR encompass a wide range of research areas. While our core research areas continue to grow, we are also expanding into new areas such as infectious diseases. Learn more about our vision and strategy on page 8.

‘What I valued most in our recent work with CHDR was the excellent communication, the responsiveness, and the team's expertise. Both the Principal Investigator and the Project Leader were great. The Project Leader took the reins on everything, from A to Z. It really made communication efficient.

Working through a pandemic was new for everybody. I was very satisfied with their promptness in communicating with us on government regulations and when we could resume – they always kept us in the loop.’

Director of Clinical Programme Management, Pharma Company *

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

Neurology and Pain

Novel approaches to the measurement of drug effects in the brain

Researchers in the Neurology and Pain group are driven to find ever better ways to measure the effects of compounds acting in the brain. CHDR's commitment to methodological innovation plays a key role here, inspiring the development of new techniques and biomarkers as well as the refinement of existing methods such as the validated PainCart® and NeuroCart® test batteries. Meanwhile, diverse new pain studies are in the pipeline in collaboration with partners across academia, and the team are looking forward to exploring retinal scans as a means to investigate neuropathology.

2020 saw a major organisational change for the Neurology and Pain group. Until this year, Prof. Geert Jan Groeneveld, CHDR's Chief Medical Officer / Chief Scientific Officer, had been leading the group as a whole. From now on, however, studies concerning the treatment of neurological disorders will largely be the responsibility of neurologist Dr Philip Kremer, who joined the team in 2020 as Associate Research Director, with Groeneveld remaining in charge of the studies on pain and analgesics (see also page 39). This move not only accommodates the expanding range of studies in these areas, but will also allow Groeneveld to devote more energy to his duties as CMO/CSO.

Groeneveld: 'We have seen increased interest from clients in both pain research and neurology research. Philip is therefore a valuable addition to our team as we expand our activities in both these areas.' Kremer: 'This team has a really impressive track record in CNS drug development, so I'm really excited to be on board. We can build on robust methods such as the NeuroCart, while we continue to develop new biomarkers to study the pharmacology of compounds in early phase clinical trials.' Joining the organisation in 2020 meant that Kremer was one of the many new hires who began working at CHDR while the COVID-19 restrictions were still in full force. 'It was an unusual experience to start this role during the pandemic. When everything returns to normal for my colleagues, it will actually be the first time for me to see the CHDR building without all the plastic screens and socially distanced walking routes. Of course, I'm not the only one who joined the organisation during the past year – so I'll be in good company as I adjust to the "old normal"!'

Medicinal cannabis

CHDR's collaboration with the Leiden University Medical Center (LUMC) in the field of pain research was further strengthened in 2020 by a large grant from the Dutch government to investigate the use of medicinal cannabis in the treatment of chronic pain. Groeneveld: 'Every week I see patients at the LUMC's outpatient clinic for chronic pain. It's a tertiary referral centre, so those patients have already received all kinds of regular treatments without sufficient effect. We try to help them using unorthodox medications such as antiepileptics and other drugs, including medicinal cannabis. We've noticed that some patients seem to benefit from medicinal cannabis, so we wanted to systematically explore its effects on chronic pain. Is it just down to the general feel-good effects of cannabis, or is there a more specific pathway involved? And what is the role of specific cannabinoids? We also want to know how best to target this treatment in the future – so, what are the characteristics of patients who are likely to benefit from additional cannabis treatment, and which patients are at risk of adverse effects such as anxiety?'

In this study, researchers from CHDR and the LUMC will focus on two major compounds found in the cannabis plant: THC (tetrahydrocannabinol) and CBD (cannabidiol). THC is responsible for most of the psychoactive effects of cannabis. These effects result from partial agonist action at the CB1 cannabinoid receptors in the brain. CBD, on the other hand, does not have marked psychoactive properties. It is registered as a medication for some forms of epilepsy and is being studied for the treatment of other neurological disorders and anxiety disorders. CBD seems to influence the effects of THC, reducing some of its psychoactive effects, possibly through allosteric modulation of the CB1 receptor. Groeneveld: 'We would like to know what combination of THC and CBD works best in the treatment of chronic pain. First, we need to get a good grasp of the pharmacology of pure CBD, so we will start with a self-financed study in healthy volunteers, using PainCart and NeuroCart to quantify the effects of this compound.' According to Groeneveld, a major source of uncertainty about the effects of CBD is the lack of purity of many

CBD preparations. ‘There are doubts surrounding the results of some previous studies involving CBD, as the preparations used in those studies may have contained trace amounts of THC, which could explain some of the outcomes.’

In addition, a study in healthy volunteers will be performed to investigate the interaction between THC and CBD. Together, these studies in healthy volunteers will provide the necessary groundwork for subsequent patient studies. Groeneveld: ‘Using the data from healthy volunteers, a protocol will be written for the treatment of patients. A group of 200 patients suffering from chronic pain will be given cannabinoids or placebo for five weeks, using a crossover design with a washout period in between. Before we begin this protocol, our colleagues at the LUMC will first perform an extensive battery of tests to establish a detailed baseline. We need to gain as much information as possible about these patients prior to treatment – not only regarding their pain condition, but also about other relevant aspects such as somatic comorbidity and psychological factors. We hope that with this information we will be able to identify the specific characteristics that determine which patients are likely to benefit from treatment with cannabinoids.’

Systems pharmacology

The Neurology and Pain group’s recent scientific output is increasingly attracting the attention of potential clients, with many more novel analgesic compounds being studied at CHDR each year. At the end of February 2020, there was more good news for the team’s pain researchers, when the international research project QSPainRelief was awarded €6.24 million in funding from the European Union. This project will be conducted by a consortium comprising ten institutions in five European countries, including CHDR. Using a systems pharmacology approach, QSPainRelief aims to help patients suffering from chronic pain with novel, personalised combinational treatments. The project is coordinated by Prof. Elizabeth (Liesbeth) de Lange, professor of Predictive Pharmacology at the Leiden Academic Centre for Drug Research (LACDR), which is part of Leiden University.

In the first preclinical phase, researchers at LACDR and other institutions will use databases (a so-called ‘in silico’ approach) and preclinical studies to determine which novel combinations of compounds can be used to improve pain relief. In order to tailor these combinations to specific (groups of) patients, the team will harness the power of predictive pharmacology – the use of computer models to predict pharmacokinetics and pharmacodynamics – along with systems biology and pharmacogenetics approaches. In 2022, these findings will be put to the test in clinical studies, some of which will be performed at CHDR. ‘We will use the powerful methodologies we have developed at CHDR, including the NeuroCart and PainCart, to empirically validate the novel combinations that emerge from the preceding phase,’ says Groeneveld. ‘From a pharmacological perspective, testing a combination of compounds and their synergy is quite challenging. It is an exciting project which aligns well with our own programme of pain research, both our self-funded and our sponsored studies.’

Beyond symptom reduction

Neurology research at CHDR is also growing, both scientifically and from a business perspective. Kremer: ‘These are exciting times for CNS drug development. The growing body of knowledge about molecular mechanisms involved in major neurological disorders has yielded an abundance of potential drug targets for us to study. For the first time in history, we are seeing the real possibility of being able to target the underlying pathophysiology of these conditions, instead of just aiming to reduce the symptoms.’ The novel compounds that are currently reaching the stage of clinical research are different from classical drugs in neurology. Not only do they aim to slow down neurodegenerative processes rather than just reducing symptoms, but they also target subgroups of patients with specific genetic characteristics. This move towards precision medicine in neurology is also reflected in CHDR’s recent work to establish a genotyped cohort of patients with Parkinson’s disease (PD). Kremer: ‘Some of these new compounds may also be effective in a variety of conditions. From basic research, we know that neurological disorders which are phenotypically very different may have pathophysiological pathways in common – such as the well-known overlap in molecular mechanisms involved in frontotemporal dementia and amyotrophic lateral sclerosis.’

This new wave of candidate drugs in neurology poses interesting challenges for researchers at CHDR, who aim to demonstrate pharmacological effects at the earliest stages of clinical research. ‘The study of these compounds requires a different approach from the one we use in developing symptom-reducing drugs. When

the compound is aimed at reducing symptoms, it is relatively easy to demonstrate the effect. For example, when a patient with Parkinson's disease responds to levodopa, the change is obvious – sometimes even dramatic. To study these novel compounds that aim to slow down disease progression, however, we need biomarkers that show pharmacological effects on a cellular level,' says Kremer. 'Clinical markers are often not sensitive enough within the time frame of early drug studies. Our goal is to develop biomarkers that can give the client an idea of whether they're on the right track before they invest in expensive large-scale studies. The biomarkers that currently hold the most predictive potential are immunological wet biomarkers from the laboratory, specific function tests, and possibly also changes in the retina.'

Wet biomarkers

There are many biological pathways that play a role in neurodegeneration. Among these, new candidate drugs are aiming to target both the destruction of neurons by immune cells (glia) in the brain, and mitochondrial dysfunction. Kremer: 'Our highly experienced Research & Development lab, led by Dr Matthijs Moerland, are already validating methods which we hope can be used as biomarkers of these pathways. As part of this process, the team purifies specific subsets of white blood cells which can be used as a proxy for the cells in the brain that will be the target of those new compounds. If it can be demonstrated that a compound is active in peripheral white blood cells – for example, if it inhibits or enhances an enzyme in a specific molecular pathway – this is a strong indication that the compound may work in the brain as well, provided that it passes the blood-brain barrier. Matthijs and his colleagues are busy validating this approach, establishing inter-individual and intra-individual variation, and studying different cell types. Once they have a standardised readout, we can use it to observe the effects of investigational compounds in healthy volunteers and patients.'

In addition to using peripheral white blood cells as a proxy for brain cells, Kremer and his colleagues can also sample cerebrospinal fluid and measure changes in its composition. This approach can be used to study changes in complement activation, another pathway involved in neurodegeneration. The complement system, which is part of innate immunity and bridges the innate and adaptive immune responses, is also a target for candidate drugs in neurology. Kremer: 'The innate immune response has been a major focus in the research of Matthijs and his colleagues, giving us a strong foundation for studying these complement inhibitors.' Read more about the work of the Research & Development lab on page 68.

Method development and retinal scans

To study the clinical effects of a new compound, it is important to have sensitive methods to quantify a patient's symptoms, including their movements. Kremer: 'For diagnostic purposes, is often enough to get a general impression of a patient's movements. For example, a cardinal symptom of PD is what we call bradykinesia – that is, slowness of movement and difficulty stopping and starting movements. This symptom is typically straightforward for a neurologist to identify. But in order to measure the effects of a drug that aims to slow down deterioration in PD, it's not sufficient to simply identify the presence of such symptoms: we need to be able to reliably quantify them. Our Method Development group is currently working on this. For example, they are in the process of validating a finger-tapping task conducted using a tablet computer, which can be used to quantify bradykinesia.' For more on the Method Development group and their latest projects, see page 84.

What about potential future biomarkers in neurology? 'I'm really excited to explore the potential of retinal scans as a biomarker,' says Kremer. 'Embryologically, the retina is derived from the same cells as the brain. There's cerebrospinal fluid around the optic nerve, and many processes that affect neurons also have an impact on the cells in the retina. So the retina may offer us a window into pathophysiological processes in the brain, including the various deposits involved in neurodegeneration, such as beta-amyloid, and their precursors.' In collaboration with the Netherlands Organisation for Applied Scientific Research (TNO), CHDR researchers plan to explore a novel camera system that promises a more detailed view of the molecular composition of retinal cells, using light absorption and scattering patterns. 'We hope to be able to use this system to study the effects of compounds aimed at eliminating molecules involved in pathological processes. I look forward to updating you on our progress next year!'

Philip Kremer to take the lead in Neurology

In April 2020, neurologist Dr Philip Kremer was appointed Associate Research Director in Neurology at CHDR. Prior to this, Kremer was employed as a neurologist at the Leiden University Medical Center (LUMC), where he will continue to spend one day a week. Kremer studied at Utrecht University in the Netherlands, where he first gained his MSc in pharmacy before undertaking an additional MSc in medicine. Following this, he completed a PhD in bacterial genetics and bioinformatics at the Amsterdam University Medical Center, performing part of his research at the Wellcome Sanger Institute in Cambridge, UK. ‘CHDR is a great fit for me. I can put my combined skills as a neurologist and pharmacist to good use, conducting research on treatments for a variety of neurological disorders,’ says Kremer. ‘I really value the scientific approach at CHDR. It’s rewarding to work at the junction of basic research and clinical application, leveraging scientific insights into molecular mechanisms to help our clients develop new treatments.’

Psychiatry

Breaking new ground in the treatment of depression, anxiety and trauma-related disorders

Current pharmacological treatment options do not provide sufficient relief to all patients suffering from depression and/or anxiety disorders, and in a significant number of cases, these disorders prove to be difficult to treat. The search is on for compounds targeting neurotransmitter systems other than those implicated in the therapeutic effects of traditional monoaminergic antidepressant drugs. Meanwhile, psychiatrists are considering alternative approaches to help people with persistent depression and trauma-related disorders, including various 'psychedelic' substances. CHDR is contributing in different ways to these developments from an early drug development perspective, ranging from conducting data-intensive first-in-human studies to developing and validating biomarkers that reflect emotion regulation.

'We have recently become involved in an interesting new development in psychiatry, studying the pharmacology of so-called psychedelic compounds,' says Dr Gabriël Jacobs, CHDR's Research Director in Psychiatry. 'In fact, the term "psychedelic" is somewhat of a misnomer – it actually refers to a group of drugs, including MDMA, psilocybin and DMT, that alter consciousness in different ways depending on their pharmacology. Several groups here in the Netherlands and elsewhere are studying the effects of such substances to treat patients with severe difficult-to-treat depression or post-traumatic stress disorder.

We have already been researching the use of ketamine in this context for a number of years, and we are glad to have the chance to contribute our pharmacological expertise to these new lines of enquiry involving psychedelics.'

Psychiatrists are cautiously turning to these substances – which are controlled substances in most countries – based on anecdotal evidence and promising results from a small number of controlled clinical studies. Increasingly, the reputation of these substances as dangerous also turns out to be unfounded: if administered in a safe and closely-monitored setting, psychedelic substances rarely have adverse physiological effects or unwanted long-term psychological effects. It is a complex field, however, in which regulatory and methodological challenges have hindered progress in previous decades. Nonetheless, the fact that a significant proportion of patients do not respond well enough to other treatment modalities provides impetus to overcome these obstacles. Jacobs, who also sees patients at the Leiden University Medical Center (LUMC) Psychiatry department, observes this unmet clinical need first-hand. 'Fortunately, we're able to help most of our patients with evidence-based pharmacotherapy, ECT and psychotherapy, or a combination of these. However, for some patients, nothing seems to work,' says Jacobs. 'For patients with chronic therapy-resistant forms of depression, life is often nothing but an unbearable burden. Nonetheless, despite the promise of recovery that psychedelics might have for these patients, it is crucial that we also scrutinise these compounds rationally, such as by applying our question-based model of clinical drug development.'

Esketamine

One of the ongoing lines of research within CHDR's Psychiatry group aims to gain a better understanding of the pharmacological mechanisms that determine the clinical antidepressant effects of ketamine in therapy-resistant depression. Typically, after a session with ketamine, the patient's mood improves significantly within the first 24 hours after administration. However, the effect is temporary, requiring repeated dosing. Using a variety of techniques, including resting-state fMRI, Jacobs and his colleagues have tried to get a handle on ketamine's CNS effects, especially in relation to the circuits that are involved in mood disorders. Chemically, ketamine is a so-called racemate, consisting of two enantiomers: esketamine and

arketamine. Both are non-competitive antagonists of the N-methyl-D-aspartate (NMDA) receptor, one of the glutamate receptors in the brain. CHDR's research into ketamine began with the study of regular (racemic) ketamine. Then, in 2019, a nasal preparation of esketamine was registered in the USA and Europe for the treatment of therapy-resistant depression, at which point Jacobs and his colleagues decided to focus on esketamine. Around the same time, researchers in Groningen in the Netherlands began a randomised clinical trial to establish the effects of oral esketamine, as an alternative to the intranasal administration route.

The pharmacokinetics of esketamine are complex, since it is metabolised hepatically into several active metabolites, such as noresketamine. Jacobs: 'This may have crucial implications for clinical research using oral esketamine. After oral administration, there is a strong first-pass effect, which means that clinical effects may predominantly result from noresketamine. This may have an impact on both desired and adverse effects, or even toxicity, because noresketamine has a unique pharmacodynamic profile and a longer half-life than esketamine.' To investigate this, Jacobs and his colleagues plan to perform a study to compare the pharmacodynamic effects of intravenous esketamine and oral esketamine, incorporating PK/PD modelling in the study design.

Synaptic plasticity?

The mode of action of ketamine and psychedelic substances differs conceptually from traditional antidepressant drugs, as they produce clinical effects that typically do not relate to the pharmacokinetics of the drug. 'We know from our studies and from the literature that the antidepressant effect of ketamine occurs 24 hours after administration. At this point, most of the parent drug already has been eliminated, but norketamine is still present. Using our NeuroCart® test battery, we see the direct effects of ketamine on a variety of neurophysiological and neuropsychological functions a few hours after administration of the drug, when the blood concentration is highest,' says Jacobs. 'So it seems that ketamine induces changes following the occurrence of those acute effects, which in turn cause those antidepressant effects 24 hours later. However, exactly how this works is still unclear. If we could address this gap in our knowledge, it may pave the way for the development of novel antidepressants that do not have the drawbacks of ketamine or psychedelic drugs.'

Jacobs explains how animal models provide clues as to what happens in the hours after esketamine administration: 'Soon after the administration of ketamine, more synapses are being formed in the animals' brains, especially in the hippocampus, a crucially important structure within the limbic system that regulates emotions. So it may all boil down to synaptic plasticity.' In humans, it is currently not feasible to reliably and cost-effectively measure changes in the number of synapses in the hippocampus. However, given that there is a putative relationship between excitability and plasticity of the brain, Jacobs and his colleagues plan to use transcranial magnetic stimulation (TMS) as a proxy for neuroplasticity, measuring changes in cortical excitability before, during and after esketamine administration.

Measuring emotion regulation

NeuroCart®, CHDR's unique CNS test battery, has been successfully applied over the past 25 years to demonstrate functional CNS effects of novel compounds and to compare these to the benchmark effects of registered compounds. 'The NeuroCart reliably quantifies higher brain functions, such as concentration, sustained attention, and vigilance. However, it doesn't map anything in terms of emotion regulation,' says Jacobs. 'Ideally, we would have a set of biomarkers, informed by the NIMH's Research Domain Criteria approach, to quantify drug effects on different aspects of emotion regulation, both in healthy volunteers and in patients. I've had this idea in mind for a few years now, but it is quite complicated from a methodological perspective and it requires a dedicated effort. So we are really fortunate to have Soma Makai-Bölöni joining us as a Clinical Scientist: he will work with me and with our Method Development group to get this project off the ground.' Makai-Bölöni first came to CHDR to do a traineeship during his MSc in Drug Development and Neurohealth at Maastricht University, and, following his graduation, was hired at CHDR. His role will involve helping to develop a robust set of tests to measure emotional state and how it can be modulated with different pharmacological compounds.

One of the most promising biomarkers, which has already proven to be of use in studying antidepressant drugs, is the emotional bias task developed by psychopharmacologist Prof. Catherine Harmer and her team at Oxford University. In this test, subjects are presented with human facial expressions that are morphed to fall on a continuum between happy and sad. When presented with each of these faces, subjects are asked to indicate the emotion of the person they see. Jacobs: 'What Harmer and her colleagues found is that depressed people select more faces as unhappy than healthy people. Moreover, the emotional bias displayed in this task can be modulated with antidepressants. Interestingly, this test has proven to be sensitive to single doses of different monoaminergic antidepressants: there are indications that a change in emotional bias following a single dose is predictive of antidepressant response weeks later. Last year, we started a collaboration with the Oxford team and we plan to include the emotional bias task in our ketamine studies. If it turns out to be useful in healthy subjects, we may also use it to explore the effects of other glutamatergic compounds on emotion regulation.'

DMT and MDMA

'It's exciting to be involved in the burgeoning field of psychedelic research,' says Jacobs. 'We've also started preparations for a sponsored study involving DMT, which is the active ingredient in the famous ayahuasca brew used in South American shamanistic rituals. The sponsor plans to develop a DMT-based treatment for addiction. We have offered to do the groundwork for

that, investigating DMT as we would study any new active compound – with single ascending doses in healthy volunteers, to study the pharmacodynamics, pharmacokinetics, safety, and other key properties.' DMT, otherwise known as dimethyltryptamine, is metabolised rapidly by monoamine oxidase (MAO). To be able to study a longer-lasting DMT experience, the team plans to use an intravenous clamp setup. 'Our PK/PD modellers are currently devising the dosing strategy for this study. Based on the limited data in the literature about the pharmacokinetics of DMT, they have devised a first dosing scheme. Of course, we will start with a safe low dose supported by data. Before we go to the next dose, we will evaluate the relationship between plasma levels and both functional CNS effects and subjective experience, to optimise the next series of measurements.'

> 'It's exciting to be involved in the burgeoning field of psychedelic research'

Another controlled substance that is being evaluated for its therapeutic potential is MDMA (3,4-methylenedioxymethamphetamine). MDMA is not considered therapeutic in itself, but rather in the context of a rigorous programme of psychotherapy. One of the groups currently investigating this approach is led by Prof. Eric Vermetten, who holds a chair in psychotraumatology at the LUMC Psychiatry department. Jacobs: 'We have recently initiated a collaboration with Prof. Vermetten. He specialises in the treatment of military personnel and police officers who have been traumatised in the course of duty. They have already established that a session of MDMA can contribute to the healing process. We are currently preparing a scientific paper together focusing on the pharmacology of MDMA in relation to the pathophysiology of PTSD.'

One theory about MDMA's contribution to psychotherapy is that, in addition to releasing serotonin and dopamine, it triggers the release of oxytocin. Oxytocin is involved in interpersonal bonding, and is released at such moments as when people hug and when a mother breastfeeds her child. 'According to this theory, oxytocin in combination with serotonin and dopamine helps to provide an atmosphere in which people feel safe enough to open up and explore sensitive and painful memories. However, this theory has never been rigorously tested in a controlled setting,' says Jacobs. 'Some people claim it is not possible to do a controlled experiment with MDMA, because subjects will always know whether they've got the active ingredient or not. But I think there are ways to work around that, using substances that alter perception without having all the properties of MDMA.'

COVID-19

Jacobs takes a moment to reflect on the impact of the COVID-19 pandemic on his research. 'We've had similar difficulties to most other researchers – including having to postpone studies and, when we could conduct studies, needing to adapt our procedures to be able to keep our subjects and staff safe. When the first lockdown was announced, we had almost finished data collection for our study in depression in collaboration with the Transparant Centre for Mental Health, a local mental healthcare provider. Unfortunately, the restrictions meant that it was not feasible to include the last two subjects: the lockdown was expected to limit physical activity and social interaction to such an extent that the data would likely be invalid for our study's objectives. Nonetheless, we did manage to collect sufficient data for the study, which we are currently in the process of analysing.' In this study, which was described in more detail in last year's Annual Report, CHDR's Trial@home remote monitoring platform was used to gather a variety of data on patients with depression. Alongside objective measurements such as physical activity, sleep, and blood pressure, participants were asked to respond twice a day to questions concerning their mood, using the platform's electronic patient-reported outcome (ePRO) functionality. Jacobs: 'We're planning to submit a proposal for a symposium at the International Society for Affective Disorders in November, and we're looking forward to presenting a poster at the Annual Meeting of the Society of Biological Psychiatry.' Over the past year, however, visits to scientific conferences were ruled out due to the pandemic. Nor were CHDR staff able to travel to meet potential clients and collaborators. 'We did all of these activities online, which has advantages and disadvantages,' says Jacobs. 'As is the case for many organisations right now, I think the pandemic will change the way CHDR considers international travel. In many cases it's really crucial to meet people face-to-face. However, some conferences have become rather commercial events, which can mean that they don't always offer the best opportunity to share scientific insights and develop networks of like-minded people. So it's a good moment to reflect on our strategy, and perhaps the pandemic disruption will even lead to a shake-up of the conference industry.'

Working from home while CHDR's facility was closed, Jacobs and his team used their new-found downtime to write articles and to contribute to CHDR's educational efforts: 'For example, one of my PhD students used the opportunity to upgrade the psychiatry content in CHDR's Teaching Resource Centre app, adding relevant new information on topics such as neuroplasticity relating to ketamine and psychedelic drugs. These upgrades are expected to go live in 2021. And of course, our regular educational activities also continued – we recently welcomed a psychiatrist who works in a general hospital and is being trained as a clinical pharmacologist at CHDR, during which time he will assist us with various projects,' says Jacobs. 'So, in spite of the pandemic, 2020 has been quite an active year on many levels – in fact, in some aspects of our work, the pandemic gave us an opportunity to gain even more ground.'

Dermatology

The data-rich future of dermatological research

The Dermatology group conducted studies on various new compounds in 2020, and thanks to CHDR's Trial@home platform for remote data collection, several of these studies could continue even as the pandemic forced the closure of the clinical facility. The team has also been hard at work expanding the DermaToolbox, CHDR's unique high-tech test battery for the objective measurement of changes in the skin. Thanks to their interdisciplinary approach, the Dermatology group continues to strengthen collaborative ties with other teams across the organisation, as well as growing their network of partners in industry and academia.

To conduct data-rich dermatology trials, Research Director Prof. Robert Rissmann and his Dermatology group use technology in two key ways. Firstly, the team makes extensive use of the remote data collection possibilities offered by CHDR's Trial@home platform. With this strategy, subjects are not required to stay at the facility and can participate from the comfort of their homes. Secondly, on the occasions when subjects do visit the facility, the team uses the DermaToolbox test battery to gain a detailed insight into subjects' skin by means of a dedicated array of high-tech dermatological assessments. These include non-invasive procedures to measure changes in skin perfusion, temperature, hydration, erythema, skin morphology, and skin barrier status, in combination with suction blisters and biopsies to obtain material for detailed immunological examination.

Rissmann: 'We aim to characterise each skin condition on various levels, including cellular, biophysical, molecular and microbiome levels, using imaging and other techniques. The better we can characterise each skin condition in this way, the more we will be able to monitor patients remotely in future. The ideal combination is in-depth, in-clinic measurements complemented by non-invasive remote assessments.' As always, the team's fundamental aim remains to pursue rational drug development using highly sensitive and objective methods. 'I think it is realistic to assume that in the coming years we will still need our subjects to visit our facility at least a few times over the course of the trial, but we are keen to embrace the possibilities offered by remote monitoring.'

Deep phenotyping

Rissmann describes this approach he and his colleagues pursue as 'deep phenotyping'. He recently submitted a grant application for a larger consortium of dermatological academic research centres, which sketches the future possibilities if additional 'omics' approaches such as proteomics and metabolomics are incorporated. 'Considering that our understanding of the various chronic skin diseases is still in its infancy, the development of a versatile platform for ultra-deep phenotyping of all skin and immunological diseases will be a game-changer. This will be a unique combination of the newest techniques – it will include spatial multi-omics in tissue and blood, non-invasive "digital biopsies" through imaging, biophysical assessments, patient-reported outcomes, and a comprehensive test battery for remote assessments. Of course, this will only become possible with the involvement of the entire academic dermatological community in the Netherlands. However, thanks to our dynamic network for dermatological trials, CONNECTED, the foundation for this collaboration is already in place.'

Precision medicine

This comprehensive approach to dermatology is already taking shape at CHDR, in the context of early clinical drug development. 'We continue to broaden our range of methods. Several tools have recently been added to our DermaToolbox, such as confocal reflectance microscopy and lipidomic deep profiling. Together with Dr Martijn van Doorn from the Erasmus Medical Center in Rotterdam, we've also studied a new drug delivery system called Enerjet. Enerjet builds on the well-known Dermojet "needleless syringe" concept, which uses electronic pneumatic pressure to precisely deliver the right dose at the correct intradermal depth,' says Rissmann. 'In general, technological progress is proceeding very rapidly at the moment. The improvements we're seeing in measurement accuracy and precision are staggering. In a skin biopsy, we can now look at the transcriptome and proteome of individual cells and the spatial interaction within the tissue. So if we start to correlate various levels of omics, it's not about averages of groups of cells any more: we can also investigate processes at the level of the individual cell.'

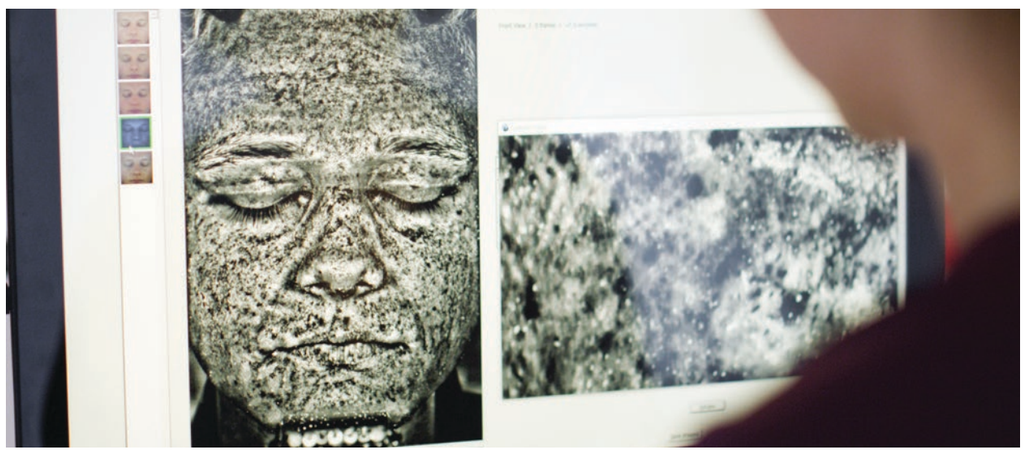
According to Rissmann, these precise measurements are not only interesting for research: they will also revolutionise the diagnosis and treatment of skin conditions. 'We are working towards a more personalised approach – towards precision medicine. We already know there are many individual differences among patients with the same skin condition, such as eczema, for example. However, these patients currently all receive the same treatment with topical corticosteroids. The better we understand their condition on an individual level, the more we can contribute to the development of new and more effective compounds for specific subgroups,' says Rissmann. 'I like to compare it to microbiology: a patient with a specific bacterial infection receives a

dedicated antibiotic treatment tailored to the particular pathogen causing the infection. In future, that will also be the paradigm in the treatment of eczema and other skin conditions: treatment will be tailored to the specific characteristics of the individual patient.'

Collaboration

At the end of 2020, Rissmann received news that in 2021, he would be appointed professor of Translational Dermatology at Leiden University, specifically at the Leiden Academic Centre for Drug Research (LACDR) (see also page 55). 'Back when I first joined CHDR, I was hired to coordinate the organisation's educational activities. Then, almost seven years ago now, I started conducting dermatological research for CHDR, alongside my educational duties,' remembers Rissmann. 'In 2017, when Jeroen van Smeden joined us, I was able to hand over those duties to him and focus entirely on my research in dermatology. Together with our PhD students, we did a lot of interesting work – often in collaboration with other CHDR research groups, especially with Matthijs Moerland's group in the area of immunology, and with Geert Jan Groeneveld's group in the area of pain research.' One of Rissmann's recently-graduated PhD students, Dr Tessa Niemeyer-van der Kolk, will soon be joining CHDR's permanent staff. Rissmann: 'It's exciting to welcome a young talented scientist like Tessa to our ranks, and to further establish the group with more permanent staff members.'

The Dermatology group has an extensive network of collaborators in clinical dermatology, both in university medical centres and in general hospitals.



As demonstrated by Rissmann's recent consortium grant application, there is growing interest in collaboration between dermatological academic research centres across the Netherlands. Additionally, Rissmann and his colleagues collaborate with physicians in other fields. This includes work with gynaecologist Dr Mariëtte van Poelgeest on the treatment of HPV-induced lesions of the vulva, and collaborations with rheumatologists to develop new approaches to conditions that affect both the joints and the skin. 'Collaboration is central to our strategy. In my experience, collaborative work yields great benefits for everyone involved, with each partner contributing their expertise and resources to a joint effort,' says Rissmann. 'Our collaboration with medical centres is about so much more than recruitment: it's really a scientific and operational synergy.'

Trial@home

Remote monitoring using CHDR's Trial@home platform can offer benefits for studies in a wide range of fields, from psychiatry to infectious diseases. And it is especially well-suited to dermatology research, as Rissmann explains: 'Dermatology is a highly visual field. By asking participants to submit daily pictures of the lesion we can learn a great deal, especially in combination with the other data that we collect. The fact that we can gain so much insight without needing to see the subject in person also lessens the burden on patients who participate in our studies.' Central to Trial@home is the use of a dedicated smartphone app, which capitalises on the wealth of functionality that smartphones offer. For example, the app can be used not only to monitor the lesion but also to remind subjects to take their medication or apply it to the skin. 'We can even use it to check compliance, by asking the subject to submit a picture of the skin with the ointment applied. The app also presents mini-questionnaires to collect data on the participant's subjective experience, for example to note any complaints such as itching or pain.' Read more about Trial@home in the interview with Product Manager Dr Vasilis Exadaktylos on page 98.

'We've always believed that the remote monitoring approach would be the future of clinical research in many fields, including dermatology. And due to the restrictions on travel and in-person contact during the COVID-19 pandemic, many more people are now beginning to see its value. Over the past year, we've all learned to do more things remotely: education, business meetings, you name it. Likewise, people are becoming more accustomed to the idea of conducting trials at home. All of this has really added to the momentum of this approach,' says Rissmann. 'I look forward to seeing all the benefits that Trial@home will bring to our studies in the years to come.'

Extraordinary professorship in Translational Dermatology for Robert Rissmann

‘I’m honoured to be appointed to this professorship, even more so because I will be working alongside my former colleagues,’ says Rissmann about his upcoming appointment as professor of Translational Dermatology at the Leiden Academic Centre for Drug Research (part of Leiden University). Before joining CHDR to coordinate activities in education, Rissmann worked as a PhD student at LACDR in the group of Prof. Joke Bouwstra. There, he explored novel treatments for eczema and other conditions, and worked on a synthetic product that mimics the lipid-rich biofilm that protects the skin of the foetus and newborn (vernix caseosa). ‘Back in 2008, I was encouraged to pursue a career in education, and so became a university lecturer in analytical biosciences,’ says Rissmann. ‘I still enjoy being in front of a class, but I’m also glad that I became a clinical pharmacologist: switching back to full-time research at CHDR has allowed me to contribute my expertise in clinical and translational drug development to the vital work of the Dermatology group.’ Rissmann, who was educated as a pharmacist in Berlin, will combine his duties as professor with his work at CHDR, continuing to drive innovative developments in translational dermatology research.

Internal medicine

Markers, models and machine learning

The range of CHDR's activities in the field of internal medicine is expanding. Building on the success of their colleagues in the Research & Development lab, the Internal Medicine group have plans to use novel biomarkers to study a variety of compounds. New approaches and novel compounds are also being studied for use in image-guided surgery. Meanwhile, existing approaches have seen new enhancements, such as the application of machine learning techniques to ECG analysis and the contribution of CHDR's pharmacokinetics modellers to research in endocrinology.

Internal medicine has always been the most diverse therapeutic area at CHDR, and with recent developments, the range of subjects being addressed is broader than ever. 'At the beginning of 2020, we were eager to explore the possibilities of expanding our activities in the fields of oncology and infectious diseases,' says Prof. Koos Burggraaf, CHDR's CEO and head of the Internal Medicine group. 'However, due to the COVID-19 pandemic, infectious diseases naturally ended up dominating the programme. We hope to continue exploring possible new lines of research in oncology and novel therapies in the course of 2021.' On page 62, Dr Ingrid de Visser-Kamerling talks more about CHDR's work on COVID-19 and other infectious diseases.

Immunology and vasculature

The immune system is involved in a multitude of different pathophysiological pathways, ultimately affecting every organ and system in the body. Increasingly, novel therapeutic strategies aim to target the immune system, modulating specific immune responses or mitigating innate immune responses and inflammation. This means that immunological research is relevant to all therapeutic areas in which CHDR is actively involved: not only the immunology therapeutic area itself, but also internal medicine, dermatology, neurology and pain, and even psychiatry. CHDR's Research & Development lab supports studies in all these fields, actively developing new biomarkers to measure the effects of drugs for a diverse range of conditions.

Another major system that is highly relevant for many therapeutic areas is the blood vessel wall and the endothelium. Atherosclerosis, for example, is one of the most important causes of morbidity and mortality worldwide. It is increasingly clear that immunological processes play a crucial role in the development of atherosclerosis and its complications, namely stroke and myocardial infarction. The close intertwining of research in these two areas is reflected in the decision to establish a distinct Immunology-Cardiovascular research group, which combines immunology research with vascular biomarker development. Another new development in this area is a research programme studying the metabolism of immune cells, or 'immunometabolism'. New insights in this area will primarily benefit the development of novel CNS therapies, but could also contribute to therapies based on a wide variety of other pathophysiological pathways. Read more about the work of CHDR's research groups in biomarker development, immunology, and vascular medicine on pages 66-81.

Image-guided surgery

In collaboration with the Surgery department of the Leiden University Medical Center (LUMC), CHDR is involved in the development of fluorescent markers for use in image-guided surgery. These markers offer surgeons visual guidance by highlighting specific structures. This approach is particularly beneficial for ensuring the complete removal of tumours in cancer surgery, or to avoid damage to vulnerable structures such as nerves or ureters during an operation. In recent years, CHDR and LUMC researchers working on image-guided surgery have tested a variety of fluorescent compounds. CHDR performs studies to assess the safety and pharmacokinetics of each compound in healthy volunteers, following which the compounds are evaluated for use in surgical practice by surgeons, pathologists and scientists at the LUMC.

Increasingly, other hospitals are joining these efforts, which in turn raises the chances of widespread adoption of this novel approach to surgery. In 2020, for example, a compound that binds to prostate cancer cells was tested at the Netherlands Cancer Institute in Amsterdam and at the LUMC. 'At the Netherlands Cancer Institute, the compound was used in patients scheduled for a curative prostatectomy, to explore the extent of the disease and achieve complete removal. Meanwhile, the study at the LUMC focused on the use of the same compound in robotic surgery for patients who had developed a positive lymph node following prostatectomy. The results of both studies are currently being analysed,' says Burggraaf. 'In conducting this research, we also benefit from the expertise of our Associate Research Director in Internal Medicine, Dr Naomi Klarenbeek.'

Meanwhile, the search continues for novel compounds for use in this approach, with laboratories worldwide working to identify optimal ligands in a variety of tumours and other structures. Burggraaf: 'In the future, image-guided surgery may even become possible

without the use of exogenous substances. Pim Gal, who works in our Immunology-Cardiovascular group, is investigating the use of imaging techniques to study the microvasculature. With near-infrared spectroscopy, he visualises the difference between oxygenated and deoxygenated haemoglobin. Theoretically, it could one day be possible to apply (multispectral) imaging to check for leakage and the vitality of tissue following anastomosis surgery. And maybe this approach could even be used for tumour detection, since malignant tumours are often characterised by changes in blood flow and central necrosis.'

Cardiology Services

In addition to his work on the development of vascular biomarkers, Gal is still very much active in the field of cardiology. 'In 2020, we provided a cardiac risk analysis for eight of our studies, focusing particularly on the QT interval, using state-of-the-art techniques endorsed by the US Food and Drug Administration,' says Gal. 'In recent years, we have actively contributed to novel developments in this field, which have also enabled us to further enhance and optimise the service we provide for our clients.' CHDR Cardiology Services aims to provide comprehensive insight into the cardiac effects of compounds under study. Gal: 'Most clinical studies already require the collection of ECG data to monitor subjects' health. Cardiology Services offers added value by further analysing this data to yield a cardiological safety profile of the drug, with particular attention to the QT interval. Our clients really value the convenience of this one-stop-shop approach.'

ECG data is also acquired in the process of screening subjects. This provides Gal and his colleagues with another rich dataset, full of potential for further study. 'Using a machine learning approach, we mine the ECG data for relevant patterns which could be used as biomarkers in the future,' says Gal. 'For example, by training a neural network on this dataset, we have been able to develop a model which correctly estimates people's age based on their ECG. Of course, our ultimate goal is not to predict subjects' ages – however, the results serve to demonstrate the potential of such an approach for gleaning insight from changes in a subject's cardiac electrophysiology.' In 2020, the team began the analysis of a dataset captured from cardiology patients, looking for changes in their ECG following an intervention to treat cardiac failure. Gal: 'The power of machine learning lies in its ability to reveal patterns which would elude you in a more classical analysis.'

Mimicking physiology

Another important focus of the Internal Medicine group is the field of endocrinology. CHDR researchers in this field use pharmacokinetic models, which are typically associated with the study of novel compounds, to study naturally produced hormones. Burggraaf: 'Hormone release is often pulsatile in character, or shows marked (circadian) rhythms. It is important to take this temporal element into consideration, not just in the analysis of an endocrinological problem, but also in devising strategies to treat it.' Burggraaf's former PhD student Dr Michiel van Esdonk has developed models to deal with such pulsatile profiles, specifically growth hormone release in acromegaly patients and healthy subjects. Such models can be useful in developing treatments for other endocrinological disorders.

Treatments that mimic the physiological pulsatile release of hormones and other substances may provide an optimal way to restore homeostasis in patients. In 2020, CHDR took the first steps in this direction, led by Dr Naomi Klarenbeek. To do so, the team used a modified version of the contraceptive vaginal ring.

'Electronically-controlled drug release promises a range of interesting possibilities'

This device can release a compound under electronic control, yielding a range of possibilities that the team intends to systematically explore. So far, it has been shown that the device can be used to administer small molecules, and the team are currently busy investigating the use of this device to administer compounds with a higher molecular weight. Burggraaf: 'It's a first step towards the wider application of electronically-controlled drug release. Given CHDR's expertise both in pharmacokinetic models and in the use of biomarkers to measure systemic effects, we are in an optimal position to uncover the possibilities of this interesting new field.'

Dr Ingrid de Visser-Kamerling, Associate Director

'It was surreal'

The Infectious Diseases therapeutic area was already marked for expansion as part of the new CHDR strategy developed at the beginning of 2020. But instead of their planned academic exploration of methods to study viral infections, the Infectious Diseases group had to hit the ground running, as the novel coronavirus took centre stage. 'Everyone threw themselves into the work, and we learned a great deal in the process,' says Associate Director Dr Ingrid de Visser-Kamerling.

A crucial foundation of CHDR's infectious diseases programme is De Visser's collaboration with Dr Meta Roestenberg, a specialist in infectious diseases at the Leiden University Medical Center (LUMC). 'The potential for synergy was clear from the beginning,' says De Visser. 'Meta had developed groundbreaking challenge models to study malaria and other infections, and we wanted to use controlled infection models to study viral infections such as influenza and respiratory syncytial virus (RSV). We had successfully applied for two European grants to study influenza. In combination with our expertise in drug research and immunological biomarker development, we felt we had something unique to offer. We planned to gradually expand our activities and set up some trials by the end of 2021.'

Fast track

But then, the pandemic hit. Roestenberg was fully occupied by the demands of patient care as COVID-19 cases flooded the LUMC. Meanwhile, pandemic restrictions led to the temporary closure of CHDR's Clinical Research Unit (CRU). De Visser threw herself into preparing for studies to test the safety and efficacy of the coronavirus vaccines that were in development. 'We were all keen to play our part, so I started to develop a basic protocol and began recruiting and screening volunteers to be ready for a vaccine study,' says De Visser. 'In order to conduct such studies, we needed to first obtain the necessary permission to do research with advanced therapy medicinal products and genetically modified organisms. However, there was another obstacle here: the procedures involved in gaining such permissions are very time-consuming.' De Visser raised this issue with the relevant authorities: the Netherlands' Central Committee on Research Involving Human Subjects (CCMO) and the Gene Therapy Office. The authorities were sensitive to the needs of De Visser and other scientists, and soon, fast-track procedures were developed. De Visser: 'The CCMO implemented a rolling submission process, in which the authorities would not wait for a complete dossier, but would instead start to evaluate the documentation that was ready while other essential documents were still being prepared. This led to a dramatic reduction of the normal timelines.'

De Visser and her team went on to prepare everything for a vaccine trial, to be ready if the need arose. And it did: Janssen Vaccines, a Leiden-based arm of Johnson & Johnson, had started developing a vaccine on their established adenovirus-based platform in early February 2020, soon after the genome of SARS-CoV-2 was published. In the summer of 2020, CHDR became one of the sites for their phase II trial. 'CHDR gave the very first injection of the Janssen vaccine in the Netherlands on 14 September, less than eight months after the publication of the viral genome. It was a miracle, made possible by a huge effort on the part of many people,' says De Visser.

Remdesivir

During the first wave of the COVID-19 pandemic, when clinical operations at CHDR were suspended and the CRU closed, Roestenberg called De Visser. 'It was a Friday at the end of March. Meta told me she was desperate: the ICU was full up with COVID-19 patients, and there were no specific medications available except for trial medications. She wanted her patients to participate in the international remdesivir trial, but she was far too busy treating them to also organise participation in the trial. So I told her I would do what I could to help out.' De Visser and CHDR's Board worked through the weekend to study the investigator's brochure and translate the international protocol. By Monday, in another example of the exceptional momentum inspired by the pandemic, the protocol was already submitted to the ethical committee for a fast-track assessment. While the ethical committee were reviewing the protocol, several of CHDR's clinical scientists and research nurses were officially appointed at the LUMC, to be ready to lend a hand where needed in executing the study. A second site was set up at the Amsterdam University Medical Center.

In the space of less than two months, the international remdesivir trial had included enough patients to reach a conclusion and the antiviral compound was the first drug to be registered for the treatment of COVID-19. 'Walking down empty hospital corridors, having to jump aside when a COVID-19 patient was wheeled through in a hurry – it was surreal,' says De Visser. 'There was a strong feeling of solidarity, of all being in this together. It was heart-warming to see how everyone – nurses, physicians, team leaders – immediately said yes when we asked them to participate. That really took some courage, because there was so much we didn't know at that moment of the pandemic.'

Future outlook

'As an organisation, we were glad to have the opportunity to contribute to the remdesivir trial and the Janssen vaccine trial,' says De Visser. 'However, our role was very much a supporting one. We strived to add value wherever we could – mostly small enhancements, such as the use of digital diaries instead of paper booklets, which was much more hygienic. Now that the pandemic is in another phase, with mass vaccinations being implemented in most countries, I'm looking forward to us returning to our long-term strategy of infectious diseases research at CHDR.

'One positive outcome of our work in 2020 has been the way in which the shared experience of the pandemic has cemented the collaboration between the LUMC and CHDR teams,' says De Visser. 'Several studies related to COVID-19 and other infectious diseases are currently being prepared, including several early-stage coronavirus vaccine trials, in which we will be able to contribute far more than in the trials we did last year.'

Above all, De Visser hopes that the lessons learned from the pandemic will yield benefits for the future of infectious diseases research as a global endeavour. ‘Before the pandemic hit, there was a tendency to view infectious diseases as an issue that chiefly concerned the developing world. Now, it is clear to everyone that infectious diseases can have a tremendous impact on all societies around the globe,’ says De Visser. ‘Even when we have learned to tackle COVID-19, this does not mean such pandemics will be a thing of the past – far from it. Companies, governments, NGOs, scientists and the general public must all be on guard against emerging pandemics. We at CHDR are ready to play our part.’

Biomarkers and Laboratory

Taking the opportunity to reflect on and refine models

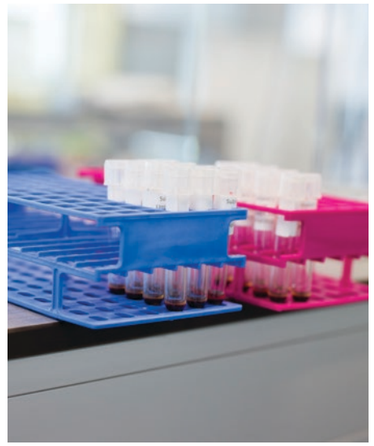
Even during the months when the clinical unit and research laboratory had to close, work continued apace for Research Director Dr Matthijs Moerland and the Research & Development lab. The team specialises in studying various immunological mechanisms, some of which turned out to be highly relevant to the development of treatments and vaccines for COVID-19. The pandemic also provided opportunities to reflect on existing models, leading to refinements and novel applications.

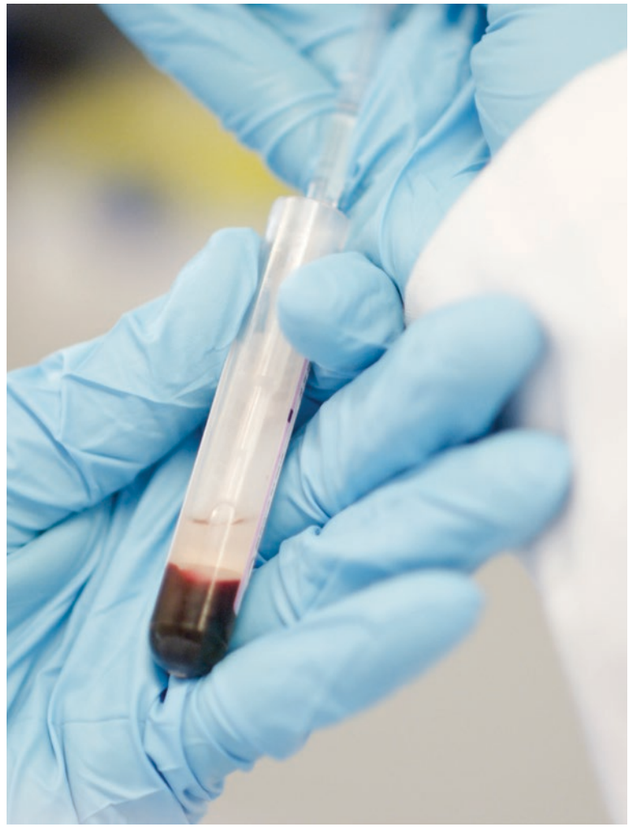
‘During the period when the facility was locked down and clinical studies were suspended, we were nonetheless very busy,’ says Moerland. ‘There were many urgent matters to be addressed as we made preparations to reopen. Studies in vulnerable populations were ruled out, as were studies with immunomodulatory compounds that could pose an extra risk given the ongoing pandemic. At the same time, we were keen to do our part to contribute to the study of COVID-19, including the vaccine trials. Any remaining downtime was quickly put to use in writing up scientific articles concerning the wealth of data that we have gathered in recent years.’

Moerland’s team includes nine PhD students, who, under normal circumstances, also play a very active role in operations. ‘For the PhD students, it’s typically a challenge to set aside time to reflect and write the articles that they need to complete their dissertation. We always encourage them to keep on top of the writing process, and when it’s time to focus on completing the dissertation, they are exempted from operational duties,’ says Moerland. ‘But with the pandemic restrictions, the chance to focus on writing presented itself naturally. Some of our PhD students were already in the writing phase, so their focus was clear. Others were about halfway through their PhDs, which is a good moment to reflect, do some writing and review plans. For those PhD students who had just started, it was an opportunity to do a literature review to lay the groundwork for their thesis. All of this work is fruitful not just for their individual scientific careers but also for our output as a scientific organisation.’

Two research groups, one director

Research Director Dr Matthijs Moerland now heads two teams: the Research & Development laboratory and the Immunology-Cardiovascular group. The Research & Development lab focuses on the development of new biomarker-based methodologies, most of them in the field of immunology. The Immunology-Cardiovascular group is one of CHDR’s clinical research groups, conducting clinical studies for the development of new therapies in immunology and cardiovascular medicine.





Hydroxychloroquine

In June 2020, when it became possible to do clinical studies again, Moerland and his team started with a self-funded mechanistic study on the effects of hydroxychloroquine. This antimalarial drug, which is also used in rheumatology, was at that time being promoted as a possible prophylactic treatment to protect vulnerable individuals against SARS-CoV-2. At the same time, there were discussions about the side effects of hydroxychloroquine, especially the risk that this drug might induce cardiac arrhythmias. Moerland, however, knew from the literature that there was another possible drawback that might influence the drug's efficacy: 'Our first line of defence against viruses is the innate immune system, which we at CHDR have been studying for quite some time now. It does not recognise any specific virus, but rather responds to anything out of the ordinary – such as extracellular RNA – triggering a so-called type I interferon reaction, which is essential for an efficient anti-viral response. Hydroxychloroquine, however, is known to dampen the innate immune response. So theoretically it may not be a good idea to give this compound in a prophylactic setting, or to vulnerable individuals with an already weakened immune system.'

In this study, healthy young and elderly volunteers received a single dose of hydroxychloroquine, following which an extensive battery of immune-monitoring tests was conducted to examine their innate immune response. In addition, Dr Pim Gal, a Senior Clinical Scientist in Moerland's group with a special interest in cardiology and vascular medicine, examined the cardiovascular effects of the drug. Preliminary results indicate that, at the dose used for COVID-19 treatment and prophylaxis, the immunosuppressive and cardiological effects are limited. 'Most research being done on hydroxychloroquine focused on clinical effects in patients with COVID-19. As far as I'm aware, we were the only group focusing on the underlying pharmacological mechanisms,' says Moerland. 'This study also provided a valuable opportunity to validate part of our immunomonitoring test battery in a clinical study for the first time.'

Boosting innate immunity

An overactive innate immune response is thought to be at the root of several autoimmune diseases. Moerland and his colleagues have been studying a number of compounds that aim to modify this response. In the context of COVID-19, however, it would be interesting to enhance innate immunity, in order to be better prepared when the virus strikes. 'We prepared a clinical study to be performed in the first quarter of 2021, using a TLR ligand with the aim of driving an innate immune response, thus enhancing the body's capability to fight off SARS-CoV-2 or another viral attack,' says Moerland. TLRs – toll-like receptors – are a class of cell surface molecules which are predominantly present on specific immune cells such as dendritic cells and macrophages. They recognise general molecular patterns common to groups of pathogens, such as bacterial lipoproteins or viral RNA. To verify whether the investigational compound activates the innate immune response, Moerland and his colleagues plan to collect nasal mucosal immune cells to show

a drug-induced cell attraction. 'It's just one example of how we hope to contribute to the development of novel compounds to help protect people from viral respiratory infections such as COVID-19.'

Pulmonology

COVID-19 is often associated with neutrophil-driven hyperinflammation resulting in lung or multi-organ injury. In light of this, Moerland expects a renewed interest in the field of pulmonary immunomodulation in the coming years. 'We did quite a bit of pulmonology research in the past, and I think it will be interesting to see if the methods we used then can be applied to future research as well,' says Moerland. 'And of course, we're interested in developing additional methods. For example, we have a range of experience with challenge tests involving LPS (see page 75). We are also currently considering an inhalation LPS challenge, which could be used to trigger some of the phenomena seen in COVID-19 in a safe and controlled way.'

One of the most dramatic lung complications of COVID-19 also involves the innate immune response, and especially the neutrophil granulocyte, as Moerland explains: 'Clinicians reported dramatic symptoms due to thrombotic vessel occlusions of the lungs. Further analysis showed that these thrombotic events were caused by immune cells, especially neutrophil granulocytes. We were already interested in this immune cell and its role in pathological processes, especially so-called NETosis.' NETosis refers to the formation of NETs: neutrophil extracellular traps. These are fibres consisting of DNA and proteins which are the result of the self-destructive activity of neutrophils, as they turn themselves inside out.

Moerland: 'Several companies are currently developing compounds that aim to reduce NETosis, or NETosis-related processes. Given the central role of these processes in a wide variety of diseases, and our contact with pharmaceutical companies targeting these processes, we have decided to invest in the development of tailored methodology. For example, we are collaborating with the Leiden Academic Centre for Drug Research to develop a whole-blood-based assay in which NETs are induced, and we are setting up staining methods to detect NETs in inflamed skin. These assays are directly relevant for the immune challenge models that we have developed in previous years, such as dermal inflammatory challenges.'

Vaccine studies and the KLH model

Moerland and his colleagues supported the work of Dr Ingrid de Visser-Kamerling and her group in their clinical studies on virus inhibitors and COVID-19 vaccines (see also the interview with De Visser on page 62). Meanwhile, the group also continued work on a vaccination model which is not intended to protect against disease, but rather to elicit an immune response in order to study cellular immunity. In this procedure, subjects receive an intramuscular injection with an antigen that their immune system has never encountered before: keyhole limpet hemocyanin (KLH), the oxygen-carrying protein of a limpet that is found off the coast of California. This neoantigen causes an immune response with the corresponding immune memory. Subsequently, when the neoantigen is applied intradermally, a local T-cell response can be observed. This model can be used to study compounds affecting cellular immunity.

'It's always beneficial to gain a deeper understanding of the models you use, especially in immunology'

'We reviewed our data and compared them to findings in the literature. It's always beneficial to deepen your understanding of the models you use, especially in immunology, because there is always so much more to be learned. In this way, we were able to put the extra time we had due to the closure of the Clinical Research Unit to excellent use,' says Moerland. 'We have now developed plans to further refine the KLH model and better characterise the cellular and molecular responses driven by KLH. We are not the only CRO using this model, but our KLH model stands out as being more mechanistic and sensitive than others: in particular, our approach integrates responses at the cellular and molecular level with imaging data, and further combines this with experimental clinical techniques such as suction blistering.' Key to this is the close collaboration with other disciplines at CHDR, such as with Prof. Robert Rissmann and his Dermatology group. Moerland: 'That has, and always will be, a strong point of CHDR: our way of combining and integrating different techniques to create a uniquely insightful approach.'

Meanwhile, the various models and techniques Moerland and his colleagues have developed over the years have continued to attract the attention of clients. 'I'm really glad our hard work in the past years is garnering interest from across the industry. Using models such as the LPS and imiquimod challenges and our KLH neoantigen challenge requires an intimate understanding of their physiological properties, their strengths and their limitations. Having made use of the opportunity to review and reflect even more deeply on our toolkit, we are confident that we can provide the insights that our clients are seeking, and more.'

LPS and imiquimod challenge tests

CHDR often uses challenge tests, which serve to evoke a reaction in healthy subjects that is similar to a pathological process. Such challenges can be used to study some of the effects of new compounds in healthy subjects. A series of challenge tests that CHDR has intensively studied and used in recent years is based on bacterial lipopolysaccharides (LPS). These chemical compounds, which do not naturally occur within the human body, are the major component of the outer membrane of gram-negative bacteria. They are a major trigger for the innate immune response, mediated through the TLR4 receptor.

LPS can be administered in several different ways. It can be used on fresh blood, to evaluate the anti-inflammatory effect of a compound in vitro. When a compound is administered to subjects, a test-tube based LPS challenge can then be performed on their blood, thereby providing an estimation of the compound's activity ex vivo. The LPS challenge can also be used in vivo, by administering LPS (with or without an investigational compound) to healthy volunteers.

In the past few years, an intradermal LPS challenge has been thoroughly studied and validated by Dr Thomas Buters, who is currently working on his PhD under the supervision of Dr Matthijs Moerland and Prof. Robert Rissmann. Moerland: 'Intradermal activation of the innate immune response, either through LPS or imiquimod which activates TLR7, offers the possibility of in vivo testing with a lower burden on the subject. We can even study different skin patches in the same individual at the same time – for example, to compare compounds or different dosages – as well as being able to investigate effects over time.' An alternative approach that CHDR is considering is the administration of LPS by inhalation, which could offer an interesting method for the study of respiratory innate immune responses.

Dr Pim Gal, Senior Clinical Scientist

'Readouts of vascular function offer fascinating possibilities'

The vasculature is an excellent biomarker of pharmacodynamic effects: a wide range of effects can be quantified non-invasively and with limited variability. 'Vascular readouts are of special importance in translational medicine because they form a bridge between the basic effects seen in a test tube and clinical effects,' says cardiologist Dr Pim Gal, working as part of CHDR's new Immunology-Cardiovascular research group. 'Vascular reactions are systemic – they say something about the way the organism as a whole reacts to a compound or to another stimulus.'

Along with the Research & Development lab, the Immunology-Cardiovascular group is headed by Dr Matthijs Moerland. This newly minted research group represents a further integration of Gal's vascular biomarker research into the biomarker development work of Moerland and his team. This new area of research developed from Gal's work in cardiology, which remains one of his focus areas at CHDR (see also page 58).

Mechanisms of vasodilation

Using a variety of state-of-the-art devices (see Table 1), Gal and his colleagues are busy validating a robust set of measurements which can be used to study the blood flow in small blood vessels (microvasculature) or larger blood vessels, and how this blood flow responds to various stimuli. Gal: 'These measurements reflect the vasodilation ability of the endothelium, which lines all blood vessels. There are various ways that endothelial function can be manipulated, including the induction of neuronal, inducible and endothelial nitric oxide synthase (NOS) and the generation of reactive oxygen species (ROS).' CHDR has developed methodology to selectively manipulate the function of these pathways, making the vasculature an ideal readout for the investigation of drugs targeting endothelial function, immune pathways and mitochondrial function.

Devices	
Laser speckle contrast imaging (LSCI)	uses laser speckle reflection pattern and variation to measure perfusion, usually on the lower forearm
Flow-mediated skin fluorescence (FMSF)	uses fluorescence to measure skin NADH content non-invasively
Near-infrared spectroscopy (NIRS)	uses infrared to measure tissue oxyhaemoglobin and deoxyhaemoglobin
Thermography	uses infrared to measure superficial temperature
Sidestream dark-field imaging (SDF)	uses microscopy and light polarisation for the imaging of capillaries under the tongue

Table 1. Endothelial function measurements validated at CHDR

'Many compounds act on the endothelium, causing changes in the amount of nitric oxide (NO) which is a potent vasodilator,' says Gal. 'Some immune reactions increase the amount of NO through the action of inducible NO synthase (iNOS). So once we have a set of robust readouts, we can use them to measure drug effects. In some cases, these measurements will tell us about the mechanism of action of the compound. In other cases, it offers a non-invasive in vivo readout of intended pharmacology. This can be much more informative than in vitro studies – there's always a lot of redundancy in any biological system, which makes it difficult to predict clinical effects from laboratory experiments.'

Many compounds that were originally designed for other purposes, such as for modulating immune responses, also act on the vessel wall. Gal: 'It is my ambition to develop a reliable platform to explore vascular effects of compounds, so we can contribute to the development of novel treatments for atherosclerosis, hypertension, and some of the effects of diabetes. And by using our methods to study microvasculature, we could also study the effects of compounds on phenomena such as Raynaud's disease and the hot flushes many women experience during the menopause.'

Challenge tests

To measure the effects of new compounds in healthy volunteers, tests of vascular function may not be sufficient: in a volunteer whose vasculature is already healthy, there may not be sufficient improvement to demonstrate drug effects. To bridge this gap, Gal and his team are also developing challenge tests that temporarily mimic a pathophysiological mechanism. A number of challenge tests are already in use by Gal and his team (see Table 2). In 2020, the team investigated the use of a mixed meal tolerance test. 'This mixed meal is basically a very rich milkshake containing large amounts of fat, sugar and protein. It leads to the production of reactive oxygen species (ROS), which in turn react with nitric oxide. Three to four hours after the mixed meal has been ingested, there is a measurable change in vascular readouts.' Gal is now studying the possibilities of using the mixed meal tolerance test as a tool to explore the vascular effects of compounds in healthy volunteers.

Another approach, which will be further developed in 2021, is to measure the vascular effects of intradermal

Challenges	
Passive limb movement (PLM)	When a subject's knee is passively flexed to 90 degrees and extended to 180 degrees again, this increases the blood flow to the leg. Using ultrasound, the femoral artery is imaged during this procedure, and the absolute increase in flow can be measured. The ensuing vasodilation is about 80% dependent on NO release.
Post-occlusive reactive hyperaemia (PORH)	A blood pressure cuff is placed over the subject's upper arm. After a baseline reading, the cuff is inflated to 200 mmHg, effectively occluding the brachial artery. After 3-5 minutes, the cuff is released. This induces hyperaemia in the lower arm, which is used as a general measure of microcirculatory function.
Local thermal heating (LTH)	A ring that can be heated is placed on the subject's skin. The ring is then filled with water and heated. As the ring heats, it heats the water, which in turn heats the skin. After the initial axon reflex, the plateau phase is highly NO-dependent. LSCI can be used to measure the blood flow in the skin through the water in the ring.

Table 2. Challenge tests developed at CHDR to temporarily mimic a pathophysiological mechanism

bacterial lipopolysaccharides (LPS). Intradermal LPS has already been established at CHDR as a useful tool to study the innate immune response (see also page 75). Gal: 'LPS triggers the induction of iNOS, which has a measurable effect on local microvasculature. We have already demonstrated that this effect can be reduced by injecting prednisolone, which inhibits the immune response and the pathway towards iNOS. Now we're aiming to fine-tune this test, which can be used to study anti-inflammatory compounds as well as candidate drugs acting on the vascular system.'

The immune system and the cardiovascular system interact on many levels, so Gal sees many possibilities for the development of new treatments in both fields. 'We know that much of the reperfusion damage after a myocardial infarction is caused by inflammation, so compounds acting on the inflammasome could improve clinical outcome after an infarction. For example, there are indications that colchicine, which is used for the treatment of gout, may have such an effect. It will be really interesting to use our endothelial readout battery to test both well-known and novel compounds acting on the inflammasome. Our aim is to develop this battery into a screening tool to select the most promising compounds for large-scale studies.'

Gut-targeted treatments

In addition to classical systemic compounds which act in a dose-dependent manner, Gal and his colleagues are studying a novel class of compounds that have a systemic effect due to local action in the gut. 'There are two classes of these gut-targeted interventions: probiotics and prebiotics,' says Gal. 'Probiotics are bacteria, while the prebiotics are a diverse group of compounds, such as fibres and nutraceuticals which affect the gut microbiome.' These probiotics and prebiotics can have a wide range of effects on digestion, the immune system, cardiovascular function, and the brain.

'Our expertise and our test batteries can be of unique value to show whether these gut-targeted treatments have systemic effects,' says Gal. 'Since these treatments remain in the gut, it is not possible to demonstrate that the drug reaches its site of action. Therefore, evaluating the systemic effects is pivotal in the development of these treatments. At CHDR, we have the expertise to be able to study systemic effects even if there is no classical pharmacokinetics to measure and the underlying mechanisms are quite complex, as is the case with these compounds. And even more importantly, we can perform a proof-of-principle study using our sensitive readouts, which is far more straightforward and far less expensive than a full-scale clinical trial.' Last year, the team conducted a study in this field in collaboration with the Netherlands Organisation for Applied Scientific Research (TNO). 'Due to the pandemic, there were many delays, so we are still analysing the results. But initial impressions from the data indicate that we are able to detect an effect of nutritional fibres, even in small groups of subjects,' says Gal. 'So it's a promising start, and I'm looking forward to how this line of research will unfold.'

Dr Diana Pereira, Bioanalytical Scientist in the Research & Development lab

'Immunometabolism offers a multitude of potential biomarkers'

A wide variety of compounds act on the immune system, and some of them influence the metabolism of immune cells, in the brain or elsewhere. To measure the effects of such compounds, sensitive and specific biomarkers are needed. Dr Diana Pereira, Bioanalytical Scientist in the Research & Development lab, is busy developing such biomarkers, with a focus on immunometabolism. 'We now can measure drug target engagement in peripheral immune cells, as a proxy for effects in a variety of conditions.'

'Immunometabolism is a relatively young field,' says Pereira. 'The term was first coined around 2011, to describe the interplay between intracellular metabolic activity in immune cells and their immunological activation and signalling.' The fledgling science of immunometabolism builds on a strong foundation, given that much is known already about both immunology and cell metabolism. Still, studying the interplay between these two complex processes, in which multiple pathways are involved, is no simple undertaking. In developing suitable biomarkers, Pereira faced the additional challenge that most prior research in this area is based on immortalised cell lines, whereas she needed to develop assays based on freshly acquired white blood cells. 'We want to use blood cells from healthy volunteers or patients to monitor the changes that occur in metabolic pathways in these cells as a result of medication. But the biological behaviour of fresh cells is different from cell lines, so we had to develop and validate our own approach.'

Metabolic master switch

To study the metabolism of white blood cells, Pereira and her colleagues focus on one of the master switches of immunometabolism, a molecule known as mTOR (mechanistic target of rapamycin). mTOR was originally discovered as the target of rapamycin (sirolimus), which has a wide variety of clinical applications. The complex of mTOR with other cellular molecules, called mTORC1 (mTOR Complex 1) senses the availability of food (and thus energy) and controls protein synthesis accordingly. If there is enough energy available, mTOR gives the green light for protein manufacturing, and if energy is scarce, it tells the cell to slow down the production of protein. This means that mTORC1 activity is a strong indicator of immune metabolic activity.

Pereira: 'We study imbalances in the immunometabolism, which happen in patients with a variety of diseases, including neurodegenerative disorders. We can also create such a metabolic imbalance in the white blood cells of healthy volunteers in an ex-vivo setting, by starving these cells. In the last two years, we have extensively validated this approach. Using phospho-flow technique, we can see how the phosphorylation or dephosphorylation of specific molecules changes due to variations in metabolic activity, reflecting the activity of mTORC1.' Bioassays based on mTOR-related biomarkers will already be used in clinical trials in 2021. To further validate these bioassays and optimise their use, the Research & Development lab plans to perform a self-funded clinical study in 2022, in which healthy volunteers will be given a single dose of rapamycin to extensively study what happens at various metabolic levels in their immune cells.

A wide range of applications

The first application of the immunometabolism assays will be the investigation of various compounds targeting neurodegenerative disorders. The assays, which focus on peripheral white blood cells, will be combined with other clinical measurements to investigate the activity of the compound in the brain. 'Peripheral immune cells from the blood resemble the target cell, are easily available, and can be used for more in-depth molecular studies in the lab,' says Pereira. Potentially, the immunometabolism assays could also be applied in a wide variety of other conditions, including psychiatric conditions, cardiovascular diseases, and diabetes. In all these disorders, there is an increasing interest in the role of immune cells and their metabolism, with new drugs being developed that modulate immunometabolism in order to tackle specific conditions.

So how was this promising research impacted in 2020 by the unprecedented events of the coronavirus pandemic? Pereira: 'Well, it was fortunate that we had this big programme to sink our teeth into. With our regular activities scaled down, I was able to really dive into this interesting field of research. Our lab technicians were able to go on working in the lab without too much disruption, and those of us who were working from home found we were able to make significant progress even under the unusual circumstances,' says Pereira. 'So, although the pandemic has made for a challenging year in many ways, the downtime due to the COVID-19 restrictions proved to be serendipitous for progress on our immunometabolism programme.'

'Our immunometabolism assays could help shed light on a wide variety of conditions, including psychiatric conditions, cardiovascular diseases, and diabetes'

WORKING WITH CHDR

‘They are more than just a service provider. They have great insight and are therefore a great discussion partner, providing advice and relevant feedback. We don’t simply run studies at CHDR: it’s a collaboration. Their high-quality, collaborative, scientific approach represents value for money.

CHDR’s focus on innovation is very relevant for the study team. They challenge us to define which direction we should go in with our drug development. We appreciate the way they proactively keep abreast of our plans: for example, they recently had a meeting with our neuroscience team where they asked what we have in the pipeline and how they can support us with those upcoming projects.’

Senior Trial Manager,
Big Pharma Company *

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

Method development

New methods to acquire objective data in clinical studies

The Method Development group has been active in a variety of fields over the past year. Even while working from home, the team have made progress developing and validating new ways to quantify the effects of interventions, analyse data, and support clinical studies, contributing to a broad range of therapeutic areas, from neurology and pain research to cardiology and psychiatry. The team have also applied their technical expertise to upgrade and expand the diverse range of measurements included in CHDR's dedicated platform for remote data collection, Trial@home.

'During the pandemic, we continued working on almost all the projects we had planned,' says Dr Robert-Jan Doll, head of the Method Development group. 'Some of us had to move some equipment to our homes, such as accelerometers or virtual reality (VR) equipment, but we were able to remain productive. We even welcomed two new colleagues to our team during this period, and several interns spent time with us.' Like many other departments that are not directly involved in the execution of clinical operations, the Method Development group moved in 2020 to an office building close to CHDR's main facility, to free up space for the expansion of the Clinical Research Unit. 'When summer came around, the relaxation of pandemic restrictions in the Netherlands made it possible for us to spend some time getting settled in our brand new office. Since there were very few people there at any one time, so we had no problem working while maintaining a safe distance.'

While working from home, Doll's main challenge as team leader was to keep in touch with all team members. 'In terms of the work itself, it's not much of a problem if almost all meetings are online. But it does make it much more difficult to get a feel for how someone is doing on a personal level.' To compensate for the lack of social contact, the team organised virtual coffee breaks and walking meetings. Doll: 'I went for walks with some team members, and team members met up with each other for walks as well. Meeting up in this way offered the opportunity to reconnect on a social level, going beyond the basic exchange of work-related information,' says Doll. 'We found walking meetings to be so beneficial, we've decided we're going to take a walk together every now and then even when the pandemic is over.'

Novel CNS measures

Many of the Method Development group's projects feed into CHDR's studies in the field of neurology. Here, the team's overarching goal is to develop robust measurements which are sensitive to changes induced by investigational compounds. One example is the finger tapping task, which is used as one of the variables to measure the severity of Parkinson's disease (PD). This task involves two buttons which light up, and the subject must tap each button whenever it lights up. An earlier mechanical version of this task was not sensitive enough to detect drug effects, so the team developed a touchscreen version which runs on a tablet computer. Doll: 'The setup with the physical buttons only registered a successful tap on the button itself – it was not able to register attempts that almost hit the correct button. On a touchscreen, however, we can register exactly where and when the screen is touched, even when the tap is outside the target area.' Two different variants of the task were developed to assess different aspects of fine and gross arm and finger movements. To evaluate the task, it was used in a placebo-controlled crossover study in PD patients, using levodopa, the well-known Parkinson's medication. The results are currently being analysed and correlated with the gold standard in Parkinson research, the Unified Parkinson's Disease Rating Scale (UPDRS). 'We also have another task that benefits from the advantages of touchscreen technologies: a spiral drawing task, in which subjects are asked to trace a spiral on a tablet computer screen using a stylus.' This task will feature in a study in 2021 involving patients with essential tremor.

To acquire even more detailed information about subtle motor control during tasks such as finger tapping, Doll and his colleagues are investigating the use of a goniometer. A goniometer is a device that continually measures the angle between the index finger and the hand. 'With this device we hope to gather much richer data, because it measures the whole trajectory of the finger, including any pauses or involuntary movements along the way,' says Doll. 'We're excited to analyse the data we've collected so far, to see if the device really lives up to its potential.' Another novel method under development involves using eye movements to provide a measure of the severity of the neurological condition myasthenia gravis. In myasthenia gravis, the patient's muscles tire rapidly, which also shows in eye

movements. If the patient is asked to look up at a point above eye level, the eyes will sink after a while due to exhaustion of the eye muscles. 'The new method aims to objectively register such eye movements, determining the exact moment that each eye starts to sink and following the subsequent movement. This data can be used to provide an objective measure of disease severity,' says Doll.

NeuroCart and PainCart

Besides developing novel methodologies, the Method Development group is also involved in maintaining and refining the many validated methodologies used in studies at CHDR. In 2020 the team invested in upgrading various methods included in the NeuroCart® test battery, such as measurements of body sway and saccadic (rapidly shifting) eye movements. The team also offers its technical expertise to support researchers as they implement new methods in clinical trials, until the application has become routine. This was the case in 2020 for the Neurology and Pain group's studies using transcranial magnetic stimulation, threshold tracking, and muscle velocity recovery cycles (MVRC).

Over many years of pioneering pain research, CHDR developed its unique PainCart® test battery. 2020 saw the upgrade of one of the pain models in the PainCart, namely the UVB-hyperalgesia model, which causes a mild sunburn as a model for inflammatory pain. 'It is now easier to use for both the clinician and more comfortable for subjects,' says Doll. Another large project is under way to augment the PainCart with VR, with the aim of modulating or intensifying pain experiences by means of visual and auditory representations of painful stimuli. 'In this approach, the subject will witness damage to their body in the virtual environment – for example, burning skin on their legs – while a pain stimulus is being applied to that same body part,' says Doll. 'We have been developing this model for quite some time now, and we are now validating the approach in a clinical study.'

The technology of Trial@home

In CHDR's Trial@home approach, subjects who participate in a study can be monitored using mobile technology while going about their day-to-day lives. Over the past six years, the Method Development group has brought Trial@home from an initial concept for remote data collection to a fully-fledged service, which can now be used by clients and researchers for studies external to CHDR (see also the interview with Trial@home Product Manager Dr Vasilis Exadaktylos on page 98). Doll: 'Our group has played a pivotal role in developing the data acquisition platform and its accompanying smartphone app, which are now routinely used in trials. We are currently working to develop and validate new tools and algorithms to further augment the platform.'

Participants in Trial@home studies are asked to download the Trial@home app on their mobile phone, which then gathers data as required by the specific trial. The app can collect both passive and active data. The passive data, which doesn't require subjects' direct input, includes GPS information, call and text logs, and physical activity patterns. Active data acquisition includes asking participants to respond to a questionnaire or to perform a task - for example, tests involving a touchscreen, such as the finger tapping or spiral drawing tasks. 'That is an additional advantage of using a touchscreen – it means that the test can be performed almost everywhere, thanks to the ubiquity of this technology nowadays,' says Doll. 'If the finger tapping task and the spiral drawing task prove to be useful, they can be used both at our Clinical Research Unit and at home, enhancing the versatility of these methods.'

Another task that the team have redesigned for mobile use is the adaptive tracker task, a standard assessment in the NeuroCart test battery. The adaptive tracker task measures visuomotor coordination and vigilance. To perform this task, the subject uses a joystick to move a small dot on a screen, aiming to keep the dot inside a continuously moving circle. During the test, the speed of the circle is adjusted in response to the subject's ability to keep the dot in the circle, ensuring that the test is adapted to the individual subject. 'The new version can be used in clinical studies elsewhere, or at home,' says Doll. 'It is another one of the many measurements we have developed for use outside our clinical unit.'

Doll and his team are also busy developing a Trial@home algorithm to measure social engagement. One of the background measurements the Trial@home app can perform is to register the amount of time that the microphone senses conversations going on within earshot of the device. However, in order to distinguish between conversations in which the test subject is actively participating and conversations between other people or on television, the algorithm must be able to recognise the voice of the test subject. Doll: 'Our team is currently training the algorithm, using annotated voice files. Some of our interns have made great contributions to this project, by painstakingly annotating these audio files to mark who is talking at which exact moment.' The team are also investigating voice as a potential biomarker, as it can be used for diagnostic or monitoring purposes, for example in PD patients. Doll: 'It is a well-known phenomenon that speech characteristics change due to PD, and that these changes reflect disease progression. We plan to develop a method to measure changes in the voice and speech of PD patients and correlate them with other measurements that reflect disease severity.'

The data gathered in Trial@home studies can be drawn from a range of portable devices, not just smartphones. A smartwatch, for example, can provide a wealth of measures, including heart rate and hand movements. 'We wanted to evaluate the usefulness of such a consumer device in clinical drug development, so we tested it in a placebo-controlled study with a drug that is known for its effect on heart rate,' says Doll. The team found that the effects of the medication could be demonstrated based on the smartwatch data already from day one. 'We also wanted to establish the best time of the day to measure heart rate, to minimise noise. We were able to confirm that heart rate is more stable and more reliably correlated with drug effects during sleep. That makes sense, of course: during daytime activities, there can be all sorts of causes of heart rate variations, which represent noise from a drug

development point of view.' Besides consumer devices such as smartphones and smartwatches, the Method Development group is also busy validating portable medical devices for integration in the Trial@home service. 'We're currently validating a brace which continuously measures hand movements, for use in Trial@home studies with (essential) tremor patients.'

Data science

The rich data gathered by new methodologies can contribute greatly to the clinimetric assessment of patients with various disorders. 'For example, we have developed an algorithm that successfully recognises how often and how long babies cry, providing an objective measure of crying behaviour. Another similar algorithm we've developed is able to objectively quantify the amount of coughing in paediatric patients.' While such data-intensive approaches offer many advantages for clinical drug development, they also come with a challenge: the enormous amount of data which has to be analysed. Doll, however, is unfazed: 'Fortunately, thanks to the diverse expertise of our team's data scientists, we are well able to discover the insights that are waiting for us in these big datasets.' A recent example of a data science approach was a study performed in patients with facioscapulohumeral muscular dystrophy (FSHD). Through this study, it was established that relevant data can be obtained in a population of patients with this neurological disease, paving the way for objective measures for the assessment of FSHD. Doll: 'Based on our data, we were able to identify a set of features that distinguishes patients with FSHD from healthy controls, and the team went on to develop and validate an algorithm that can objectively assess disease severity.'

Data scientists at CHDR have also lent their expertise to gain new insights from detailed cardiovascular data. Recently, the team developed an algorithm for the analysis of the ECG data routinely gathered during the screening of potential study participants and in the course of clinical trials. 'Using a machine learning approach, we were able to find a robust correlation between the ECG data and the subject's age. This is just a first step, but already an indication that ECG data may be further leveraged in the future to reveal subtle cardiovascular effects of new compounds,' says Doll. Read more about cardiology at CHDR on page 60.

> 'The rich data yielded by novel methods can contribute greatly to the clinimetric assessment of patients with various disorders'

Psychiatry

Innovative technology-based approaches are set to play a vital role in the development of many therapeutic areas in years to come, meaning that there are many interesting projects still on the horizon for the Method Development group. One such area where such an approach is still to bear fruit is psychiatry. 'To support drug development in psychiatry, it would be ideal to have more robust measurements of a subject's emotional state, which could be combined with objective data from NeuroCart and Trial@home. In 2021 we will begin pursuing a joint project with the Psychiatry group headed by Dr Gabriël Jacobs,' says Doll (see also the interview with Jacobs on page 40). 'We are looking forward to this new collaboration, which we hope will pave the way for new methods to quantify relevant constructs in psychiatry.'

‘CHDR is an active, cooperative team that also takes the initiative at the right moments. They have a lot of expertise. During the execution of the study, a problem was never raised without suggesting a solution: when bringing problems to our attention, they had always already thought internally about how to solve them. This was refreshing and a positive experience. As a result, we made consistent forward progress.

As for COVID-19, I knew that it would be difficult. However, I have a lot of respect for how CHDR has managed to begin studies within three weeks if they are COVID-19 related. That’s impressive.’

Director, Biotech Company *

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

Statistics and Pharmacometrics

Informing all stages of the study life cycle

The Statistics and Pharmacometrics group plays a crucial supporting role in CHDR's scientific work, from informing study design and performing data analysis to generating complete reports of data and outcomes for both clinical study reports and scientific publications. It is no surprise, then, that 2020 was another busy year for the group, despite the restrictions on operations due to the pandemic. Alongside their core activities, the team also worked to bring the various CHDR departments involved in biometrics into closer alignment, against the backdrop of organisational growth.

'Fortunately, when the pandemic hit, we already had all the tools in place to work remotely,' says Dr Kirsten Bergmann, who leads the Statistics and Pharmacometrics group. 'We can easily and safely access all relevant data via our virtual desktop, meaning that we can move seamlessly between office and home.' The group's expertise was in high demand, even when all operations were put on hold. With project leaders shifting their focus from operational duties to scientific output, the group's statisticians and pharmacometricians were frequently called on to provide support in analysing data and preparing manuscripts for publication.

Pharmacometric modelling

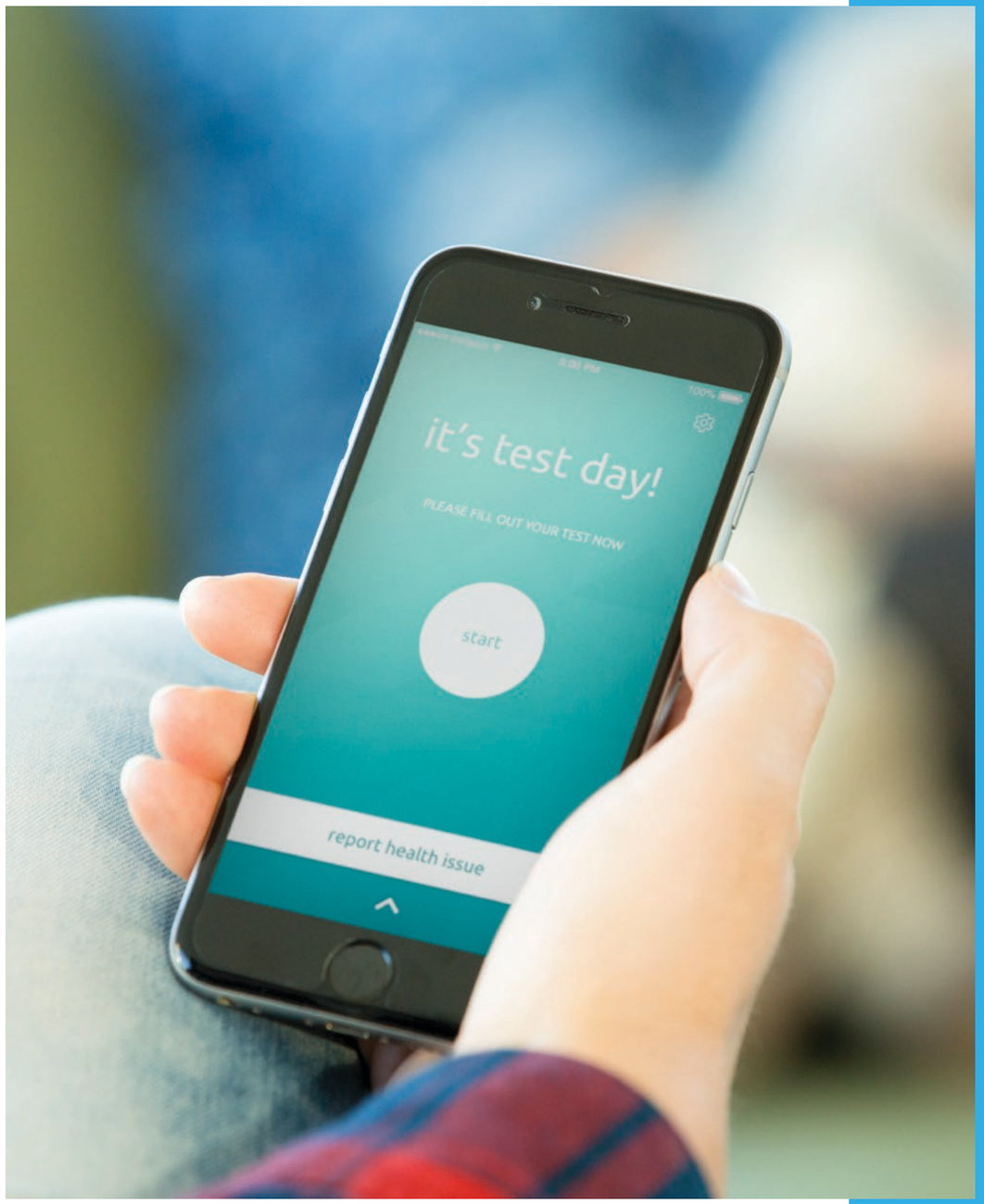
CHDR uses pharmacometric models both in the process of designing studies and in analysing the resulting data. These models, which predict the pharmacokinetics of a compound based on available preclinical and clinical data, help to ensure a safe dosing regimen while also providing important insight into the relationship between pharmacokinetics and pharmacodynamics. This is not only important in investigating novel compounds, but may also contribute to the study of well-known compounds in a new context.

CHDR's research into the use of ketamine for the treatment of depression is a case in point. In these studies, led by Dr Gabriël Jacobs and his Psychiatry team, the enantiomer esketamine is given orally to healthy volunteers and patients with treatment-resistant depression (see also the interview with Jacobs on page 40). 'In 2020, we prepared a manuscript about the performance of existing pharmacokinetic models of esketamine, to be published in 2021,' says Bergmann. Since ketamine has been in use as an anaesthetic for over half a century, there is an abundance of data about its pharmacokinetics, and pharmacokinetic models had already been developed. 'There are even several pharmacokinetic models on the esketamine enantiomer. But the pharmacokinetics of esketamine are complex because several of its metabolites also establish pharmacological activity. The oral route complicates matters even further, because more of the compound will be metabolised during the first pass through the liver.' Pharmacometrician Dr Michiel van Esdonk and his colleagues tested the performance of the available pharmacokinetic models using data from earlier studies by the Psychiatry group. The team identified the model that was best able to predict the data and worked to refine it further. 'This model will contribute to a better understanding of esketamine kinetics, improving our future clinical studies with this compound.'

Integrated biometrics

The collection and analysis of biological data lies at the heart of CHDR's activities. The application of statistical analysis to biological data is also known as biometrics. The various CHDR departments involved in biometrics have naturally always worked closely together. However, with the growth of the organisation, Bergmann and her colleagues leading CHDR's Data Processing and Data Programming groups felt the need for an even closer alignment. Bergmann: 'Each of these groups has its own core activities, but there is much overlap. All three groups work closely with the project leaders, delivering crucial input at all stages of the study life cycle.' Now, the three teams have set up a collaborative working group that meets every two weeks to discuss operational topics and ensure optimal data quality. 'The way our biometrics groups are organised is different from most pharmaceutical companies and CROs. With closer internal collaboration, we are able to present a clearer picture to the outside world, bringing better visibility to all that we have to offer.'

'Our pharmacokinetic model of esketamine will contribute to better understanding and improve future clinical studies of this compound'


it's test day!
PLEASE FILL OUT YOUR TEST NOW
start
report health issue

Trial@home

Bringing Trial@home to the outside world

In recent years, much effort has been invested in developing and validating Trial@home, CHDR's robust remote monitoring platform which enables clinical trials to be expanded into the world outside the Clinical Research Unit. The platform has been extensively validated and deployed in a number of CHDR studies, and is now fully ready for use by external partners.

In spite of the challenges imposed by the worldwide COVID-19 pandemic, Trial@home Product Manager Dr Vasilis Exadaktylos and his team have been busy. '2020 was an exciting year, as it saw the initiation of the first Trial@home study led by an external partner. At the same time, we have been working to increase the visibility of Trial@home to external parties. As part of the evolution of Trial@home to a fully-fledged service, we are also preparing to transition from our own servers to the cloud, to accommodate a wider use of the platform. This will make it easier to increase dataflow where necessary, and allow clients to use the service while remaining independent of our in-house IT infrastructure.'

CHDR began to develop the Trial@home approach more than six years ago, to make it possible to monitor and collect data from participants as they go about their daily lives. This in turn reduces the requirement for study participants to visit the Clinical Research Unit in person, thus lessening the burden on participants in patient studies, offering new possibilities in fields such as paediatric clinical research. Moreover, with remote monitoring through portable devices, far more detailed data can be gathered, and over longer time periods. Exadaktylos: 'The Trial@home strategy was first conceived of by CHDR's founder, Prof. Adam Cohen, as an innovative way to gather ever richer data in the course of early phase clinical drug development. Its strength lies in the possibility to complement the in-depth data that we gather in-house with real-world measurements acquired through remote monitoring.' The first successful studies using the Trial@home platform were in the field of Dermatology, studying the effects of topically applied drugs on eczema or psoriasis lesions. These studies also demonstrated the value of the platform in improving compliance: through the Trial@home app, subjects can be sent daily messages asking them to apply the study medication, fill in questionnaires or submit photos of their lesions. Over the years, Trial@home has been developed into a truly versatile platform, which is now ready for use in a variety of fields, ranging from paediatrics to orthopaedic surgery. Read more about the use of Trial@home in Dermatology on page 48, and in Psychiatry on page 40.

Trial@home philosophy

Trial@home offers a wealth of possibilities for trials aiming to establish pharmacological action of novel compounds. However, establishing that a drug works is easier than demonstrating that it helps. To show that a drug works, it is enough to measure its effects on a pathophysiological mechanism. To demonstrate that it helps requires having the appropriate data to make a value-based evaluation of the compound's impact on the daily lives of patients. Trial@home offers unique possibilities to bridge this gap, by offering electronic monitoring of objective data in addition to regular subjective reporting from patients regarding their symptoms, mood, and quality of life.

> 'Trial@home makes it possible to collect data from participants as they go about their daily lives'

Successful application of digital endpoints gathered via Trial@home and similar approaches hinges on thorough validation. The Trial@home team's pragmatic approach to the selection and fit-for-purpose validation of digital endpoints is presented in a paper published in the October 2020 issue of Pharmacological Review. The article stresses the importance of value-based measurements: in other words, measurements that relate to meaningful outcomes for patients. It also highlights the need for devices used in remote monitoring to be stringently assessed for technological validity, and the importance of rigorous clinical validation to assess tolerability, difference between patients and controls, repeatability, detection of clinical events, and correlation with traditional endpoints. The first author of the article, Dr Matthijs Kruizinga, has also published a number of papers on the use of Trial@home in a paediatric setting.

Broader application

'Having already benefited so much from the use of Trial@home in our own studies, we are excited to now be able to offer it as a service for external researchers, other contract research organisations, and clients in the pharmaceutical industry,' says Exadaktylos. 'By sharing our platform and increasing its visibility among our clients and partners, we hope to contribute to a high standard of remote naturalistic data collection in clinical research.' In 2020, a number of steps were taken to make Trial@home easier for use by external researchers. In addition to the transition to a cloud-based infrastructure, standard operating procedures were developed for the use of the platform, along with a training module on how to use Trial@home on various devices. 'This training module is a valuable part of the package, as it enables us to easily explain how to get started and, importantly, how to handle the wealth of data that is generated by this approach.'

The first external group to work with Trial@home will be the Gastroenterology department of the Leiden University Medical Center (LUMC). This team is conducting a trial in patients with colorectal cancer in order to compare two surgical interventions, focusing on the recovery time of patients. Trial@home will be leveraged to provide insight into the activity levels of patients after they have been discharged from the hospital. Exadaktylos is confident that this is the start of great things: 'Remote monitoring is rapidly proving itself to be an essential tool in clinical research. In light of the COVID-19 pandemic, in which everyone has become more accustomed to doing things online, we also expect the shift towards these novel remote technologies to accelerate. We are therefore proud to be able to offer a fully ready-to-use platform.'

'We're excited to offer Trial@home as a fully ready-to-use platform for external partners'

Education

Accelerating the development of online education in pharmacology

When all in-person activities had to stop due to the COVID-19 pandemic, it was all hands on deck for a swift transition to fully digital education. Education Director Dr Jeroen van Smeden reflects on a year in which CHDR rose to the challenges of providing education exclusively online, leveraging earlier investments in digital teaching materials and blended learning. ‘We’ve learned a lot this year about educating through the digital medium: from how to exploit the advantages it offers, to ways to bridge social distance and keep learners motivated.’

When Leiden University had to close its doors due to the pandemic, students were promised that all lecturers would switch to online teaching within a few weeks. For Van Smeden and his colleagues, this was no mean feat: ‘We undertake an extensive range of teaching activities in the Bio-Pharmaceutical Sciences and Medicine study programmes, so it was quite a challenge to transition to fully online learning in such a short timeframe. On the other hand, we were well supported by the university. And of course, we had a head start due to the fact that CHDR has already been investing in digital education for several years now. For example, the pre-recorded lectures that we had already created turned out to be extremely useful, because some of the doctors who would usually give crucial lectures were now badly needed in the ICU,’ says Van Smeden. ‘Some aspects of my work even became easier – planning lectures, for example. Normally, scheduling is a tedious task in which you have to balance a number of factors, juggling the availability of different lecture rooms while also ensuring that the resulting timetables are reasonable and practicable for the students. Many such problems disappear when students attend lectures online from their homes.’

Upholding high standards

The switch to fully online education in the Netherlands proved largely successful. Van Smeden: ‘Of course, in the beginning, there were concerns from students that the quality of education might suffer. However, from our own course evaluations and from what I read in the papers, it seems that the move ultimately went well. There are of course major differences between online education and in-person interaction in the classroom. As a teacher, you even start to miss the inevitable whispering and chit-chat of students during your lectures. The digital environment can be eerily silent, making you wish for the vibrancy of the lecture theatre – whispers and all!

‘The more accustomed lecturers become to this form of education, the more they feel stimulated to explore how different modes of teaching can be employed most effectively. For example, which parts of the material can be pre-recorded, and which parts need live discussion? For students, there are also benefits. The threshold for participation in a lecture is much lower when it’s possible to ask questions via online chat rather than having to speak up in front of a packed auditorium. Moreover, when lectures are delivered online, they can easily be recorded and watched later, which allows students to catch up on missed sessions or consolidate their learning. In that sense, the digital format means that we can make education available to students 24/7, enabling a much more flexible schedule for all concerned.’

While the online format certainly has some advantages, Van Smeden is well aware of the downsides of fully digital education for both students and lecturers. ‘We are all longing for the moment that we can meet in person again – for all its flexibility, there is definitely something missing in exclusively online education. In the future, I look forward to having the best of both worlds: online learning for acquiring the basics, combined with in-person interaction for deeper exploration and understanding.’

Sparking motivation

A high point of every week at CHDR is the Education Hour, a weekly lecture open to all staff covering a variety of topics related to pharmacology, given by different members of staff and sometimes even invited speakers. Due to the pandemic, however, the Education Hour also had to move online. With all regular social activities at CHDR cancelled due to COVID-19, the Education Hour became even more valuable as an opportunity to maintain social connections with colleagues across the organisation. Van Smeden: ‘In addition, almost all of the Education Hour lectures we did online were also recorded and made available to watch later. And that got me thinking about the potential of pre-recorded lectures not just

for our students, but also for the ongoing education and development of our staff. I began to formulate a plan to record a series of lectures on fundamental topics, for example about pharmacokinetics and PK/PD modelling. Currently, those are subjects that we schedule about once every two years in the Education Hour. On the one hand, this is rather infrequent for new staff members or for those who want to refresh their knowledge. On the other hand, senior staff who know this information like the back of their hands will likely end up skipping those lectures. By recording these lectures we can make this information available at any time for those who want it, and during the regular weekly lectures we can then focus on themes that are interesting to everyone.'

As with all educational activities, taking the Education Hour online came with an additional challenge: how to engage participants and keep them interested, especially when a regular day of work or study already involves several hours in front of a screen. 'Even the most motivated people find it difficult to maintain focus when everything is online,' says Van Smeden. 'In education, the key to engagement is to help people reconnect with the original spark of interest that motivated them to study the subject. For the Education Hour, I came up with the idea of adding a weekly quiz. The questions in this quiz are diverse – sometimes more technical or mathematical, sometimes more clinical or related to patient treatment. It has been really successful: participants are often eager to discuss the questions afterwards in more detail, and several people have even asked me if we could make it into a competition! As an educator, it makes me really happy to see all my colleagues getting excited about this challenge that taps into their professional and scientific interests. Such activities really help to reignite intrinsic motivation, which can help give people the lift they need to stay engaged.'

Comprehensive clinical pharmacology training

Every five years, CHDR's clinical pharmacology training is assessed during an inspection visit by the Dutch Society for Clinical Pharmacology and Biopharmacy. This regular assessment took place again in December 2020. CHDR and the Leiden University Medical Center (LUMC) used the opportunity to apply for a broader, more integrated training licence. Van Smeden: 'In the Netherlands, we have three clinical pharmacology training programmes: one for internists, one for pharmacists and a general one. Before, we offered the general training in collaboration with the LUMC, and our LUMC colleagues also provided the training for pharmacists. Internists, however, had to go to another city to receive their clinical pharmacology training,' says Van Smeden. 'But now we are able to offer the complete spectrum, particularly thanks to the input of Prof. Teun van Gelder, an internist and clinical pharmacologist who has recently joined the LUMC, and CHDR's Dr Naomi Klarenbeek, an internist who is also soon to qualify as a clinical pharmacologist.'
The assessment committee returned a positive evaluation of the training offered at CHDR and LUMC, opening the doors to a comprehensive spectrum of education in clinical pharmacology, combining the varied range of pedagogical and training activities offered by these two institutions.

'We saw many benefits in drawing up a proposal for integrated training, as there is so much we can learn

from each other,' says Van Smeden: 'We are excited about the possibilities offered by closer collaboration with the LUMC: CHDR trainees will now be able to participate in educational activities offered by the LUMC, and we can also welcome LUMC trainees, for example at our weekly Education Hour lectures. For the trainees, this also offers the opportunity to study additional subjects that may be interesting for their future careers.' Writing the integrated plan had benefits for the trainers, too: 'As trainers, writing the plan gave us a valuable opportunity to formulate detailed descriptions of all components of the training, and to clarify which parts are mandatory and why.'

Education for all ages

In spite of the pandemic, CHDR has continued to play an active role in the education of undergraduate students in Bio-Pharmaceutical Sciences, Medicine, and Biomedical Sciences, as well as postgraduate trainees and professionals. With a grant from Leiden University, the Teaching Resource Centre (TRC) app has been made more interactive (see also page 111). The TRC is an important educational resource that benefits students and professionals both in the Netherlands and abroad, including members of the British Pharmacological Society. 'We even have been working on educational resources for primary school pupils in the Netherlands,' says Van Smeden. 'Our links to primary education were already established by Prof. Adam Cohen, CHDR's founder, who regularly visits schools to talk about pharmacology and drug development. Leiden University's ICLON department, which is developing science teaching resources for many target groups including primary school kids, invited us to develop a programme for 8 to 9-year-olds about medicines and how they work. So we are now busy creating a teaching package that we have called "The Journey of Medicines".'

The journey starts with the ritualistic use of substances in Ancient Egypt and tells the story of how supposedly medicinal plants sometimes did actually contain pharmaceutically active compounds. The children also learn how gradually, a more scientific approach gained ground. They will, for example, hear the story of the 18th-century British physician William Withering, who demonstrated that the foxglove flower that was used in folk medicinal concoctions contained an active ingredient that effectively treated oedema due to congestive heart failure (then known as 'dropsy'). Van Smeden: 'These stories really bring the journey of medicines to life for young learners. We are also considering including some hands-on elements – for example, letting the children try their hand at making an Ancient Egyptian throat remedy using honey, milk and figs. It's a fun project, and it's always interesting to develop educational resources that target different age groups. In that vein, we are also developing a lecture series targeted towards more senior members of the public. Ultimately, we see learning as a lifelong pursuit, and we're keen to share our expertise with everyone – from eight years old to eighty, and beyond!'

Interactive pharmacokinetics in the Teaching Resource Centre

In recent years, CHDR's Teaching Resource Centre (TRC) app has undergone a major overhaul. The app – an online reference guide to pharmacology, aimed at medical students – now has a better and more modern-looking user interface. To ensure that TRC users have access to the latest evidence and insights regarding all major (groups of) medicines, the content of the TRC is regularly updated by CHDR's scientists. One of the major features of the TRC is a language of graphical symbols used consistently across the app to illustrate the various pharmacological topics covered. Dr Jeroen Van Smeden, CHDR's Education Director: 'Educators from other universities are increasingly embracing our TRC and its clear pictorial language, particularly in the context of the recent explosion in online learning. For example, our style of illustrations will now be used in a reader to help students prepare for a test that's mandatory for all Dutch medical students. Thanks to this increased interest, we will now have a nationwide team contributing to these illustrations, which will in turn result in further improvements to the TRC.'

In 2020, preparations began on another new TRC feature, as Van Smeden explains: 'Thanks to a grant from Leiden University, we have finally been able to realise a dream that we've had for years: that is, to include an interactive module for pharmacokinetics. The module will allow students to adjust various parameters by moving visual sliders, and then explore the impact of those changes. This means that students will be able to discover answers to pharmacokinetic questions for themselves in a hands-on way. For example: would a diminished clearance of the drug through the kidneys affect plasma levels after one or more doses of the drug? And what if you give a similar drug with a shorter half-life? We believe that this intuitive, interactive approach will be highly beneficial for students as they learn about pharmacokinetics.'

The new interactive module will also be used as part of a pharmacokinetics course offered by the British Pharmacological Society (BPS), a close collaborator of CHDR's in the area of education. 'We meet regularly, at least once every two months, and we have created a dedicated committee to discuss all matters concerning TRC modules,' says Van Smeden. One exciting development in the pipeline is a counterpart to the TRC, focusing on drug development and clinical trials. This new app will be used for postgraduate training in the Netherlands and possibly also in the United Kingdom. Van Smeden: 'We have recently written a detailed funding proposal for postgraduate education in drug development, in collaboration with a number of partners, in which this new TRC app will play an important role. We hope to soon get the green light, as we are excited to get started on developing that curriculum.'

Operations

From a year of challenges to a future of growth

Clinical operations at CHDR were affected by the pandemic – and the measures to contain it – in unprecedented ways. Clinical Operations Director Dr Ard Vink and his staff had to reschedule all studies, many of them several times. And now, as the world recovers from the disruptions of 2020, there is another challenge on the horizon: how to accommodate the growing demand for studies. 'While this is a challenging time for operations, the increased interest in our services points towards positive times ahead.'

In any clinical study, there can be unforeseen circumstances, ranging from delays in the delivery of investigational products to obstacles in recruitment. Flexibility in the face of complex challenges has always been key to the success of CHDR's clinical operations. However, the COVID-19 pandemic took the complexity of operations to a new level. First came the requirement to put all clinical activities on hold. This was followed by the need to prepare for the reopening of the Clinical Research Unit (CRU), incorporating a whole slew of extra procedures to comply with the guidelines set by the Dutch government and the European Medicines Agency.

This complexity can be seen in the radical changes required in simply welcoming participants to a study. Vink: 'When people arrive at our building to participate in a study, they must check in at reception, where they are given a mask. They are asked if they feel well and whether they have any of the symptoms of COVID-19. If they feel unwell or have symptoms, a doctor is called and the participant must immediately leave. Otherwise, they go to the 7th floor where they are welcomed by nurses in protective gear to undergo a PCR test for SARS-CoV-2. Following the test, each participant must be isolated in a separate room while waiting for the test results. Only when the PCR test result has come back negative are the participants allowed into the Clinical Research Unit.'

Planning and communicating

When operations were resumed in June, several valuable weeks had been lost in what was already a very tight schedule. And of course, the ongoing pandemic continued to result in constraints on operations. Due to the extra measures required to prevent coronavirus transmission at the facility, the CRU could only be used at 50% capacity. In addition, some studies had to be postponed for safety reasons. Vink: 'Ideally, we would have performed all studies in the order they were originally planned, but that was simply not feasible. At first, for example, we could not do any studies with compounds that affect the immune system, or any studies in vulnerable populations.' Changing guidelines and government policies concerning public transport, lockdowns and other measures to contain the novel coronavirus all affected planning. Even when studies were able to go ahead, recruitment proved to be particularly challenging, with the pandemic not only impacting the possibility for recruiters to meet potential volunteers, but also restricting the distance that study participants could travel to the unit. Read more about how CHDR's Recruitment department rose to these challenges on page 118.

'Despite the pandemic, the expansion of the Clinical Research Unit continued as planned'

'From the beginning, it has been our policy to communicate clearly and openly, both with our clients and with our employees,' says Vink. 'Especially in these times, when there is so much uncertainty, it is crucial to invest in communication. Internally, we set up a dedicated COVID-19 team, including neurologist Prof. Geert Jan Groeneveld and internist Dr Naomi Klarenbeek, who were available to answer any questions from staff about issues related to the novel coronavirus. Our board also took measures to regularly inform clients about current policies: every time there was a government press conference in the Netherlands, we issued a letter to our clients informing them about any changes with consequences for our operations. Everyone was really understanding – there was a strong feeling of all being in this together.'

Expanding capacity

Even while the pandemic was still raging throughout the world, Vink and his colleagues faced another, more positive challenge: a growth in demand for CHDR's services. 'More and more companies throughout the world see the advantages of our scientific approach to early-stage clinical drug development. They know we will provide expert input to their protocols and that we are keen to invest in the development of biomarkers and other methods to investigate pharmacological action in early-stage trials.'

While the growth of the organisation against the backdrop of the pandemic can present its own difficulties, work is continuing apace to implement existing plans to expand the capacity of the Clinical Research Unit. 'As we had already planned, we moved most of our offices to another location close to our

main building. By the end of 2020, we were ready to transform the newly vacated office areas into clinical research spaces,' says Vink. The planned conversion is quite extensive, involving the reconstruction of four floors of the main facility. To prevent further delays in the operational schedule, clinical studies will continue during the transformation process. Special measures have been put in place to avoid disruption to participants, particularly when they are engaged in completing test batteries that require sustained focus, such as the NeuroCart. Vink: 'We have put up temporary accommodation close to the main facility where nurses and research assistants will be able to carry out testing undisturbed.'

Expanding operations requires more than just space and beds, of course: it is crucial to ensure sufficient numbers of qualified personnel are recruited to undertake all the various tasks involved in clinical research. 'Our Human Resource Management department is working hard to recruit the additional operational staff needed to support our growth. We need a diverse range of personnel, from nurses to scientists and database experts – all kinds of professionals who are currently in high demand. We foresee a large number of new hires joining us in the years to come,' says Vink. 'Thanks to our newly-gained experience with remote work across the organisation, we are also looking forward to offering a more flexible working experience in the future, while striving towards ever more efficient use of our facility.'

Herbert Anholts, Head of Recruitment

'We continued to reach out to study participants throughout the pandemic'

The pandemic posed several challenges for the Recruitment team. In addition to restrictions on public transport and two periods of lockdown, the cancellation of student events and other public gatherings drastically reduced the team's opportunities to come into contact with potential volunteers. Nonetheless, the team managed to continue recruiting volunteers even under these unprecedented circumstances. Herbert Anholts, head of Recruitment: 'I'm proud of what we've accomplished in this difficult year – not just the Recruitment team, but the organisation as a whole. Sometimes, it was far from ideal. Given the size of CHDR as an organisation, we prefer to allow plenty of time when implementing changes to procedure. But when the pandemic hit, we needed to move fast to keep up with the situation as it developed. Thanks to our versatility and flexibility, we were able to adapt quickly and effectively.' Drawing on a range of communication expertise, CHDR's Recruitment department comprises a core team of staff members supported by a broad base of on-call recruiters, many of whom are students. 'Our recruiters bring a great deal of energy and zeal to their work. We normally all work in the same office, which fosters a positive team spirit and allows us to easily provide support to one another.'

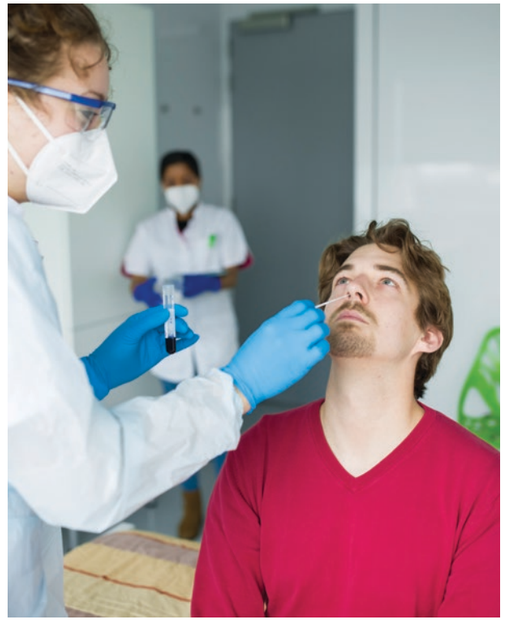
The situation changed radically with the pandemic, when almost everyone had to work from home – including, of course, the recruiters. Apart from losing the vibrant social atmosphere of the office, the shift to remote work posed particular technical issues for Anholts and his team: calls to the Recruitment department use a dedicated switchboard at CHDR, so this work could not easily be done off-site. 'In the case of staff members who were not required to work on the phone, such as supervisors, it was simply a case of supporting them to set up a home workspace. For the team members who work on the phones, however, it was quite a complex issue to solve, and it took us a few weeks to overcome the technical challenges involved,' says Anholts. 'Now, our callers all have dedicated mobile phones at home, which they use to automatically log in to our phone lines at the office.'

Vaccine study enthusiasm

Anholts describes how the number of volunteers signing up for one of CHDR's studies fluctuated in the course of the year. In the spring, when the entire Netherlands went into lockdown, the number dropped to near zero, but bounced back after the decision was made to reopen the Clinical Research Unit. 'Like every year, we saw a dip at the beginning of the summer holidays. But then the news got out that we would participate in one of the vaccine trials, and things went a bit crazy! Our call centre was inundated with calls from people who wanted to participate, vastly exceeding our call capacity,' says Anholts.

Normally, after the summer, the number of volunteers rises, partly due to CHDR's presence at various student events. At the start of the academic year, the universities all organise introduction weeks for first-year students. This provides the Recruitment team with many opportunities to spread the word about participating in clinical research and the benefits of volunteering in a trial. 'In most university towns, for example, there will be an information fair where we have a stand. We're there to chat to students and answer any questions they might have about participating, and we give out branded freebies – such as socks or coffee mugs – to improve awareness of CHDR among the student population,' says Anholts. 'In a normal year, we attend six or seven such events, and each event will yield quite a lot of potential volunteers. But in 2020, there was hardly anything along these lines. We participated in the online introduction week at Leiden University, which was good for maintaining our relationship with the organising committee, but wasn't the same in terms of outcome.'

CHDR normally sponsors a range of other events during the year in order to come into contact with potential volunteers from different backgrounds. In 2020, these too were cancelled or scaled down.



Anholts: 'The 30th edition of the Leiden Marathon was scheduled for March 2020, and CHDR would have been one of the main sponsors. The organisers of the marathon were very keen to have the event take place in spite of the pandemic, but they couldn't get permission from the authorities. Honestly, we were relieved – event sponsorship is a key component of CHDR's publicity, but we would certainly not want to be associated with an event that could put people's health at risk.'

Reaching out during lockdown

The impossibility of engaging directly with potential volunteers was only one of the recruitment challenges Anholts and his team faced. For much of the year, the government imposed restrictions on travel and advised strongly against the use of public transport, all of which limited the geographical area that potential volunteers

could be drawn from. During the strict lockdowns in spring and at the end of the year, volunteers had to be recruited from within a radius of just a few miles. Even in Leiden – a bustling student town in a densely populated area of the Netherlands – recruiting enough volunteers under these conditions proved to be tough.

Fortunately, the team already had an effective social media strategy in place, developed in collaboration with a marketing agency. 'We not only increased our budget for online marketing, but also produced a series of creative advertisements with a nod to the current situation. For example, referring to the fact that higher education was mostly online during the pandemic, one of our adverts showed a student with the tagline: "I stay up-to-date with all my online lectures while I'm a study participant at CHDR". Other taglines played on the experience of life under lockdown, such as: "Now that the pub is closed, you can find me at CHDR". The performance of every advert was closely monitored, to allow us to fine-tune the campaign to reach certain target groups.'

Whenever an opportunity arose for in-person contact – at a safe distance, of course – the Recruitment team was there too. When public transport opened up again during the summer, all passengers were required to wear a mask. CHDR's recruiters headed down to Leiden's central train station to hand out masks branded with the CHDR logo and website. Thanks to these creative strategies, the team managed to reach most of their recruitment targets for 2020 despite the obstacles thrown up by the COVID-19 restrictions. 'The last month of the year saw the strictest lockdown in the Netherlands, including a curfew. Under those circumstances, it became almost impossible to recruit enough people. But overall, we managed well,' says Anholts. Read about study participation at CHDR from the volunteer's perspective on page 122.

Taking care of the team

Throughout the year, Anholts and his core staff took care to monitor the wellbeing of all team members and the quality of the team's output. Anholts: 'When everyone is working remotely, not only do you miss the social dimension, but there are also extra steps involved in asking for advice or correcting mistakes.' In response to these challenges, a new role was created: Call Team Coordinator. This coordinator would stay in touch with all the team members who were calling or answering enquiries from prospective volunteers. If there were any questions or problems, the coordinator would be available to deal with them. Additionally, the coordinator would monitor the quality of the data the calling team entered into CHDR's database, and intervene if needed. Anholts: 'When everyone is at the office, this all happens almost automatically, with senior members of the calling team providing guidance to their colleagues. But now, we needed to explicitly organise that. And it worked even better than expected: our callers, most of them students, really gave their best, and managed to work effectively even without their supervisors sitting nearby.'

In adapting to the 'new normal', the Recruitment team was able to build on its robust organisational structure, the result of switching to a Scrum framework in 2019. Scrum is an agile approach to collaborative work, originating from the field of software development. A key element of this approach is a short daily meeting in which all team members share their progress and mention any problems they have encountered. 'This daily meeting played an essential role in fostering a team spirit while everyone was working from home. We also maintained our sense of community by organising virtual social events with quizzes and more,' says Anholts. 'The lockdown was tough on many of us, especially those who spent much of the time alone. To combat this, we participated in a session with the coaching agency Solid Sense that was organised by our Human Resource Management department. That provided a really valuable space for people to share their feelings and experiences. Everyone had a chance to be heard, and together we were even able to come up with solutions to some of the problems that people raised.'

> 'We took care to foster team spirit and maintain our sense of community while working from home'

The Recruitment team are hoping to be able to return to the office soon. But reopening the office does not have to mean losing the benefits that can come from working remotely: 'The majority of us, myself included, would prefer a hybrid schedule in which we can work from home on some days and at the office on others. So I think there will be some lasting changes even after the pandemic is over,' says Anholts. 'All in all, I think we have learned a lot this year, and I can see that the insights we've gained from this experience will bear fruit in the years to come.'

Robbert, clinical study participant at CHDR

'Volunteering in trials is a chance to contribute to society'

In autumn 2020, Robbert participated for the seventh time in a CHDR trial. 'My first study at CHDR was in 2007, before they moved to the current building. I've seen how the organisation has grown and developed over the years. Many things have changed, but what's remained constant throughout is the high level of hospitality and professionalism. Starting with the friendly phone call from the Recruitment department, to the clear information at the screening, and the facilities for study participants – I like it all,' says Robbert. 'This time was no different – well, apart from the first day when we had to have a coronavirus test and stay alone in our rooms until the results came back. I can imagine that for some people that could be a bit challenging, but for me it was no problem: I took my work with me to do while I waited, so the day was well spent.

'Over the years, I have participated in many different trials, including various tests such as the NeuroCart and PainCart. In this study, for the first time in my life, I underwent a lumbar puncture. I must say I was a bit nervous, but the CHDR staff reassured me. By the second time, it was no longer a big deal. One of the things I really like about participating in a trial is the opportunity to connect with other people. I've noticed that during the first days particularly the younger people spend a lot of time on their mobile devices, but after a few days, everyone is chatting to each other. There are often students among the volunteers, and they use the time to attend online lectures or prepare for exams. Many of the students I've talked to who are volunteers at CHDR are medical students themselves and they find it interesting to see how new drugs are being developed.

'For me, the main reason to participate in these studies is that it gives me the opportunity to contribute to society. Of course, I also appreciate the fact that I receive a thorough medical screening as part of the volunteering process. I like being at CHDR – some staff members even recognise me from previous studies. So when I get the next call from the Recruitment team, it's likely to be a yes from me!'

Bart Plug, Clinical Study Nurse

'I jumped at the chance to be part of the remdesivir trial'

One Sunday evening in April 2020, Bart Plug, study nurse at CHDR, was relaxing at home with his wife and four-year-old child when the phone rang. 'It was our Clinical Operations Director, Ard Vink. At first, I was a bit worried – why would a member of our Management Team be calling me so late on a Sunday?' Vink was calling to offer Plug a special mission: to be part of a CHDR team at the Amsterdam University Medical Center (Amsterdam UMC), tasked with helping to set up an additional branch of the international remdesivir trial in patients with moderate to severe COVID-19.

'In those early days of the pandemic, there was still much uncertainty about the new virus, particularly about the risks involved,' says Plug. 'So Ard asked me to think it over and call him back the next day. But honestly, I didn't need that much time – I saw it as a unique opportunity to be part of the worldwide effort to combat SARS-CoV-2. I talked it over with my wife, and within an hour I was already calling back to say that I wanted to participate.'

Plug immediately got to work reading the study protocol, and soon he and five other CHDR staff members – two study physicians and two other study nurses – were signing in at the Amsterdam UMC. 'The hospital was deserted, apart from the floors where patients with COVID-19 were being treated,' remembers Plug. 'Our job was to enter data from the hospital's computer system into the study database. At first, we were allocated a room at the Department for Tropical Diseases. But soon, it became clear that we could equally do this work from home. We divided the tasks among ourselves – my task was to monitor data quality. And sometimes, one of us had to go to Amsterdam to deliver the study medication, which requires a GCP-certified staff member.'

So in the end, the risk of contamination with the novel coronavirus turned out to be very low. But how did Plug and his wife weigh up the risks on that Sunday evening back in April 2020, when they had to decide if he should go to Amsterdam? 'My wife is pretty pragmatic, and she knows that dealing with infection risks is all part of a day's work for me,' says Plug. 'Before I joined CHDR, I worked at the Leiden University Medical Center, and there we regularly encountered patients infected with resistant bacteria such as MRSA and drug-resistant tuberculosis.'

Plug finds his work at CHDR very different from his earlier role as a hospital nurse. 'I worked on the gastroenterology and pulmonology ward. I gained a lot of experience there, but after seven years, I was ready for something new,' says Plug. 'The patients on our ward were often gravely ill. I found my work very fulfilling, especially being able to support patients in the last phase of their lives. But when you witness so many deaths, it inevitably takes a toll on you. Coming to CHDR meant being able to apply my skills in a totally different way. I used to tell my friends that the only similarity to the hospital was that blood is still red!' Plug values still being able to contribute to the health of the wider population, albeit in a completely different manner from working in a hospital. 'At CHDR, I constantly have the opportunity to study and learn new things. In fact, I've always had an affinity for science. At school I was never a very good student, but through my work at CHDR, I've discovered that I'm pretty good at it after all!'

‘They are very efficient, dedicated, resourceful and pragmatic. We got things done during a pandemic, which is excellent. They did a great job of starting up and running our studies in a very short time and during the pandemic. They were really exceptional at sticking to the plan: they kept to their timelines and did what they said they would do. Whenever a problem arose, they had a sensible approach to dealing with the problem, and we agreed with their solutions.

It is a blessing that we were able to find this organisation that could do everything in a short time frame. I have already recommended CHDR to others.’

Senior Vice President of Clinical & Regulatory Affairs, Biotech Company *

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

Human resources

Investing in resilience

The Human Resource Management (HRM) department was instrumental in facilitating and supporting the transition to working from home necessitated by the pandemic. Meanwhile, the department succeeded in maintaining momentum across various ongoing HRM activities, such as recruiting nurses and other essential staff, measuring job satisfaction, and updating the job classification system. 'CHDR's staff have done a tremendous job in dealing with the various challenges of the pandemic,' says Human Resources Director Yvette Akkermans.

'The HRM department has contributed in a number of ways to CHDR's resilience as an organisation during the pandemic,' says Akkermans. 'At first, the main challenge was to facilitate the rather abrupt transition to working from home. In collaboration with our IT department, we worked hard to help employees set up healthy and safe home workspaces, with the right computer equipment, chairs, ergonomic aids, and so forth. Our IT team ensured that all the IT systems worked as needed, including of course communication channels like Microsoft Teams, which have played an indispensable role during this period.' Thanks to these efforts, many activities could continue despite the temporary closure of the Clinical Research Unit. Moreover, by preserving continuity in this way, the organisation was better able to weather the storm and resume clinical studies later in the year.

Along with the other members of the Management Team, Akkermans quickly identified communication as a top priority during the COVID-19 crisis. 'There was so much uncertainty, especially in the beginning. We found it important to keep everyone up-to-date as best we could. To communicate the latest developments internally, we held regular online live events in which our directors, CEO Prof. Koos Burggraaf and CMO/CSO Prof. Geert Jan Groeneveld, provided updates and answered questions from staff members.' With much of the staff working remotely, it was also a challenge to maintain the vibrant social fabric of the organisation. 'We are lucky to have a very proactive staff association, who played a vital role in keeping the team spirit alive with a variety of online social events throughout the year.'

Mental resilience

Akkermans and her colleagues were well aware of the potential impact of the pandemic on the mental wellbeing of employees. 'We all experienced a major change in our daily routines. Operational staff had to temporarily stop working altogether and then, when clinical trials resumed, they had to follow a multitude of new procedures, all while maintaining social distance and wearing special protective gear. For the office staff, the change was just as radical: many had to transition to working entirely from home, while those who were needed on site had to adjust to spending their working day in an empty office,' says Akkermans. 'We wanted to support our staff through this experience and help them tackle problems as soon as they emerged. Therefore, we partnered with Solid Sense, a coaching and training agency with a lot of experience in preventive measures around workplace stress.'

> 'We aimed to create an atmosphere in which people could freely discuss their experiences and ask for help'

Together with Solid Sense, the HRM department set up a training programme aimed at fostering increased mental resilience among staff and creating an open atmosphere in which people could freely discuss their experiences and ask for help. Akkermans: 'We offered a three-layered programme. The main component of the programme comprised webinars and online clinics to create awareness among everyone in the organisation, as well as providing tips on how to deal with certain issues. For more specific support, we offered team coaching: this approach helps to strengthen the connections within a team, which is especially important when team members have to work from home and with different routines. Finally, individual coaching was also made available for those who needed that one-to-one input.

'The programme was helpful for learning to recognise the early warning signs of stress. Stress can manifest itself in different forms: cognitive, emotional, physical, and behavioural. We think it's crucial to be able to recognise it in yourself or in your colleagues, so that you can talk about it, or ask others for help. We made clear from the beginning that, as an employer, CHDR would provide support whenever a team or an individual needed it,' says Akkermans. 'My impression is that people appreciated our concern, and moreover, that our staff members have managed to navigate these difficult times successfully, despite the fact that many of us have experienced more stress.'

The online learning platform GoodHabitz, which had been made available to all staff following a successful pilot project in 2019, also contributed to employee wellbeing. In addition to practical skills such as Office 365 and business English, the platform offers training in other areas such as personal effectiveness, relaxation techniques and creating a healthy balance between work and leisure – exactly the kind of soft skills that may make life easier during a lockdown.

Implementing plans

The measures taken against the spread of the coronavirus affected many regular HRM activities.

Staff recruitment, job interviews, annual evaluation meetings and other essential communications all took place online. ‘Our organisation as a whole has proven itself to be quite resilient. We have managed to do almost everything we had planned, despite all the changes due to the pandemic. It did take extra effort from all corners of the organisation, of course. This was especially true for those who were hired during this period, and for their colleagues who had to onboard them and introduce all the relevant procedures, often without being able to meet in person. Regardless of whether work is done remotely or on site, I think it would be challenging for anyone to start a new job under such circumstances.’

Akkermans and her team, too, demonstrated resilience: they pursued their original planning, and even managed to achieve most of their goals for the year. This included implementing an Enterprise Resource Planning package, provided by AFAS Software, which integrates various systems relating to staffing and finance. Another item on their agenda was a survey of all staff to gain insight into what employees value about working at CHDR, what they are most proud of, and what they would suggest as improvements. ‘We considered postponing the survey in view of the unusual circumstances during 2020, but ultimately decided to continue as planned. It was clear that it would take some time for everything to become “normal” again, and we wanted to establish a baseline against which to assess the effects of various changes we’ve set in motion. In any case, the basic idea has always been to repeat the survey every year, at least for the coming four years.’

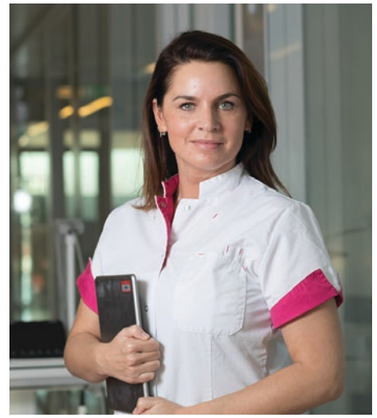
In collaboration with consultancy firm Leeuwendaal, Akkermans and her colleagues are currently busy updating the job classification framework and reviewing all job descriptions at CHDR. ‘We’re building on the existing framework, which was adequate for some jobs, but too narrow for many others which were added to the organisation during CHDR’s recent period of expansion. The rapid growth of the organisation in recent years had given rise to a few career bottlenecks, which we are currently repairing. It is important that each job description fits meaningfully and logically into the organisation as a whole. This not only facilitates movement between roles within the organisation, but also provides a framework that is sustainable for the future and which can accommodate continued growth. We are looking forward to completing implementation of the new framework in the first quarter of 2021.’

Recruiting nurses

To accommodate the growing demand for clinical studies, CHDR has been hiring more personnel. It is increasingly challenging to find enough operational staff, especially nurses. Employers throughout the Netherlands struggle to recruit nurses, and the precisely planned, time-sensitive style of work at CHDR’s Clinical Research Unit doesn’t suit every nurse. ‘In addition, in the early months of the pandemic when Dutch hospitals were inundated with COVID-19 patients, we made an important decision to stop hiring nurses for ethical reasons. We did not want to exacerbate the problems our hospitals were already experiencing,’ says Akkermans. ‘Later in the year we did increase our recruitment efforts again, targeting operational staff and nurses in particular.’

The recruitment campaign, combining a strong social media presence with billboard advertisements, proved effective. The adverts referred interested applicants to a dedicated website and podcast, which provided information about CHDR and the requirements of working at a clinical research unit. ‘Usually we would attend live events during the year where we could come into contact with potential recruits. Even though in 2020 all such in-person gatherings were cancelled, we still managed to hire 54% more nurses than the year before,’ says Akkermans.

All in all, 2020 has proven to be a successful year from an HRM perspective. Still, Akkermans longs to return to her office. ‘As planned, our department has moved to a new office location to make space for the expansion of our Clinical Research Unit. But I’ve hardly been to the new location – in fact, since I joined the organisation in 2019, I’ve spent more working days at home than in the office,’ says Akkermans. ‘Being an extrovert by nature, I get my energy from being around people. So I’m really looking forward to the day when I can work with my colleagues under the same roof again.’



Willem Nijgh, chair of the Works Council

'With effective communication, we were able to support each other through the crisis'

As the COVID-19 restrictions made their impact felt on CHDR's operations, there were potential consequences for the whole organisation. Willem Nijgh, member of the Recruitment team and chair of the Works Council, looks back on a turbulent year in which colleagues across the organisation pulled together to overcome the challenges brought about by the pandemic. 'Especially in the beginning, there was a lot of uncertainty,' says Nijgh. 'It was clear that the pandemic and the measures issued by our government would have an impact at every level of the organisation, but nobody knew exactly what the consequences would be over the longer term.

'That's why I was really glad that the Board always made sure that everyone was well informed and that they included us in the discussion regarding possible courses of action. Apart from the open dialogue with the Works Council, there were regular information sessions in which the Board updated all of the staff regarding the ongoing crisis. Each team also received coaching to deal with the challenges involved in working from home, with the option of additional coaching at the team level or the individual level. There was practical assistance, too, for those of us who needed support in setting up our home workspaces. As employees, it was clear to us from the very start that CHDR would support us through the crisis however possible.'

Salaries and solidarity

One of the main worries for the Works Council – indeed, a common worry across many organisations during the pandemic – was that COVID-19 would have such an impact on finances that layoffs would become necessary. Nijgh: 'We have always been a close-knit organisation, so having to lose colleagues would have been difficult for everyone involved, not only those leaving. And we also foresaw that losing members of staff would put us in a tricky position when pandemic restrictions were lifted and operations resumed pre-pandemic levels.'

The Work Council's concerns were shared by the Board and the Management Team, who came up with a plan to avoid layoffs, drawing additionally on the special support provided by the Dutch government to organisations facing loss of revenue due to the pandemic. However, the plan could only be implemented if the staff collectively agreed to forfeit their expected annual salary increases. 'CHDR participates in a collective labour agreement shared by Dutch university medical centres, which assures employees of an incremental annual salary increase. In addition, individual employees typically expect to be moved a step up on a predetermined salary scale every year,' says Nijgh. 'The Board could guarantee that everyone kept their job, so long as we all agreed to forego both these increases in salary.'

This may sound like a tough proposal for a Works Council to pitch, considering that the primary task of the Council is to advocate for the interests of employees. But, as Nijgh and his fellow representatives discovered, a consensus quickly emerged among the staff that a temporary salary freeze would be preferable to layoffs. 'It was really encouraging to see how the vast majority of our staff came out in favour of the rescue plan. There was definitely a sense of relief when people learned that we would be able to keep everyone on board despite the difficult period for operations.'

Ongoing dialogue

In the course of the year, the Works Council met with the Board every six weeks to discuss current developments and plans for the upcoming period. Additional briefings were organised whenever necessary. 'Every quarter, our Financial Director Bart Mooy informed us about the current financial situation. We were glad to learn that, by the end of the year, CHDR had performed better than initially expected.'

Now that CHDR has weathered the worst of the pandemic and the future looks brighter once again, Nijgh can take time to reflect on the mutually beneficial relationship between the Board and the Works Council. 'It is an ongoing dialogue, in which we balance the interests of the employees and the interests of the organisation as a whole. Essentially, the two often are the same. The organisation needs staff who are committed and motivated to keep delivering the high level of service and scientific output that CHDR is known for. And we need an organisation which is not just a nice employer today, but which will also be financially healthy tomorrow,' says Nijgh. 'When I was training for my role on the Works Council, I was given an important piece of wisdom: the Works Council advocates for the employees, but that doesn't mean it is necessarily in opposition to the Board. In the end, we all want the best for the organisation and its staff.'

Finance

Staying financially resilient as a foundation

Due to the impact of the COVID-19 pandemic, 2020 was not a successful year in financial terms. Still, Financial Director Bart Mooy (MSc, RA) is not unhappy with the results. ‘We managed to avoid any layoffs, and we even invested in future growth by converting office floors into clinical research space,’ says Mooy. ‘We owe much of our success in navigating the crisis to the continuity reserve that we had built up from profits in previous years.’

CHDR has the legal form of a foundation, meaning that there are no shareholders, allowing the Board more flexibility in its decision-making. This organisational structure already has benefits in the best of times, but it was crucial to CHDR’s resilience during the pandemic: thanks to the continuity reserve, the organisation was equipped to survive the more than three months of no revenue, followed by many months of reduced capacity. Mooy: ‘Not only does our status as a foundation mean we are free to reinvest our profits into our R&D activities, but we are also able to set aside an amount as a reserve in case of unforeseen circumstances – such as those that transpired in 2020.’

Keeping everyone on board

When the Clinical Research Unit (CRU) had to be closed because of the pandemic, the Board and the Management Team began mapping out future scenarios to chart a course through the crisis. Would it be necessary to restructure the organisation and lay off staff in order to survive? Mooy: ‘We knew that we had a full portfolio and good long-term prospects. We all agreed that it was far preferable to keep everyone on our payroll if at all possible. Firstly, we felt a strong duty to support our employees through the difficult period. Secondly, our scientific and operational staff possess a unique blend of expertise: if we laid off staff now, we would be faced with a long hiring and training process when we eventually returned to full operational capacity.’ To retain all staff, the organisation was able to draw not only on the continuity reserve but also on Dutch government support for businesses affected by the pandemic. In return, the staff too demonstrated solidarity, agreeing to a temporary salary freeze in order to keep their colleagues on board.

Green light for expansion

Back when COVID-19 was yet to emerge on the global stage, CHDR was busy making plans to increase operational capacity. To meet growing demand, the CRU would be expanded, with several non-clinical departments moved to a nearby building to free up the necessary space in the main building. When the pandemic hit, the Management Team had to decide whether it would be feasible to proceed as planned, despite the inevitable reduction in revenue. Mooy: ‘Given the uncertainty of the situation, it would have been easy to argue for a more conservative approach, to play it safe. But entrepreneurship involves taking calculated risks. Even as the pandemic was unfolding, we set our sights on being ready for the post-COVID future.’ So the planned changes went ahead, and in the summer of 2020, the new office space was ready to welcome employees who needed to return to working on site. ‘Since there were relatively few people around, the move itself was quite straightforward – notwithstanding all the preventive measures such as social distancing,’ says Mooy.

Corona-proof

In addition to finance, Mooy’s responsibilities include overseeing internal services such as catering, office space, and facilities. ‘I’m fortunate to be able to rely on a very capable Office and Facility Manager, Helma Nederend. Helma and her team adapted admirably to the challenges of the new situation.’ These challenges included the shift to remote work across the organisation, which meant providing employees with the necessary equipment to set up safe and healthy workspaces in their own homes. When operations could be resumed, the building also had to be made ‘corona-proof’, with socially distanced walking routes and a host of other safety measures. ‘It was no mean feat: everyone had to adapt to performing their role in compliance with the new measures, and people were naturally concerned about the potential risks to their own health,’ says Mooy. ‘So it was certainly a tough year, but I think we can be proud of what we have achieved.’


Execution
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Done
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Nightly
Backup
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Smart AM
Ortec
Afas
koppeling
New Production
Server
labware
EXHA
UPS
Xitrix
ePro
Firewall
VPN
Trainings
AD

Technology

Support for growth and innovation

With CHDR's mission to conduct data-rich trials using cutting-edge methods, information technology has always played a central role in the organisation. The development of new techniques and biomarkers demands innovative technological solutions, and in turn, tech innovations open up novel possibilities for scientists. The growth of the organisation also poses challenges for the Technology team's day-to-day work, with more staff working at various locations.

'The first thing I noticed when I joined the organisation is the enthusiasm of the Technology team,' says Bart van der Kroef (MSc), who became CHDR's first Director of Technology in March 2020. 'The regular staff and the contractors are all dedicated professionals who have worked closely together in recent years to put in place the IT infrastructure and applications that the organisation needs to evolve. The relatively smooth transition to working from home during the pandemic was made possible by their previous efforts. We have a flexible system, partly cloud-based, in which staff are able to work remotely and on-site using the same tools. Of course, the rather abrupt change from everyone working on-site to nearly everybody working from home posed a challenge for the team. Joining at the start of the pandemic, I was impressed with how the team had performed under those unprecedented circumstances.'

Infrastructure for growth

With the rapid growth in recent years and the ambitious plans for further growth in the years ahead, CHDR's Management Team was in need of a Director of Technology. 'Our data infrastructure is the backbone of our organisation,' says Van der Kroef. 'It serves to orchestrate the whole machinery of our operations, to gather reliable data and protect data integrity, to report to our clients and support scientific analysis. So with the organisation growing and studies becoming ever more data-intensive, investment in the data infrastructure emerged as a top priority.'

The long process of transitioning to a cloud-based infrastructure continued in 2020. Some elements have now been successfully implemented, such as the Azure virtual desktop. This application, which is now cloud-based, is a shell which allows for safe access to the system from any location, including from home. 'Staff can now do exactly the same things on the system from home as in the office, without having to worry about the underlying components and their integrity. System updates, bug fixes – all those things will be taken care of under the hood. That also includes protection from the many cybersecurity threats that an organisation like ours has to deal with on a daily basis. Those routine jobs may not be the most exciting tasks for our team, but they are crucial to security and smooth operations.' In another recent development, the team responsible for the Promasys clinical data management system has rejoined CHDR from Anju Software. The team now reports to Van der Kroef, and will focus on delivering new functionality in the next version of Promasys.

Service meets innovation

The activities of the Technology team fall largely into two categories: either supporting and maintaining infrastructure and responding to requests from within the organisation, or working on projects to innovate parts of the infrastructure. This combination creates a workload that can be challenging. Van der Kroef: 'We are currently working on 37 different projects, while there are also 400 to 500 tickets per month with incidents and service requests from within the organisation. I'm glad to say that the Board has granted us an expansion of our team. With the extra staff and effective work planning, our team will be in an optimal position to meet the organisation's various technology needs as they arise.'

CHDR's focus on the innovative use of technology for early-phase drug research means that the tasks of the Technology team are much more diverse than that of a typical tech support job. Advanced technologies for data collection at CHDR, such as the NeuroCart test battery and the Trial@home remote data acquisition platform, all generate rich, complex data which need to be analysed. Van der Kroef: 'We aim to improve the speed of analysis, enabling more efficient use of this valuable equipment.'

In addition, the updates to the technological infrastructure of the organisation feed back into the scientific side of things, with new tech opening up fascinating possibilities for future studies. 'For example, with all study data in the cloud, it becomes easier to apply a machine learning approach to these data, improving the detection of patterns that can inform the development of digital biomarkers,' says Van der Kroef. 'Machine learning and other artificial intelligence approaches can even be leveraged to improve operational efficiency. CHDR is currently studying algorithms which could in the future be used to reduce the need for some measurements or blood samples, potentially reducing study costs and easing the burden on subjects.'

Creativity and diversity

Joining CHDR at the start of the COVID-19 pandemic may not have been ideal, but Van der Kroef adapted

quickly. ‘In a previous role at Janssen Pharmaceuticals in Belgium, I coordinated technology teams across many different locations, so I was already used to digital meetings. I was given a warm welcome by CHDR’s Management Team and even though I work from home most of the time, I think I’ve got to know the organisation quite well already. There is an interesting balance here between the scientific spirit, which demands freedom and flexibility, and the need for strict compliance with standardised procedures. Having worked in similar organisations, I feel at home in that creative tension. Another thing I like about CHDR is its cultural diversity – I have people from many different backgrounds in my team, making for a dynamic blend of experiences and perspectives,’ says van der Kroef. ‘It’s the best of all worlds.’

Bart van der Kroef is CHDR’s new Director of Technology

Bart van der Kroef, the organisation’s first Director of Technology, brings a broad experience in information technology to his new role. Van der Kroef gained his MSc in telematics in 1999 from Middlesex University, UK, while working as a network engineer at KLM Royal Dutch Airlines. Soon, he progressed to a management role. After KLM, Van der Kroef worked at Nokia Networks for several years before joining Centocor, now called Janssen Biologics, a Johnson & Johnson company. At Centocor, he gained experience of IT in a biopharmaceutical context, working chiefly on a production site, with additional activities relating to drug development and regulatory and clinical affairs. Three years after joining Centocor, Van der Kroef was asked to lead the EMEA Infrastructure team for J&J at Janssen Pharmaceutica in Beerse, Belgium. In 2014, he moved to T-Systems to lead a large team delivering cloud solutions to Shell, Heineken and Philips. Before joining CHDR, Van der Kroef worked as Head of Infrastructure Europe at Vistra, a financial company.

Quality assurance

Quality assurance in times of COVID-19

The wide-ranging nature of the adaptations that the organisation had to make during the pandemic becomes evident in conversation with Margreet Rienstra, CHDR's Compliance Director. 'Quality assurance touches all aspects of our operations. It was a challenging time, but with dedication and teamwork we were able to uphold our high quality standards and even learn valuable lessons in the process.'

When COVID-19 took hold in the Netherlands in March 2020, the Management Team adapted rapidly to the crisis, holding daily online meetings to deal with the multitude of questions that emerged. Rienstra: 'We had to find ways to do as much as we could while working at home. For many tasks, such as reviewing standard operating procedures, this was fairly straightforward. However, for some key processes we needed to make adaptations. For example, we still had a number of processes in which documents needed to be signed with a "wet signature" – that is, an ink signature on paper. Although many of our systems were already using other forms of authentication, we still needed those wet signatures. So we had to urgently devise alternative procedures.'

Working from home

When the decision was made to temporarily cease all clinical research, Rienstra sat down with her QA team to discuss how they could best play their part while working from home. 'With hardly any clinical activities being performed and no new studies able to start, we all agreed that we would use the opportunity to get up to date on all our outstanding work. It seemed that our colleagues were thinking the same thing, as we started to receive more documents to review than we had in the weeks before,' says Rienstra. 'We have over 300 written standard operating procedures that have to be reviewed every two years. So we worked on making sure that everything was up-to-date before clinical operations started again.'

Soon after clinical activities were suspended, the Management Team began planning for a resumption of clinical studies under strict conditions. The QA team played a crucial role in writing and reviewing the additional procedures that were needed to conform to the guidelines of the Dutch Health Inspectorate and other regulatory bodies. As Compliance Director, Rienstra was responsible for keeping abreast of developments and making sure that CHDR's procedures complied with all current regulations. 'Of course, most of the measures were temporary. In addition, several guidelines were adapted multiple times – especially in the beginning, when new information about the virus was emerging day by day,' recalls Rienstra. 'For that reason, we chose to write an overarching standard operating procedure for COVID, instead of adapting all applicable SOPs to the situation. There were some procedures that we did have to change, but which we hope to revert when the pandemic is over – for those procedures we wrote an addendum.'

Auditing from afar

The recommendations to limit travel and in-person contact had consequences for the regular internal and supplier audits performed by CHDR's QA department. 'There is a whole list of suppliers that we need to audit regularly, particularly those that are relevant to our clinical operations. We also audit internal systems and processes. Simply postponing all of those audits would cause more problems by creating a backlog in our audit schedule, so we devised a system to do it remotely. Our auditing procedure already allowed for remote audits, but we needed to develop the tools to actually implement the procedures in this way.' The team got to work putting together an extensive questionnaire for supplier audits, with a modular structure to capture all the nuances involved in working with a range of suppliers, from IT companies to laboratories.

Thanks to the hard work of the QA team members, the questionnaire was finished in a very short time and the first remote audits could start. 'Using online tools to share and review documentation, we found it was possible to get a good overview of a supplier's procedures. Where necessary, we conducted interviews to clarify any questions we had,' says Rienstra. 'The system worked wonderfully and turned out to be quite efficient. We even found that it provided new benefits compared to the traditional method of in-person visits. For example, if you forget to ask something during a two-day visit, you have to reach out to the supplier again. With the remote audits, our suppliers provided us with access to everything we needed for the report for a period of time following the audit. Of course, when you do things completely online, you miss out on the more intuitive part of auditing: when I visit a company, I can gain an overall impression of the way they operate just by looking around. So, I do think that we will continue to do things online in the future, but we may combine remote auditing with a short on-site visit – that way, we can get the best of both worlds.'

External audits

Just like the supplier audits performed by CHDR's QA team, the external audits of CHDR by clients also had to be rescheduled or conducted remotely. And, like

CHDR, clients also had to develop ways to gather all the necessary information from a distance. Rienstra: 'Having faced the challenge ourselves, it's interesting to see how clients approach it. Some basically do the same things remotely that they would do if they were with us on site. Others use the opportunity to be more thorough – for example, taking time to meticulously review each and every procedure. We of course do what we can to accommodate their wishes, although there are limitations, especially during the pandemic. For example, we would usually give our clients a live tour of the unit. However, with very strict procedures in place to prevent the transmission of coronavirus among volunteers and staff, access to the clinical unit has been extremely limited.'

> 'In the future we may combine remote auditing with short on-site visits to get the best of both worlds'

Here, too, the team found ways to adapt. When an opportunity arose to produce video material for the benefit of auditors, Rienstra jumped at the chance. In order for clients to be able to look around the Clinical Research Unit without visiting in person, CHDR's Business Development team decided to produce a video tour of the facility, as well as videos of some specific methods used for specialised measurements. Rienstra asked the crew to make some additional recordings of aspects that would be relevant from the perspective of an auditor, such as the presence of alarm buttons and cords in all rooms including toilets and showers, or labels showing the inventory numbers on equipment. Rienstra: 'Those details would not be so interesting for someone who just wants to have a general idea of our CRU and procedures, but they're crucial for an auditor whose focus is on subject safety and data integrity.'

Rienstra thinks it likely that many future external audits will be performed remotely, even after the world has recovered from the COVID-19 pandemic. 'I don't see us going back to the frantic flying back-and-forth all over the world that we used to do. Much can be gained by doing audits remotely. We and our clients are still optimising the process, of course: for example, although auditors need to be able to access documents remotely, we need to make sure that they aren't able to download them – that would be undesirable from the point of view of confidentiality. Being audited always requires mutual trust, but even with the best of intentions, downloaded documents can begin leading their own lives, remaining on external servers indefinitely.'

Inspection success

As CHDR was resuming clinical operations, the Dutch Health and Youth Care Inspectorate (HYCI) announced that they would perform a GCP inspection of the facility. The HYCI is responsible for the supervision of all clinical research in the Netherlands, aiming to ensure that all trials are conducted in accordance with the Dutch law on clinical trials and other applicable regulations. One of their tasks is therefore to visit clinical research sites across the Netherlands and inspect studies. Rienstra: 'They visited in person, reviewed study data and procedures, and interviewed several members of staff. Such an inspection can feel a bit like being graded in school – everyone inevitably feels nervous. However, there were no critical findings, which means that we performed well. They also gathered information about our COVID-19 procedures, as part of a more general evaluation of the situation which they conducted at various clinical sites.'

No sooner had the first HYCI inspection been completed than a second inspection was announced. This second inspection focused on a vaccine trial CHDR was participating in (see also page 62). 'At that time, the whole world was following the development of COVID-19 vaccines with intense interest, and much was hanging on the outcomes of the trials. It was therefore natural for the HCYI to want to conduct a thorough review of the study.' The study in question was a multicentre study, in which several Dutch clinical sites participated. Rienstra: 'The study was executed with the utmost care and closely monitored by the sponsor, so we did not expect any problems. Indeed, the Inspectorate did not have any critical findings.' Rienstra reflects on the inspections as a challenging, but ultimately rewarding experience. 'I must say, although the inspections were a lot of work, it was a great feeling to be back in the office again!'

WORKING WITH CHDR

‘Our study involved three sites in total. CHDR was the first site that started and the site with the highest enrolment. The Principal Investigator provided expertise that other sites did not have, and helped us to design our protocol. They were really supportive and helped us to start the programme from the ground up. They offered an enhanced service compared to other sites.

Our company is pretty small, which means we are only as good as the people we bring on board. We really valued CHDR’s collaboration on this study, and we appreciated their expertise. They surprised me positively – it’s difficult to think of anything they could improve. They are definitely the best CRO that I have worked with.’

Clinical Trial Manager, Biotech Company *

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

Scientific output

Publications

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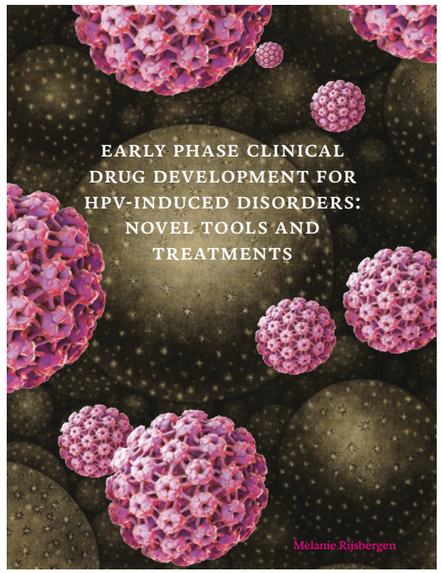

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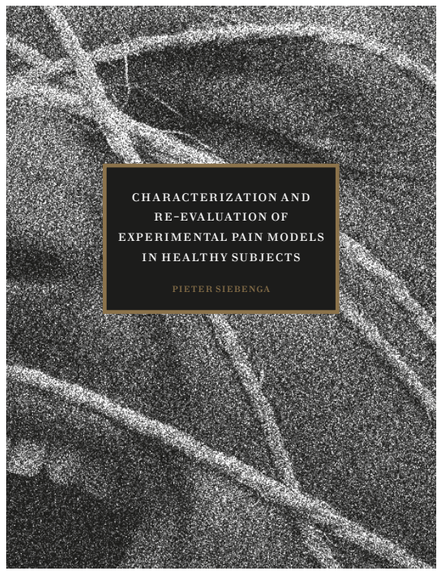

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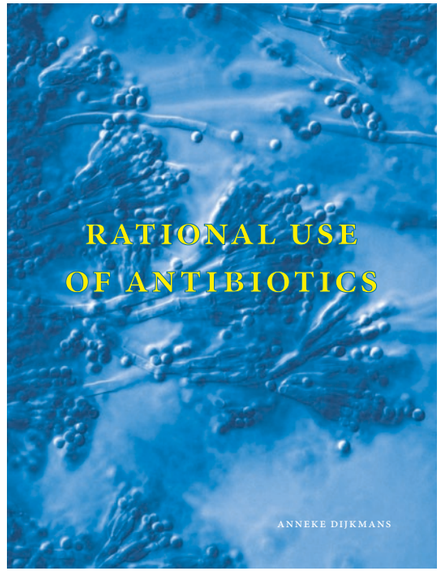

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