CHDR
Centre for Human Drug Research

Annual Report 2016

Word from the CEO

This annual report describes CHDR's 30th year. Although our annual reports have become more elaborate and – hopefully – more readable than our first report published three decades ago, they still describe exactly the same thing: fascinating research by a highly talented group of clinical scientists and researchers dedicated to developing new medicines using innovative techniques. In this year's report, you can read about our exciting array of activities over the past year, ranging from travelling to the peak of Mont Ventoux in France to studies regarding the human skin. It's been a pleasure watching the harmonious and highly productive efforts of our growing organisation, with staff members who originate from nearly thirty countries around the globe. This rich tapestry has helped CHDR maintain its unique nature for so many years.

This report also marks a change in upper management at CHDR, as I step down as CEO after three decades to serve as the Director of our new venture, Innovation Services. Next year, I look forward to reading the opening remarks to the 2017 Annual Report by our new CEO. On behalf of the entire Board, I would like to express our deepest gratitude for all of the hard work by our entire staff. On a personal note, I am of course extremely grateful and honoured to have had the opportunity to successfully lead this stellar team for so many years.

Adam Cohen, CEO

'It's been a pleasure watching the harmonious and highly productive efforts of our growing organisation, with staff members who originate from nearly thirty countries around the globe.'

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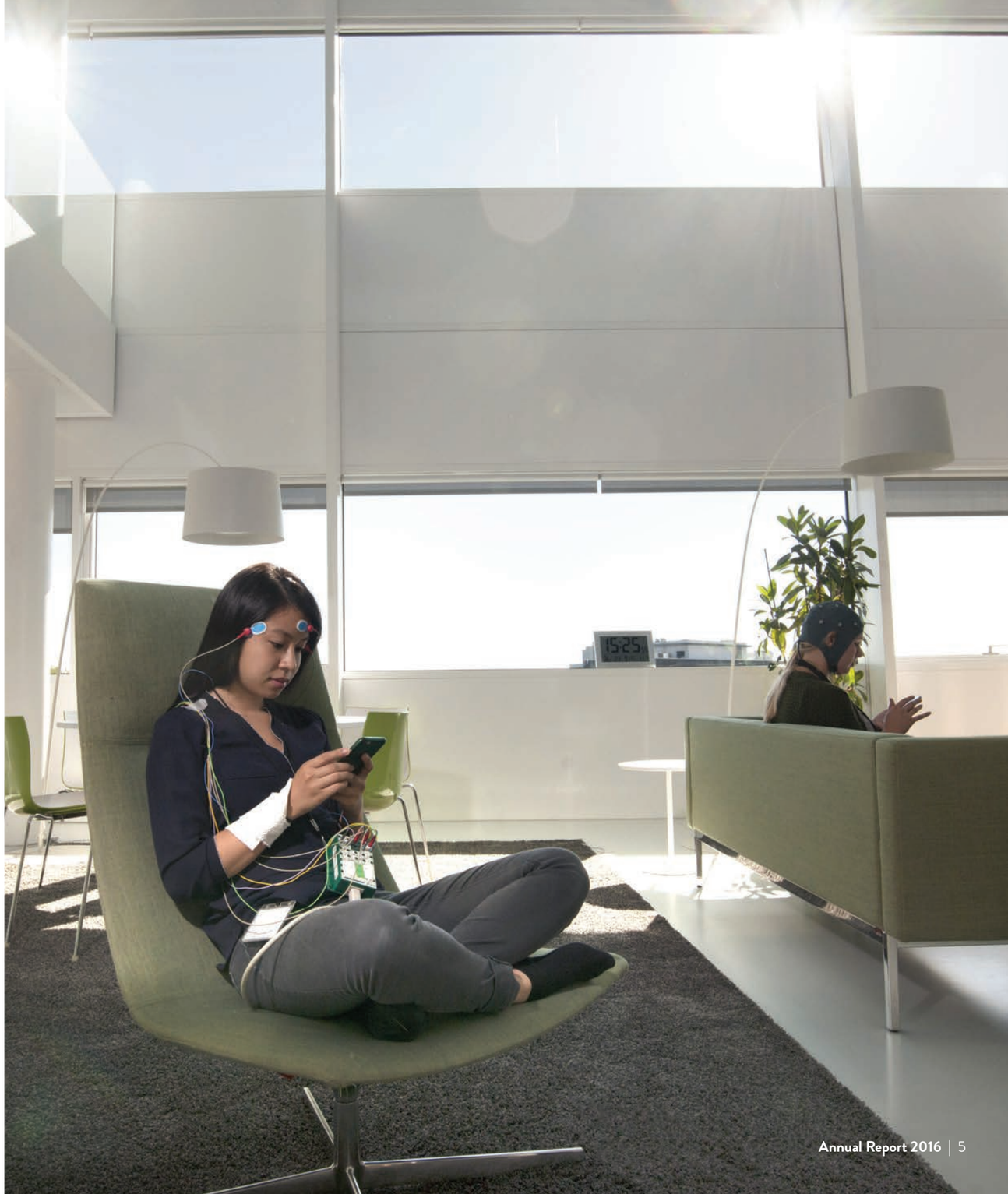
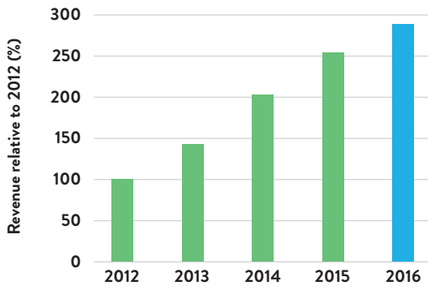
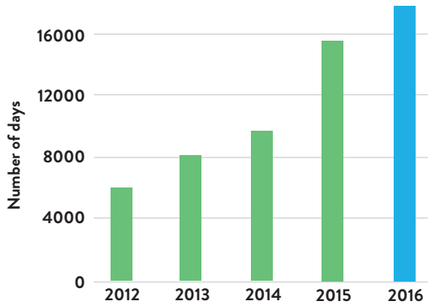


CHDR at a glance

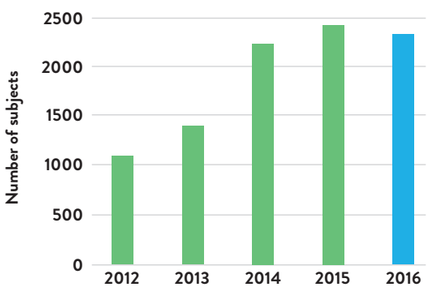
Contract revenue



Accomodation days



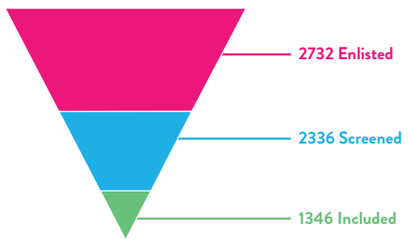
Subjects screened



2016 at a glance

- 58 studies
- 41 contracts signed
- 27 articles published
- > 46,000 volunteers available
- > 7500 patients available

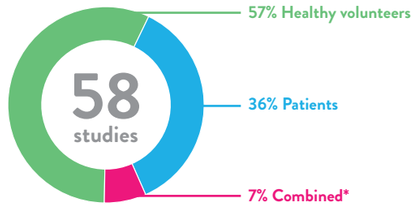
Subjects recruited



Overall client satisfaction

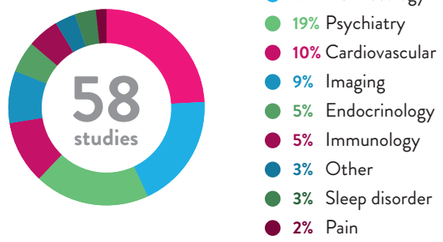
9.1 ★★★★½

Studies with healthy volunteers and/or patients

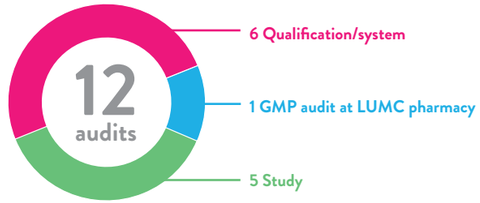


*both healthy volunteers and patients

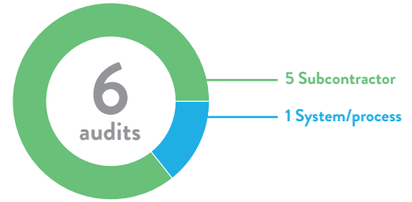
Studies per research area



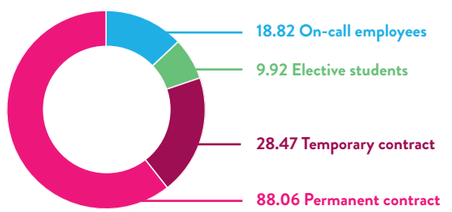
Number of external audits



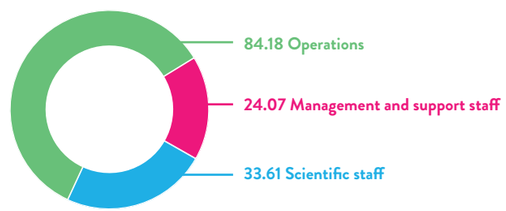
Number of internal audits



FTE by contract type



FTE by department



Where we come from

Afghanistan
Antilles
Argentina
Australia
Belgium
China
Germany
Egypt
Greece
India
Indonesia
Iraq
Iran
Italy
Kurdistan
Morocco
Mexico
Moldavia
Netherlands
Pakistan
Poland
Russia
Scotland
Suriname
Thailand
UK
USA
South Africa
Switzerland

Innovation Services

A change at the top after 30 years

In May 2017, CHDR will celebrate its 30th anniversary. What started as a small research unit with a handful of employees has grown into a thriving organisation with significant scientific output and an international list of sponsors. CEO Prof Adam Cohen reflects on the past year and announces his decision to step down from this position and start CHDR Innovation Services.

'It's been yet another good year,' says Cohen. 'We performed both sponsored studies as well as research that we funded ourselves, including the EPO study (see page 34). We also sold our building and then signed a contract to rent the building back from the buyer, which has left us in the comfortable position of being entirely debt-free. Financially, we're in a very good position. CHDR is not dependent on investors, we have no shareholders, and our solid working capital enables us to plan ahead for several years. So, this is an excellent moment for us – for me – to focus on something new. I'm confident that the Board of Trustees will soon find a successor to serve as CEO, and then I'll devote my time to establishing CHDR Innovation Services.'

Making organisation-wide changes

If we had to use just one word to describe CHDR's development in 2016, that word would have to be 'consolidation'. After several years of major growth, our goal now is to remain at our current level of operations. To keep these operations running smoothly, we implemented new software; this combination of new platforms for advanced planning, financial project management, and customer relationship management (CRM) means that our processes have become more efficient and more easily scalable (see page 46).

Another organisation-wide change was the introduction of dedicated funds for research and development (see page 24). Cohen explains: 'Having these funds available means that if someone at CHDR has an idea for a new research project, they no longer have to look for an external sponsor; they can apply for funding from our own R&D budget. In a way, we've become one of our own sponsors.'

Building bridges through Innovation Services

At CHDR, Innovation Services will become a new business unit focusing on building strategic partnerships with biotech companies and providing consultancy services for the biotech and pharmaceutical sectors. 'More than half of all new pharmaceutical products that enter the market were developed at small biotech companies,' says Cohen. 'While most of these companies have a strong foundation in science and technology, they have little expertise in translational or clinical development. This is where we see an opportunity to provide an integrated scientific consultancy service that connects the worlds of academia and clinical drug development with the marketplace.'

'Our expertise in drug development can help companies and investors establish – and achieve – realistic targets.'

Providing both proactive and retroactive consultancy services

Having a strategic partnership with CHDR Innovation Services may benefit a fledgling biotech company looking to make the right choices and set feasible targets. 'One of the potential pitfalls faced by new biotech companies is having to allow their investors to set the scientific agenda,' says Cohen. 'We can use our expertise in drug development to help both companies and investors establish realistic targets together, thus avoiding unnecessary losses to both parties. We've seen these pitfalls occur time and time again, and we can help prevent them. Another good way of keeping the process on track and avoiding expensive mistakes is to apply our "question-based" drug development approach.' Of course, CHDR Innovation Services will also assist companies that have encountered problems in the drug development and/or regulatory process. 'We'll provide both proactive and retroactive consultancy.'

At the cutting edge

It is not unusual for someone with Cohen's experience and background to become a consultant. But this CEO likes to do things differently. 'Because Innovation Services will be an integral part of CHDR, it won't depend on one person,' explains Cohen. 'A single individual – no matter how much experience he or she has – can't possibly stay up to date with all of the new developments in the field. By remaining at the cutting edge of innovation in drug development, CHDR Innovation Services will be a dependable partner.'

Supplying interim managers

An additional service will be to provide young biotech firms with an interim Chief Medical Officer and/or Chief Scientific Officer. Cohen explains: 'This is just one way in which we can help biotech companies make it through the vulnerable first years. Depending on the situation and the client's wishes, we can provide the company with either an experienced manager or a recent graduate who will be coached by experienced staff members.'

Educating biotech entrepreneurs

In addition to being linked to CHDR, Innovation Services will also be linked to other recently developed initiatives. One such initiative is Paul Janssen FutureLab, an international training programme created by Leiden University Medical Centre in collaboration with Leiden University and CHDR. This unique programme provides postgraduate training to biomedical and pharmacological scientists who are looking to become biotech entrepreneurs. 'Consulting offers unique opportunities for education,' says Cohen. 'When students and young scientists work with an experienced consultant, they learn relevant skills while also providing valuable input. Of course, CHDR's own PhD students and clinical pharmacology trainees also benefit, making CHDR even more attractive to smart young physician-researchers and other scientists.'

A think tank for drug development

CHDR has always sought to contribute more than just data, and they have a long track record of developing projects that go the extra mile, including question-based drug design, reflecting on the ethics of clinical experiments, and coming up with creative solutions to problems commonly encountered when financing the early stages of biotech development. Cohen: 'Our new Innovation Services unit will afford us both the time and manpower to expand upon these strengths, becoming a kind of think tank. I envision the production of research articles, reports, and white papers, all of which will help move the industry forward. And of course it will create yet another strong connection with education. I'm really looking forward to seeing these new ideas develop and be put into practice.'

‘I value CHDR’s unconventional approach’

‘Innovation is essential in my field, and it’s something I’ve come to expect from all of my collaborators. In a successful collaboration, innovation has to come from both sides, and CHDR meets our expectations thanks to their proactive approach. When I work with CHDR, the projects are truly innovative, as CHDR conducts studies in a less conventional way. CHDR’s staff are always accessible, and they always think with us, so communication flows freely in both directions. CHDR is even able to plan meetings with us on short notice.’

Director, Experimental Medicine,
Top 10 Big Pharma Company*

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

CHDR Research Budget

Research budget: CHDR's new in-house Medical Research Council

For the sake of clear accounting, and to stimulate staff members to formulate their project goals clearly, CHDR has set aside a dedicated research budget. At 10% of our annual revenue – about €2.5 million – this budget is large enough to accommodate an ambitious research programme, which will facilitate CHDR's methodology development programme as well as Ready-4-Research and Trial@home.

'CHDR is an independent foundation without shareholders, and we have always used part of our revenue to finance research projects, in addition to conducting sponsored studies,' says Prof Adam Cohen, CHDR's CEO. 'But now that our organisation – and our annual revenue – has grown, it has become important to structure this self-financed research. Most importantly, having a dedicated research budget gives us the freedom to decide which projects we want to fund.'

How it works

Staff members with an idea for a new research project can write a project proposal, much like applying for a grant from the US National Institutes of Health, the UK Medical Research Council, or ZonMw in the Netherlands. If the Research Director agrees that the project is worth pursuing, the proposal will be evaluated formally by the Management Team. If the Management Team approves the proposal, it will then be evaluated by CHDR's Scientific Advisory Board, which makes the final decision. Cohen: 'If a project is approved, we reserve funds in the research budget for the duration of the project. Most projects last more than one year.'

Priorities: validating methods and strategic goals

Although each application is judged on its scientific and methodological merits, the research budget is not designed to finance our staff members' scientific hobbies, no matter how valid. The project should contribute to CHDR's overarching goals. Specifically, the research budget is dedicated to three main areas: methodology, Ready-4-Research, and Trial@home. Cohen explains: 'One of CHDR's long-term goals has always been to establish new methods for improving clinical drug development. We've been quite innovative in this respect. Now, we're also investing in systematic validation both in healthy subjects and in patients. The value of our methods will increase if we can demonstrate the precise predictive value of these methods. For example, with Ready-4-Research – in which we create cohorts of specific patient groups before a sponsor or protocol even exists – we need to invest in methods for clinically evaluating these patients, and we need to invest in building a strong network and recruiting subjects. Finally, in the context of Trial@home – our innovative programme in which a complete clinical trial is performed in an outpatient setting – we need to develop and validate technologies for measuring all relevant parameters in the patient's home. In all of these areas, many interesting questions still remain. So we're quite fortunate to have many young scientists who are dedicated to finding answers to these questions.'

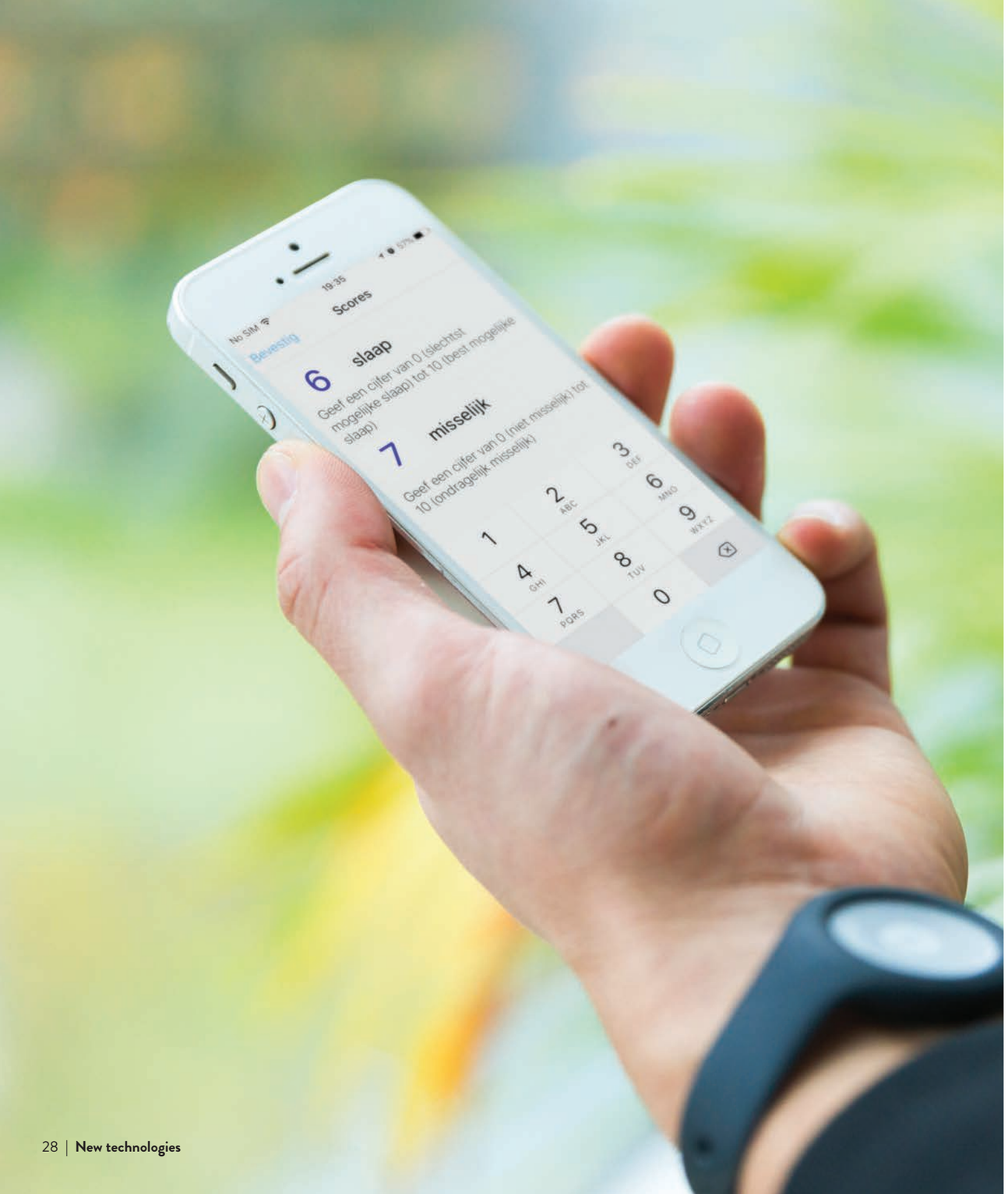
Keeping track of immunosuppression

A good example of using the new CHDR research budget is a project designed to develop, apply, and validate a battery of functional tests to measure immunosuppression in kidney transplant recipients. To prevent rejection of the transplanted kidney, the patient needs to take immunosuppressive medications. These medications must be balanced carefully in order to avoid inducing immunodeficiency and/or toxicity. Our new test battery will monitor the patient's overall immune status, as well as both patient-specific and antigen-specific responses. These results can then be compared with the drug's concentration in the plasma, allowing optimisation of the dosage in each patient, based on his/her response. This project, which will be coordinated by CHDR, is made possible thanks to our long-standing collaborations with Leiden University Medical Centre (LUMC), the Leiden Academic Centre for Drug Research (LACDR), and Erasmus Medical Centre in Rotterdam.

Using mitochondrial function to predict outcome following total knee replacement surgery

Another exciting new CHDR-funded study will examine whether mitochondrial dysfunction can be measured and used to predict recovery following total knee replacement in elderly patients. To quantify mitochondrial function, researchers will measure mitochondrial proteins and enzyme activity in muscle tissue, as well as mitochondrial membrane potential in circulating blood cells.

At the same time, researchers will also obtain a detailed picture of the recovery process following orthopaedic surgery in elderly patients by measuring clinical and physical parameters on a daily basis using Trial@home. These measurements will include the patient's weight, body mass index, physical activity, and metabolism.



New technologies

Investing in new technologies

In addition to developing functional, biochemical, and cellular biomarkers, CHDR also invests heavily in developing new technologies. Technology has always been a key component to CHDR's success, and new approaches such as Trial@home are creating the need to focus on developing these technologies. At CHDR, two researchers are helping design innovative methods for measuring drug-induced changes in both healthy subjects and patients.

CHDR has always taken a high-tech approach to early-stage clinical drug development. For example, NeuroCart, PainCart, and other systematic measuring tools require state-of-the-art hardware and software. However, there is always room for improvement. Research Director Dr Geert Jan Groeneveld explains the concept. 'As pharmacologists and physicians, we tend to underestimate the complex challenges associated with technology,' says Groeneveld. 'But once you focus on technology, it quickly becomes clear how valuable it can be to work with someone who can proactively develop and strategically think about advanced technologies in clinical drug development.'

'The quality of our data depends heavily on the technologies that we use.'

CHDR welcomes two new staff members

'To study the central nervous system (CNS), as well as in other fields such as cardiology and dermatology, it's important to invest in the best tools available,' says Groeneveld. 'The quality of our data is not only maximised by using clever methodologies and data management systems, but also depends heavily on the technologies that we use. That's why we recently hired two new researchers.

'Dr Ernst-Jan Bos is a medical researcher who studied 3D bioprinting and implant design. Ernst-Jan also launched several start-up initiatives based on developing medical technologies. Dr Robert-Jan Doll is an electrical engineer; for his PhD thesis, Robert-Jan developed methods to observe nociceptive processing. These new colleagues will contribute to our ongoing efforts to develop cutting-edge tools and methodologies.'

Facilitating collaboration through clinical validation

To facilitate the development of emerging technologies, CHDR offers clinical validation services – either at no cost or at a reduced rate – in exchange for early access to novel technologies such as new sensors. This win-win approach has already resulted in successful collaborations with pharmaceutical companies and technology start-ups.

Wearable devices and Trial@home

Our unique approach for collecting data in an outpatient setting, Trial@home, is an important part of CHDR's strategy. Of course, this new approach comes with its own set of technological challenges. To collect data from subjects while they go about their daily business, both at home and around town, CHDR is developing portable devices that contain biosensors for monitoring and recording electrical currents, movement, body temperature, blood/tissue oxygenation, and other parameters. These so called 'wearables' transmit data to a mobile device such as a smartphone or tablet; at regular intervals, the data are then transmitted securely to a central database at CHDR. In addition, subjects can complete brief questionnaires on their mobile device, and they can take pictures of their lesion (for example, in a dermatology study) or their medication (for example, to show compliance with the protocol). If the study calls for biochemical parameters, a courier can be sent to collect saliva, urine, or other biological samples.

Big data

The power of Trial@home lies in the ability to collect vast amounts of data in the subjects' natural environment. These data can be used to study the subject's physiology and responses to the test compound. Importantly, these large datasets ('big data') offer a unique opportunity to zoom in on the details and identify new patterns. At the same time, collecting and analysing big data also poses a challenge. Groeneveld: 'Although several commercial providers claim to have expertise in this area, you need to have a certain level of expertise yourself in order to judge the validity of these claims. This is particularly true when the data are highly sensitive and/or confidential, which is always the case with our data. In this respect, Ernst-Jan can help us make the right decisions.'

Measuring pain

Another example of the importance of technology is a subject close to Groeneveld's heart – the study of pain and pain medication. Using a laser combined with electroencephalography (EEG), researchers may be able to study the pathways between a painful stimulus and the response in the CNS with extremely high precision. 'That might sound easy,' says Groeneveld, 'and to be honest, that's what I thought at first. But Robert-Jan has shown me how difficult it can be to build a robust setup. More importantly, we now know how to build it.'

The increasing complexity of EEG

EEG has always played an important role in neuropharmacology research. In the past, CHDR used a relatively simple 4-lead EEG, which provides a general impression of overall brain activity. In recent years, however, many international guidelines have changed, and they now recommend using a 21-lead EEG. Groeneveld: 'These additional leads provide a lot more information, which is of course valuable, but it comes at the cost of increased complexity. Robert-Jan is now helping us build a robust EEG setup and is coordinating with commercial providers.'

Investing in the future

Groeneveld believes that these two new staff members are a sound investment in our future, similar to CHDR'S investment in developing biochemical and cellular biomarkers. 'We have something unique to offer, and technological development is a top priority. Next year, I hope to be able to report on some of our progress in this exciting new field.'

The EPO study

Can EPO really help you win the Tour de France?

The issue of doping by athletes is rarely investigated in pharmacological experiments. At CHDR, we tested the hypothesis that erythropoietin (EPO) can improve the performance of a well-trained cyclist. By combining laboratory results with a unique field experiment, researchers found that EPO actually has no beneficial effects in terms of helping professional cyclists climb Mont Ventoux, one of the most challenging legs in the Tour de France.

'Doping is essentially the same as pharmacotherapy,' says Jules Heuberger, the project leader in the EPO study. 'You give someone – in this case, an athlete – a substance designed to alter his or her physiology. However, the science behind doping is much less clear compared to the science behind clinical pharmacology. This has led to a lot of prejudice and superstition. With our study, we hope to provide a more rational, fact-based approach to preventing the use of doping in sports. Of course, we don't advocate doping, but current efforts to fight doping are extremely expensive and often irrational, and athletes are frequently exposed to shady practices.'

Prof Adam Cohen, CHDR's CEO, came up with the idea of investigating the efficacy of EPO doping. Cohen explains: 'Every week, in order to stay in touch with clinical practice, I see patients at the nephrology outpatient clinic at Leiden University Medical Centre. Recombinant human erythropoietin – or rHuEPO – is a highly useful drug in patients with chronic kidney failure. In these patients, the kidneys do not produce sufficient levels of erythropoietin to stimulate the body's production of red blood cells. But what works in an anaemic patient might not necessarily help improve the performance of a healthy athlete. In fact, I've always doubted whether EPO actually helped Lance Armstrong win the Tour de France.'

A systematic review reveals no ergogenic properties

The CHDR research team started their investigation by reviewing published literature, looking for potential performance-enhancing (ergogenic) properties of EPO. Their conclusions were clear. The authors writeHeuberger: 'The results of our search revealed no scientific basis to conclude that rHuEPO has any ergogenic properties in elite cyclists. Indeed, the studies had many shortcomings with respect to translating their results to professional cycling. Moreover, the possible harmful side effects of doping had not been adequately researched in this population. Thus, although the use of rHuEPO in cycling is widespread, it's scientifically unsupported by the available evidence, and its use in athletes is tantamount to medical malpractice.'

Developing a field test to measure the efficacy of EPO in sports

No scientific justification for doping with EPO could be found; but at the same time, we were also unable to rule out the possibility that EPO could have a positive effect in professional cyclists. The published studies were performed in groups that do not necessarily reflect professional athletes; the subjects were either non-athletes or had only basic athletic training. More importantly, the endpoints measured in these studies were an increase in haemoglobin and maximum oxygen uptake, not athletic performance. Therefore, a randomised controlled trial measuring actual cycling performance was needed in order to test whether EPO can truly improve an athlete's abilities.

Hurdles in the way of studying doping

Although the study was met with enthusiasm, it was difficult to actually get the trial organised. As Heuberger explains, 'We experienced the same major obstacles faced by scientific researchers studying sports doping in general – obtaining financing and finding suitable subjects. There was – and still is – hardly any funding available for this type of research. And of course, because we wanted to study an off-label use of EPO in the context of sports doping, manufacturers were not interested in sponsoring the study. In the end, CHDR provided the funding for the project. The next challenge was to find subjects comparable to professional athletes. Of course, professional athletes are not willing to participate in a study in which they might receive a banned substance; once a substance has been banned, it can't be studied in the very population that will probably take it. So from a scientific perspective, this is quite a catch-22.'

Sending well-trained amateurs up Mont Ventoux

In 2016, CHDR's efforts finally paid off. A group of 48 amateur cyclists embarked on a three-month trek that ended with a gruelling 130-km race to the top of Mont Ventoux. Half of the cyclists received eight weekly doses of EPO, and the other half received a placebo. At the start of the study, each participant completed an exercise endurance test, which confirmed that baseline performance did not differ significantly between the two groups.

Finally, in June 2016, the 48 cyclists and the CHDR research team travelled to France for the field test. It was an exciting time, and it was challenging for the research nurses who had to maintain GLP procedures as they collected blood samples and other measurements along the side of the road. After the last cyclist passed the finish line amidst the clouds above Mont Ventoux, Heuberger and his team received the first preliminary results: on average, the control group

– the 24 cyclists who received only placebo – were slightly faster than the group that received EPO. ‘Of course,’ says Heuberger, ‘there were still many more variables to analyse, but this first result seemed to confirm our belief that EPO may not be the miracle drug that cyclists believe it to be.’

Can you feel the effects of EPO?

CHDR’s field study generated plenty of interesting results, many of which still need to be analysed and published. One important result concerns an athlete’s ability to ‘feel’ the effect of doping. Heuberger explains: ‘We asked all 48 participants whether they thought they had received EPO or the placebo. If the participants simply guessed, there would be a 50% chance that each participant would guess correctly. To our surprise, the participants who received EPO had less than 50% accuracy, suggesting that a well-trained cyclist likely cannot feel when he uses EPO. Of course, in real life an athlete will know whether he’s doping or not, so there’s probably a placebo effect. Although cyclists often claim that EPO makes a difference in their performance, we now know that the objective effect on the physical performance of trained athletes in a race is rather “underwhelming”; saline injections seem to work just as well.’

Testing for doping

In addition to the promising initial findings from this study, the jury is still out regarding another test; urine was collected from all participants and sent to an internationally accredited laboratory that tests for doping in professional athletes. It will be particularly interesting to see whether this lab can accurately detect the subjects who received EPO, and – more importantly – whether all of the subjects who received placebo will come up clean. ‘Every expert in the field of clinical chemistry will tell you that no laboratory test is always a hundred percent sensitive and specific,’ says Heuberger. ‘False positives and false negatives are inevitable. But in the battle to eliminate doping in professional sports, it’s a common misconception that tests are always perfect. Athletes who test positive – whether accurately or not – will always be viewed with suspicion, even if subsequent tests come back negative.’

‘Even if EPO might not improve athletic performance, it can still pose a threat to the athlete’s health.’

Ineffective, but also unsafe?

So, what is the final verdict regarding the use of EPO in professional sports? Based on the early results of our field test at Mont Ventoux, it is highly unlikely that EPO improves the performance of cyclists, at least to the extent commonly believed. CHDR expects that the remaining results from the study will provide further insight. Regardless of the outcome, EPO will certainly stay on the list of banned substances in professional sports, and rightly so, says Heuberger. ‘Substances and/or methods that meet the following criteria will always be banned: if they enhance performance, if they pose a threat to the athlete’s health, or if they violate the so-called “spirit of sports”. Even if EPO does not improve performance, it can still pose a threat to the athlete’s health; EPO stimulates the production of red blood cells, increasing the blood’s viscosity. This can affect circulation and may cause dangerous blood clots to form.’

These health risks are more than just a theory. Between 1987 and 1990, when EPO became a highly popular form of doping among professional athletes, at least 20 Belgian and Dutch cyclists died in their sleep from a heart attack. There are strong suspicions that many – if not all – of these untimely deaths of healthy, young athletes were caused by EPO or another form of doping. Cohen: ‘We know that in sports, superstition often prevails over rational judgement. Nevertheless, we hope that our study results will convince athletes to avoid taking EPO.’

A study riddled with many challenges

Cycling up Mont Ventoux is a challenge for every athlete. But for the research team from CHDR, the entire study was nearly just as challenging. Prof Cohen explains: 'Performing a study in a well-equipped, highly controlled research unit is completely different than running a study by the side of the road at the top of a windy mountain, particularly if you want to maintain the same standards of high quality!'

CHDR's EPO study was challenging long before the team made the trip to France. 'Each of the 48 participants came to our facility 18 times, either to receive an injection or to undergo an endurance test,' says Project Leader Jules Heuberger. 'As with other clinical trials, timing is key. Ideally, you want to administer the drug or placebo to all participants at the same time, and you want to collect the measurements at the same time. Usually, you can divide the participants into smaller groups, but here all of the participants had to follow the same schedule to guarantee they would be ready for the final test at Mont Ventoux on the 19th of June. So, we worked hard to ensure that both the injections and the tests were administered as closely as possible.' Heuberger adds, 'With each participant spending about two hours at the facility each visit, it was quite an intense protocol.'

Blinding both the participants and the researchers

The double-blind procedure used for this study was more complex than usual, as the EPO dose had to be adapted to match the drug's effects. Heuberger explains: 'We wanted to keep the subjects' red blood cell counts within strictly defined limits. When each participant came for their injection, we took a sample of blood for analysis at our facility. We then used an algorithm to calculate the appropriate dose for each participant in the EPO group. A random generator also produced different volumes of placebo, so there was no visible difference among the vials. We also used a special soluble and colourless form of EPO. We organised everything carefully so that both the investigators and the participants had no idea who was receiving EPO and who was receiving placebo.'

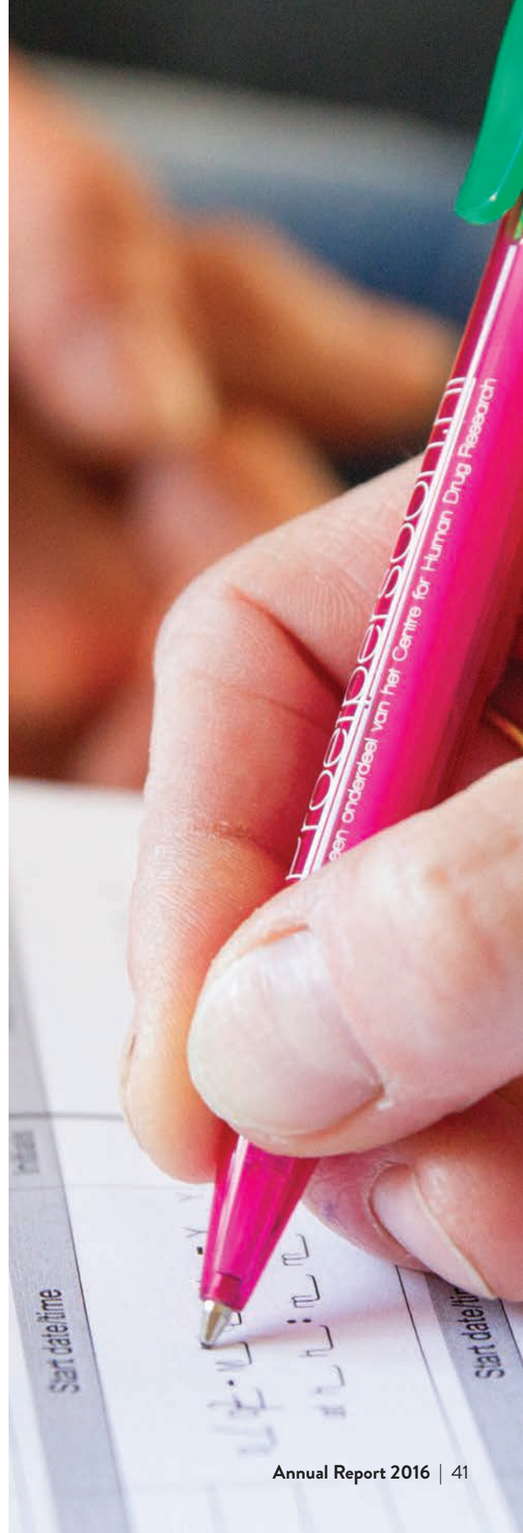
Expensive cargo

'A very intense weekend.' That's how Heuberger describes the Mont Ventoux adventure. His enthusiasm is clearly visible as he tells the story. He talks about the meals together, the ride in a tour bus, and the moment of truth at their final dinner in France when the statistician revealed the surprising news that the placebo group performed a little better than the EPO group. He also talks about the hard work, for example stowing all of the racing bicycles safely in a truck for transport. 'With more than 50 top-notch racing bikes, that was an expensive truckload!' And he talks about the sheer complexity of it all, from ensuring the study protocol was followed, to the logistics associated with a cycling race.

A bit of luck

'We made a small lab in one of the apartments where we were staying,' says Heuberger. 'And we had a similar setup in a van, where we could analyse the blood from the cyclists both before they started and after they finished. Having a team of five nurses ensured that we could draw blood from all participants almost simultaneously. And just in case, we had technical equipment for the bikes and a traumatologist on hand.'

In the final stretch of the race, on the misty wind-swept mountain, Heuberger and Cohen had to show the route to the cyclists. Finally, each participant passed the finish line, providing the most essential data point in the study: the time. Heuberger: 'Everything went exceedingly well. Of course, we spent months in careful preparation, but we also had a bit of luck. On the Saturday when we arrived, Mont Ventoux experienced heavy rains and extremely low temperatures, so the road was covered in ice; it would have been impossible to complete the race on that day. That's when I realised just how lucky we were.'



‘Highly knowledgeable and professional’

‘CHDR offers services that are quite unique; in this respect, CHDR does not have any real competitors. CHDR is also highly professional. Of course, small issues can arise from time to time, but that’s to be expected when two companies work together. Importantly, though, regardless of the issue, CHDR always deals with it in a very professional way. I’m very satisfied with our relationship with CHDR. Communicating with their staff is always easy, and they’re knowledgeable, responsive, and friendly.’

Clinical Pharmacologist,
Pharma Company

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

Operations at CHDR

Operations at CHDR: streamlining innovative research support

We are pleased to report that the trends established in previous years continued in 2016. Studies conducted by CHDR – including trials with patients – continue to increase in both number and complexity. To accommodate these increases, CHDR has invested in personnel, automation, and the overall support of operations. Chief Operations Officer Dr Pierre Peeters is proud of his team's achievements. 'We now have the tools to support this growth, and we can continue to accommodate our sponsors' wishes and develop new innovations.'

The past year has again been highly productive, as reflected by 58 studies involving nearly 1000 healthy subjects and more than 400 patients. Most of these volunteers stayed at CHDR; however, a growing number of volunteers participate in outpatient trials (for example, using CHDR's Trial@home). In short, business continues to thrive.

Keeping operations up-to-date through automation

'When you scale up operations, you often need to organise and think about things differently,' says Peeters. 'In recent years, we've had to keep up with our own growth. In some ways, we were still using the tools and approaches of the past, when things were much simpler. If the number of studies is relatively limited and you don't have many subjects staying at the facility, then planning can be quite simple. But thanks to our growing workload, we've had to introduce software to support the entire process, from initial contacts with potential sponsors through to the final evaluation – and everything in between. In this respect, we've made several key improvements over the past year. For example, the acquisition and planning of operations are now fully automated. To increase our efficiency even more, we are now streamlining the processes involved in writing protocols and planning statistical analyses.'

Becoming fluent in the 'language' of clinical data

Updating our software and ICT support has been essential for helping sustain our organisation's growth; moreover, it helps us comply with changes in external requirements. A case in point is the FDA's official adoption of new standards from the Clinical Data Interchange Standards Consortium (CDISC), which will soon become the worldwide standards for pharmaceutical dossiers. Peeters explains: 'The CDISC standards, including the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM), have become the "Esperanto" of dossiers. For agencies such as the FDA and EMA, it provides a complete overview of all studies performed on any given topic. For example, all dossiers prepared in accordance with these standards use "AE" for "adverse effects". To conform to this international standard, we have updated our Promasys software, which we use to collect data. And beginning in the second quarter of 2017, we will be able to deliver SDTM and ADaM datasets for nearly all of our trials.'

'At CHDR, we've streamlined and improved the entire planning process to accommodate our increased workload.'

Recruitment

Finding the right subjects at the right time

Recruiting enough subjects to accommodate the increasing number of trials at CHDR can be challenging, particularly given the growing demand for patients with specific conditions. Overcoming this challenge requires some highly creative solutions.

In 2016, CHDR's Recruitment Department included 6 employees. 'It's not a big team,' says Herbert Anholts, head of the department, 'but it's a good team.' During his time at CHDR, Anholts has witnessed a growing need for test subjects. In the early days, sufficient numbers of participants could usually be obtained locally, for example among the students at Leiden University. Today, however, recruiting efforts require an active database of healthy volunteers and patients in order to meet the needs of CHDR's studies. The majority of healthy volunteers are young adults – usually students – who like staying at CHDR's facility because it provides a nice atmosphere, they are treated with respect, and in many cases there is plenty of time to study and relax. There is also a growing group of healthy elderly volunteers who participate in trials to study medications designed for their age group. Anholts explains: 'Many people who volunteer for a study readily volunteer again. Of course, there are rules and regulations that prevent a person from participating too frequently, so we sometimes have to ask them to wait. Overall, you can tell that they really like it here.'

Timing is everything

When recruiting healthy volunteers, the main challenge is timing. Although we cannot begin to recruit until the protocol has been approved by the ethics committee, after the protocol has been approved, the study could be scheduled to start in just a few weeks. This creates a rather narrow window in which to recruit sufficient numbers of patients. 'Usually, that's not a problem,' says Anholts. 'But sometimes the protocol has highly specific selection criteria, or it's planned for a time of year in which students are busy with exams. In these cases, it can take extra effort to ensure that enough volunteers are ready, and at the right time. We also need to consider that many volunteers do not come in for pre-screening, and some subjects may not complete the study for various reasons. So as a rule of thumb, we always try to recruit at least twice as many subjects as the study requires.'

More patients

In recent years, CHDR has been conducting an increasing number of patient studies, often following up on previous studies with healthy volunteers. Anholts explains: 'If we need patients with a relatively common disease such as diabetes, psoriasis, or depression, our

department can usually recruit a sufficient number of subjects. We place ads in both conventional and social media, we contact patient organisations, and we place banners on Facebook pages dedicated to specific disorders – anything to help us reach potential subjects. In addition, some patients will be referred to us by their physician.

'On the other hand,' continues Anholts, 'some studies focus on a relatively rare disease or a specific subgroup of patients; in this case, in addition to the methods listed above, the project leader will usually turn to his or her network of medical specialists in order to find enough patients.'

Cyclists and doping with EPO

In terms of recruitment efforts, our 2016 study on sports doping with EPO (erythropoietin) posed a unique challenge (see page 34). Our Recruitment Department needed to find amateur cyclists who were willing to receive injections of either EPO or placebo. The cyclists were also required to visit CHDR fairly often for testing and to receive the injections. And finally, they needed to participate in a field test conducted on Mont Ventoux, one of the most notoriously difficult legs of the Tour de France.
'Initially, our call for subjects drew quite an enthusiastic response,' says Anholts. 'More than 570 people were interested. But for various reasons, the majority were unable to participate. For example, quite a number of people from abroad were interested, but we wanted participants who understood Dutch, especially for informed consent. We also needed to recruit well-trained cyclists who were physically comparable to professional cyclists. Finally, most amateur Dutch cyclists are affiliated with the Dutch cyclists' organisation KNWU[1]. Initially, KNWU was strictly opposed to exposing their members to a study in which they could receive EPO injections; in a way, that's understandable, given the stigma associated with EPO in cycling. So even though more than 130 volunteers were eligible for the study, we worried that we would not have enough participants. Luckily, we found a solution that satisfied KNWU: they allowed the cyclists to temporarily leave the union, participate in the study, and then return to KNWU. Thanks to this compromise, we had nearly 50 well-trained cyclists, and we could finally begin the study.'

To France

The EPO trial is also a nice example illustrating how the Recruitment Department is often asked to go above and beyond simply recruiting subjects for a study. CHDR recruiters arranged to transport the cyclists, the researchers, the cycling gear, and the laboratory equipment from Leiden to Mont Ventoux for the crucial field test. They also had to arrange housing, local transportation, and catering for the entire weekend. As Anholts explains, 'Our team loves to organise. This passion shows in our willingness to participate in student activities and other events in order to draw attention to CHDR. Sometimes, if subjects need to stay at our facility for an extended study, we'll organise special entertainment programmes. It's important for our subjects to have fond memories of CHDR, and it's fun for us to go the extra mile for our subjects.'

[1] *Koninklijke Nederlandsche Wielren Unie (in English: the Royal Dutch Cycling Union)*

‘CHDR consistently delivers high quality’

‘CHDR’s staff are highly knowledgeable and innovative, making CHDR a rather unique CRO. I expect high quality, and CHDR always delivers within the agreed timeframe. Our recent study was run successfully, so it was win-win for both parties.’

Clinical Study Manager,
Top 10 Big Pharma Company*

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

Neuro-degeneration

Drug development and neurodegenerative diseases

CHDR is contributing to the development of new drugs against neurodegeneration. For example, we are developing biomarkers to demonstrate a compound's effects in healthy volunteers, and we are expanding our abilities to perform research in patients with Alzheimer's disease and other neurodegenerative diseases.

Treating neurodegeneration is one of the most pressing – yet currently unmet – issues in modern medicine. Both the prevalence and incidence of patients with these diseases are increasing as a result of our ageing population and improvements in healthcare. Fortunately, basic and clinical research provide important insights into the pathogenesis of these diseases, and an increasing number of drug targets are being investigated. In many cases, these targets will likely be relevant only within a subpopulation of patients, as several pathways can have the same pathological outcome and the same clinical diagnosis. Dr Geert Jan Groeneveld, a neurologist and Research Director at CHDR, explains. 'This is a challenge in drug development,' says Groeneveld. 'Several of these compounds will receive an orphan designation, as the drug will be effective in only a relatively small subset of patients. With these new drugs, I believe it's even more important to obtain as much information as possible in the earliest stages of development; in turn, this will help design the clinical trials.'

Common pathways

In their final pathogenic steps, various neurodegenerative diseases can have common pathways. Genetics research regarding neurodegenerative diseases has identified many such common pathways, including inflammation. If a compound can slow – or even stop – these pathways, it might be effective for treating several neurodegenerative disorders.

New approaches

The new compounds that reach the initial stages of clinical drug development – both today and in the coming years – require a new approach at CHDR. Groeneveld: 'Unlike classic CNS drugs, these compounds do not act on synaptic receptors. Because of this, in many cases the standard NeuroCart tests in healthy volunteers will not be particularly relevant, so we will have to rely on other biomarkers. We are currently developing and validating new biomarkers and methods, and we're ready to test these new compounds.' For more information, see page 94.

More patients

'In addition to strategies designed to provide proof-of-pharmacology in healthy subjects, we also need to increase research in patients,' says Groeneveld. Indeed, this is one of CHDR's main strategic goals. Using Ready4Research, CHDR's unique approach to patient recruitment, a wide variety of strategies are used to recruit specific patient groups even before an applicable research protocol has been developed. Our collaboration with outpatient clinics for recruiting patients with cognitive problems is a good example (see text box).

Cholinergic compounds

For years, CHDR has been involved in the development of several compounds that act on the cholinergic system in the CNS. For example, cholinergic agonists are used to improve cognitive function in patients with Alzheimer's disease, and CHDR developed so-called 'challenge tests' to demonstrate the pharmacological effects of these compounds in healthy volunteers. In the past year, CHDR

Using biomarkers to measure the action of next-generation CNS drugs

New drugs are currently being developed to slow disease progression in neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and ALS. However, it is often not possible to measure the pharmacodynamic effects of these compounds in healthy subjects. Usually, CHDR's solution is to use a challenge model, in which we temporarily and safely induce a symptom in a healthy subject. For example, to measure the effects of cholinergic drugs on cognition, a healthy subject can be given an anticholinergic compound (e.g. scopolamine or mecamylamine), thereby experiencing a temporary decrease in cognitive performance. In this context, the test compound can then be administered, and its ability to restore cognitive function can be measured. Groeneveld: 'In the case of enzyme inhibitors designed to stop neurodegeneration, such a challenge model would be ethically irresponsible. Nevertheless, we plan to measure the effect of the test compound on pharmacodynamics in the earliest stages of the drug's development.'

Testing novel neurodegeneration-related pathways

In some cases, it may be possible to determine whether such a drug is active in healthy subjects. For example, in collaboration with a sponsor, CHDR developed an indirect way to measure the effect of a compound designed to inhibit a cell death pathway related to inflammation. This compound inhibits the activity of specific enzymes involved in signalling. To measure the drug's effect in healthy subjects, Dr Matthijs Moerland and his colleagues at CHDR developed an *ex vivo* assay in collaboration with the sponsor. They found that healthy volunteers who received the test compound had a dose-dependent decrease in enzyme activity, providing a robust method of quantifying the drug's pharmacological effect. Of course, the next step is to test the drug's effects in patients with a neurodegenerative disease.

completed several studies using a muscarinic M1 receptor agonist in healthy subjects of various ages. Next year, patients from CHDR's Alzheimer's disease network (see text box) will participate in a follow-up study to investigate the effects of this agonist in patients with cognitive symptoms.

At risk for developing Alzheimer's disease

In the future, Groeneveld and his colleagues plan to establish a cohort containing several thousand people age 70 and older with no sign of Alzheimer's disease. These people will all be screened using NeuroCart, additional cognitive tests, and basic blood tests. They will also be asked to undergo a lumbar puncture to collect cerebrospinal fluid (CSF), which will be tested for known biomarkers associated with Alzheimer's disease. Groeneveld explains: 'We will use these biomarkers in the CSF to develop an algorithm for predicting the likelihood that someone with a specific biomarker profile will develop Alzheimer's disease. We will test this algorithm using PET [positron emission tomography] data. This will provide a cohort of individuals who have a biomarker profile consistent with Alzheimer's disease but no cognitive symptoms. This is really the Ready4Research approach at its best; when compounds designed to prevent Alzheimer's disease reach the clinical development stage,

'In addition to providing proof-of-pharmacology in healthy subjects, we also need to increase studies with patients.'

we'll already have a large pool of potential subjects. Of course, from an ethical perspective, we'll need to be very careful and respect the individual subject's wishes regarding whether they want to know if they are at risk or not.'

Measuring myelination

A good example of using elegant methods to demonstrate pharmacological effects in patients is our 2016 study in patients with multiple sclerosis (MS), which is characterised by the destruction of the myelin sheath that surrounds neuronal projections. 'This study was possible thanks to our close collaboration with ophthalmologists and neurologists at VU Medical Centre (VUmc) in Amsterdam,' explains Groeneveld. 'We were looking for sensitive methods to measure myelination in order to test the efficacy of a new generation of compounds designed to restore myelination in patients with MS. Their solution was to monitor internuclear ophthalmoplegia (INO), a phenomenon often observed in patients with MS in which lateral eye movements are affected.

A growing network of collaborations with outpatient facilities for Alzheimer's disease

Most hospitals in the Netherlands have an outpatient clinic that specialises in elderly patients with impaired memory and/or cognitive function. In addition to providing diagnostic facilities (for example, to determine whether a patient has a treatable condition or a non-treatable form of dementia), these clinics offer advice and guidance to patients with Alzheimer's disease and their families. To tap into this valuable network, CHDR is establishing collaborations with these outpatient clinics, thereby facilitating the recruitment of patients with Alzheimer's disease who may wish to participate in upcoming drug trials.

The monocentre approach

If a sponsor wishes to evaluate the specific effects of a test compound, CHDR can easily find a suitable group of patients with the required clinical characteristics, thanks to our vast network. The research itself can then be conducted at the CHDR facility in Leiden. Healthcare professionals from the referring outpatient clinics help design the study protocol and contribute to the resulting publication, but patient selection, drug administration, and all relevant measurements are done centrally at CHDR. This so-called 'monocentre approach' is one of CHDR's key strategies, and it has been highly successful, reducing study variability, allowing researchers to perform complex, sophisticated measurements, and contributing to patient safety.

Easy to implement

From a practical perspective, implementation is relatively clear and simple. Samantha Prins, a staff neuropsychologist at CHDR, has established contacts with all hospitals within a radius of approximately 60 km around CHDR. Prins also attends multidisciplinary meetings at the hospitals' outpatient clinics and helps with patient selection. If a patient is found to be eligible for a specific study, the patient's neurologist will ask if he or she would like to participate in the study. Interested patients can then contact CHDR for more information. From that point on, everything – including the taxi ride to Leiden, if necessary – is handled by CHDR. Groeneveld explains the benefits: 'For our colleagues at the hospital, our approach provides a unique opportunity to participate in clinical research without detracting from their clinical responsibilities. For us, it means that we have clear access to a group of patients who would otherwise be difficult to reach. And the most important element – the patients themselves – retain the freedom to decide whether they wish to participate.' Clearly, this approach works: the first study in patients with Alzheimer's disease is scheduled to begin in 2017.

Together with CHDR, VUmc acquired a device that can measure these eye movements with extremely high accuracy, at a rate of 1000 frames per second! We then used this device to measure eye movement in patients with MS. Thanks in part to our innovative recruitment strategy, we quickly enrolled 24 MS patients with INO and completed the study within a year.'

Using a registered drug to demonstrate effects

In these 24 patients, researchers attempted to identify a correlation between changes in INO and demyelination of the affected nerve tract – in this case, the medial longitudinal fasciculus – visualised using a 3-Tesla MRI. Changes in eye movements are believed to reflect impaired conduction in the nerve fibres between the ocular muscles and the brainstem nuclei involved in lateral eye movements. Groeneveld: 'The added value of this new method is that it allows for extremely precise measurements of these eye movements, enabling us to detect highly subtle abnormalities. This allowed us to track precisely how the disease leads to reduced nerve conduction.'

In their study, Groeneveld and his team also exploited the high sensitivity of the measurements in order to study pharmacological effects. In a placebo-controlled cross-over experiment, patients received the potassium channel blocker fampridin (Fampyra®) and placebo. Fampridin is registered for use in treating walking difficulties in patients with MS.

The results were striking – compared to placebo, giving patients a single dose of fampridin significantly affected eye movement. 'This shows that we have a highly sensitive test, says Groeneveld. 'If I want to test a compound designed to restore myelination, I would select MS patients with INO who had a positive response to fampridine, as these patients may have intact, functional nerve fibres that are simply demyelinated. Then, in this cohort we could use our device to monitor whether eye movements improve following treatment with a putative myelination-promoting compound. At CHDR, we believe strongly in validating a new methodology using a well-known and well-characterised drug. In collaboration with University Medical Centre Utrecht, we also performed a similar study to validate a different clinical measurement in patients with amyotrophic lateral sclerosis (ALS).'

CNS function

Investigating brain function in both sickness and health

At CHDR, we can study the pharmacology of CNS drugs using functional test batteries such as NeuroCart, PainCart, and driving simulators, as well as imaging techniques such as resting-state fMRI and PET. Using these tools, CHDR researchers investigate how the target systems function both in healthy subjects and in patients.

For nearly three decades, our NeuroCart test battery has been one of CHDR's most essential tools. NeuroCart covers a wide range of neurophysiological and neuropsychological functions, and it can be used to show that a compound changes a specific function in the brain in a dose-dependent manner. At the very least, NeuroCart can be used to demonstrate that the compound passes the blood-brain barrier. In many cases, NeuroCart can also provide additional information regarding the neurological systems that the compound affects, providing an early glimpse into the compound's desired effect and/or adverse effects.

As Research Director Prof Joop van Gerven explains, NeuroCart is always evolving. 'To study a specific neurotransmitter system, we sometimes have to add new features. Plus, because more of our studies include patients, we also characterise how the disease state affects the results of the test batteries. We've already learned quite a bit about how our tests reflect changes in neuropharmacology, and now we're learning about the effects of disease.'

Green Dino: a driving simulator test

In addition to NeuroCart, CHDR also uses a driving simulator made by the Dutch company Green Dino. 'We can use the simulator to test whether a compound affects the driving performance in both healthy volunteers and patients,' says Van Gerven. 'Importantly, many regulatory authorities such as the FDA now accept evidence obtained using a driving simulator; in the past, these agencies would require that real-life driving tests were performed. And of course, with a driving simulator, you can introduce specific situations – for example, a near-collision – in order to safely measure the subject's response in ways that would be impossible or impractical in actual traffic. It's also quite interesting from a scientific perspective, as driving a car is a highly complex skill involving many systems. In contrast, many of the tests in NeuroCart involve relatively simple tasks such as following a moving dot using a joystick. Combining these two approaches provides a more complete overview of how changes in CNS functioning affect real-life complex skills such as driving.'

Using the driving simulator in patients with Huntington's disease

CHDR scientists are now studying how Huntington's disease affects driving skills, as well as the effects of presymptomatic patients identified with genetic testing. A standard set of tasks in the driving simulator and NeuroCart is applied to presymptomatic patients and early-stage patients, and the results are compared against a control group of healthy subjects who are not carriers of the Huntington mutation.

As Van Gerven explains, 'One of the goals of this study was to objectively measure the effect of developing Huntington's disease on driving ability, which is an important first step to helping patients drive safely, allowing them to keep their licence as long as possible. For us, it shows the clinical relevance of using the more practical driving simulator compared to the basic tests used in NeuroCart. And of course, we can now evaluate new drugs for treating Huntington's disease, as we have a baseline score for comparison.'

Some neuroactive drugs do not necessarily change brain activity

NeuroCart has been an invaluable tool in neuropharmacology, helping identify dose-dependent changes in the brain. But as Van Gerven explains, some neuroactive compounds do not directly change activity in the brain. 'Sometimes, the brain's activity remains unchanged by the drug, but the sensitivity of the target area to certain stimuli changes. To measure the effects of such compounds, our standard test battery may not be enough. It's similar to testing the performance of a car with a supercharged engine. If you measure performance only when the engine is idling, you'll miss the effects of the supercharger. So, you need to develop specific tasks and challenges designed to investigate the effects of these drugs.'

'Because many of our studies include patients, we can also investigate how the disease state affects test results.'

Prof Joop van Gerven, Interim President of the Central Medical Ethics Committee

In the first half of 2016, CHDR Research Director Joop van Gerven was asked to serve as the Interim President of the Dutch CCMO (Centrale Commissie Mensgebonden Onderzoek; in English: the Central Committee for Research in Humans) the central medical ethics committee in the Netherlands. The CCMO serves as the Competent Authority for clinical studies and is responsible for evaluating protocols regarding specific types of medical products such as gene therapy and other ethically complicated studies. As a member of CCMO since 2011, Van Gerven finds it interesting to play a role in cutting-edge ethics and methodological questions. 'I enjoy contributing to the committee's work,' says Van Gerven. 'Thanks to my highly capable colleagues here at CHDR, our work has continued uninterrupted despite my absence while serving as Interim President. Of course, I try to be here at CHDR as often as possible, but I've had to delegate many of my responsibilities. In 2017, I plan to return to CHDR full-time.'

The elusive function of the orexin-2 system

To illustrate how complicated neuropharmacology can be, Van Gerven discusses their study regarding the neurotransmitter orexin and its receptors. 'The orexin-1 receptor plays a role in wakefulness and attention, and patients with narcolepsy fall asleep suddenly due to a lack of orexin. We've been investigating the potential of using orexin-1 antagonists as a sleep aid. In contrast, the function of the orexin-2 receptor is poorly understood. I'm convinced it has to do with a specific form of attention in the context of threats and gathering food. To be an effective hunter, you probably need a well-functioning orexin-2 system. But if you're just sitting on the couch watching a romantic comedy, you may not even notice if orexin-2 function decreases in your brain. As you can imagine, it can be difficult to measure the activity of orexin-2 – or its antagonists – until you have a clear picture of the receptor's function. Now that we have an idea, we can develop functional tests. That's what makes our work so interesting – we're always looking at problems from the perspective of brain function.'

Setting the standard for resting-state fMRI

In the past decade, CHDR, Leiden University, Leiden University Medical Centre, and Oxford University have been pioneers in the application of resting-state functional MRI (RS-fMRI) in neuropharmacology. With conventional fMRI, the subject performs a mental or sensory task during an MRI scan. fMRI is used to visualise blood flow through various brain regions, revealing which regions are active during the task. With resting-state fMRI, the subject is instructed to simply relax with his/her eyes closed. Several neural networks have been discovered by analysing synchronous activity in several brain areas at rest. Moreover, the activity of these networks often changes under pathological conditions such as depression and psychosis, and psychoactive drugs can cause a measurable change in activity within these networks.

Over the course of several years, CHDR and its research partners created a library of RS-fMRI profiles using well-known drugs. Now, RS-fMRI is being used to investigate new compounds. As Van Gerven explains, 'Together with sponsors, we are now developing a standardised approach for studying, analysing, and presenting pharmaco-MRI results.

'Next year, we hope to delve even deeper into the CNS networks involved in depression in order to explain the antidepressant effect of ketamine. When you know more about disease mechanisms and the pathways underlying pharmacology, you can develop better drugs.'

‘The right partner for specialised studies’

‘CHDR has a strong scientific background and many specific and specialised pharmacodynamics tools, including NeuroCart, a unique tool not available elsewhere. This makes CHDR the right partner for highly specialised studies. In our study, the various phases went well, and I was pleased with the quality of service at each stage. I’m very satisfied with our relationship, and I found the staff at CHDR to be easily accessible and helpful.’

Experimental Medicine Clinical Scientist,
Top 10 Big Pharma Company*

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Psychiatry

A tighter focus on patient studies

Since it was founded nearly 30 years ago, CHDR has been studying how candidate psychiatric drugs affect the central nervous system (CNS). While most of this work has been conducted in healthy volunteers, CHDR' focus has shifted towards studies in patients with mood and/or anxiety disorders. This shift has meant tackling various practical challenges, for example choosing validated methods for demonstrating relevant drug effects, as well as recruiting and caring for patients.

'We're currently taking the next step in our ongoing CNS drug development programme,' says Dr Gabriël Jacobs, the Research Director of Psychiatry at CHDR. 'Sponsors familiar with CHDR will already know that we have nearly three decades of experience developing and applying robust psychopharmacology methodologies. For example, our neurological test battery, NeuroCart, is now practically a household name in the field. Moreover, in collaboration with Leiden University Medical Centre (LUMC), we're one of the first research organisations to offer pharmacological resting-state fMRI (see page 73). We're also in the process of developing and validating various new methodologies, including wearable biosensors and new smartphone apps that record patient-reported outcomes (PROs). Together, these technologies enable us to study drug effects even when the patients are at home, going about their daily business. We believe this combination of technologies and methodologies will improve our understanding of how new psychiatric drugs work. We also hope that these new methods will help us streamline the traditional approach to trials, an approach that often requires the use of psychometric questionnaires and semi-structured interviews in a controlled environment.'

Recruitment efforts

The recent shift towards patient studies has been gradual. But now that Jacobs is in charge of clinical studies involving psychiatric patients, the number of studies involving patients is increasing at a steady rate. To keep up with the demand for subjects, CHDR has put considerable effort into improving the process of recruiting patients with mood and/or anxiety disorders. 'In addition to our well-established recruitment infrastructure, which uses various forms of social media,' says Jacobs, 'we're teaming up with an increasing number of partners who are interested in referring patients and collaborating on projects.' For example, CHDR has established collaborations with the psychiatry departments at several academic medical centres. Close contacts have also been established with NedKAD (the Dutch knowledge centre for anxiety and depression) and with various patient advocacy groups. Jacobs: 'These are well-known institutions and societies, and patients who see our recruitment notices on their websites can be confident that CHDR is a trusted partner.'

Communicating with healthcare professionals

Jacobs notes that when a patient agrees to participate in a study, it is important to involve his/her general practitioner, psychologist, and/or psychiatrist. Jacobs: 'In general, mental healthcare providers who treat patients with depression are hesitant to recommend that these patients participate in a scientific study. And I think that's fair. As a psychiatrist myself, if one of my patients chooses to participate in a study, I want to be certain that his or her safety and well-being have the highest priority. Some of my colleagues are even more sceptical, particularly if the research is sponsored by a drug company. So it's essential to involve healthcare providers in the recruitment process by communicating with them clearly and being completely transparent about what we do and what CHDR stands for. Of course, this is the key to successful patient recruitment, but it also provides patients with the best possible care

Demonstrating relevant yet short-term effects of psychiatric drugs

Evaluating new compounds in small patient cohorts within a relatively short period allows CHDR researchers to determine whether or not a compound has relevant pharmacodynamic effects. If an effect is found, we know that the drug may be suitable for future testing in larger trials. On the other hand, the limited duration of these studies occasionally presents us with an additional challenge: when testing drugs that are currently available for treating depression, several weeks of treatment are usually needed before any clinically relevant effects are seen. The same is true for the anxiolytic effects of drugs used to treat anxiety disorders. This leads to the question of whether it might be possible to determine the potentially beneficial effects of a new drug for mood disorders or fear in such a short time frame.

CHDR is currently conducting research and developing methods that could help us answer this question. For example, sleep deprivation often induces an acute – but short-lived – antidepressant effect in patients with unipolar depression. Researchers at CHDR are now studying whether new compounds can prolong these sleep deprivation–induced antidepressant effects. Similarly, in both healthy volunteers and patients with panic disorder, temporary inhalation of carbon dioxide (CO_2) can induce symptoms that resemble a panic attack. Therefore, a new compound that helps prevent or mitigate these CO_2-induce symptoms is likely to have an anxiolytic effect. In both of these examples, comparing the effects of various doses of the compound with the effects of placebo helps us build a strong case in support of the candidate drug's relevance within the intended patient group.

Dr Gabriël Jacobs becomes the new director of clinical psychiatry studies

In May 2016, Dr Gabriël Jacobs became the Research Director of the Psychiatry unit at CHDR. Jacobs trained as a psychiatrist and clinical pharmacologist at both LUMC and CHDR, and he conducted his PhD research at CHDR, studying methods to measure function in the hypothalamus-pituitary-adrenal (HPA) axis. Jacobs then worked as a consultant in psychosomatic medicine at the VU Medical Centre (VUmc) in Amsterdam, while continuing to conduct research at CHDR.

'As a psychiatrist,' says Jacobs, 'I was trained to see myself as a primary tool in diagnosing and treating patients with psychiatric disorders. While this is of course true, we should always remember that pharmacotherapy is also an indispensable tool. That's why I believe that psychiatrists need to incorporate knowledge regarding clinical pharmacology into their daily practice. At CHDR, we give psychiatrists-in-training the opportunity to become clinical pharmacologists and conduct their PhD research in psychopharmacology. From my own experience, I know that this approach can make you a more effective psychiatrist.'

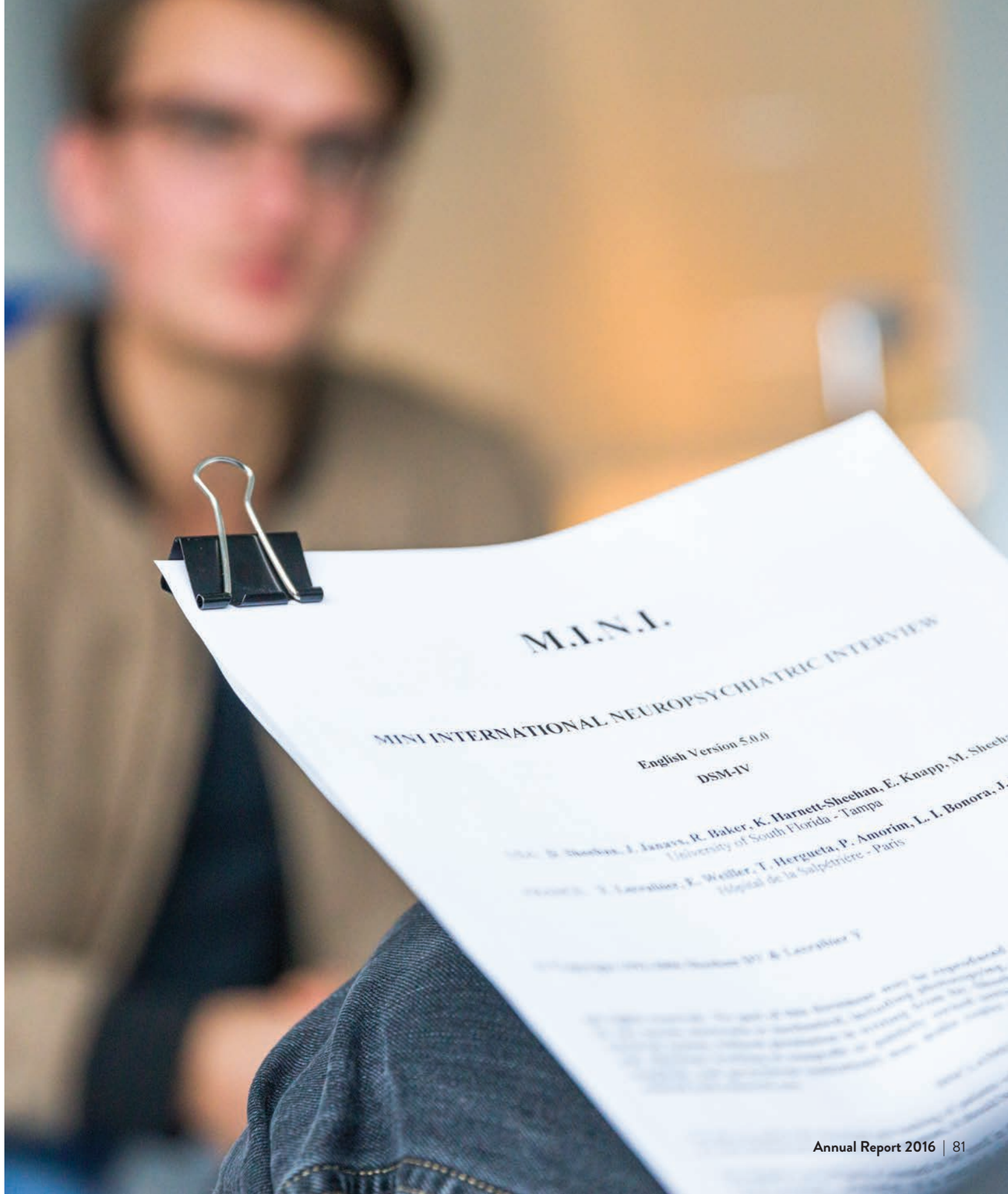
In addition to his position at CHDR, Jacobs also works as a consultant at LUMC, where he runs an outpatient department that specialises in therapy-resistant depression. Jacobs also shares his knowledge and experience in psychiatry and clinical pharmacology through teaching, for example by writing textbooks on various psychopharmacology topics and by helping develop guidelines.

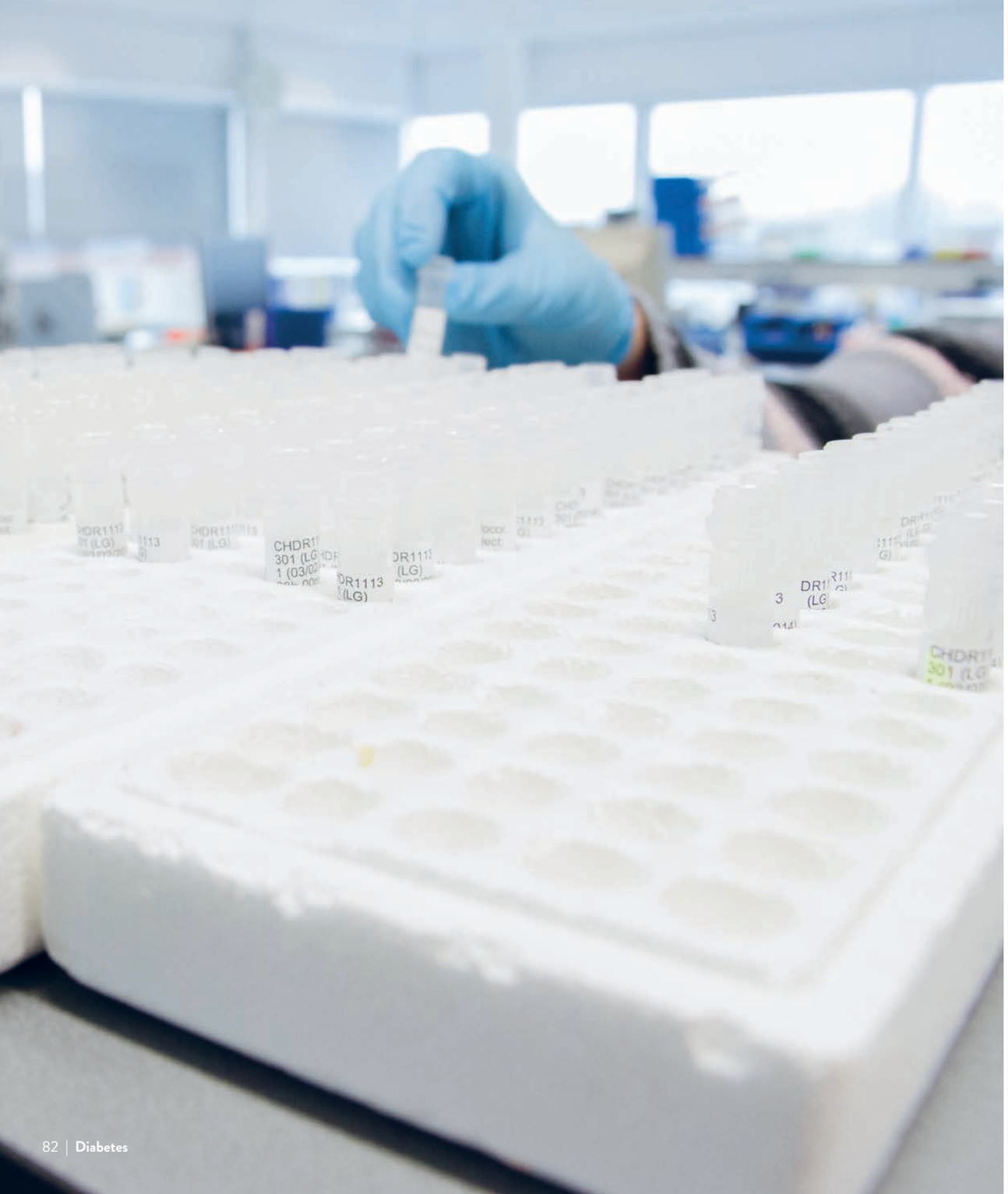
during their participation, and it ensures adequate follow-up after the study has ended.'

Caring for patients

For CHDR's staff, caring for patients with depression and/or anxiety obviously requires a different approach compared to healthy volunteers and patients with a more physical illness. 'We now have a dedicated group of physicians who have been trained to select patients for psychiatric studies,' says Jacobs. 'During the selection process, these doctors administer a series of widely used and well-established psychometric tests, all under my supervision. The nurses and research assistants who will care for the patients receive specialised training, and they also receive refresher courses at regular intervals.'

Carefully selecting subjects before a study and closely monitoring the patients during the study help prevent psychiatric emergencies. Nevertheless, if the need arises, our staff members are fully trained to deal with such emergencies, and the local psychiatric emergency service is always on hand to evaluate or even treat any patient who needs additional help. Jacobs: 'At the end of each study, we always ask the patients about their experiences, including their stay at our facility. And any comments and suggestions are then used to help us improve the patients' experiences even further.'





Diabetes

Can a drug truly ever replace bariatric surgery?

As in previous years, last year CHDR tested several promising compounds that affect the cardiovascular system and metabolism. Here, we discuss a particular study designed to test a new class of drugs for diabetes. The scientific story of these gut-derived hormones, called incretins, started over a century ago. Hopefully, these compounds also have a promising future.

The World Health Organization has classified type 2 diabetes mellitus as a global epidemic. In 2010, an estimated 285 million people worldwide had diabetes, an increase of nearly 1000% compared to 1985. According to Prof Koos Burggraaf, Research Director of the Cardiovascular System and Metabolism research unit at CHDR, 'Treating type 2 diabetes is notoriously difficult. The problem is that we try to treat it using the same approach we use to treat type 1 diabetes, which is a different disease entirely. With type 1 diabetes, the body does not make enough insulin; with type 2 diabetes, the body produces enough insulin but the body fails to respond to it.'

'The only approach that really works in type 2 diabetes is drastically limiting caloric intake,' says Dr Ingrid de Visser-Kamerling, a Senior Clinical Scientist who studies incretins at CHDR. 'That's why bariatric surgery is the only treatment shown to be effective at improving all aspects of type 2 diabetes. Unfortunately, though, surgery is not a viable solution for most patients, and lifestyle-changing interventions are rarely effective when evaluated at the population level. The majority of currently available pharmacotherapies are designed simply to limit the damage that results from altered glucose metabolism. If we could develop a therapy that can increase the body's insulin response while reducing caloric intake, this would represent a major advance in the treatment of type 2 diabetes. We believe that incretins may provide these benefits.'

A blast from the past

More than a century ago scientists theorised that gut hormones might influence glucose metabolism. For example, Ernest Henry Bayliss and William Starling[1], and later Benjamin Moore and colleagues[2], estimated that these hormones are responsible for 50-70% of total insulin production following an oral dose of glucose. Decades later, these hormones – incretins – were chemically identified.

The next chapter in the story involved treating diabetes using these molecules, their analogues, and their modulators. Several compounds are currently available, including a subcutaneous preparation of glucagon-like peptide-1 (GLP-1) analogue and a new class of oral drugs that inhibit dipeptidyl peptidase-4 (DPP-4), an enzyme that rapidly inactivates incretins. Although these compounds reduce insulin resistance, they do not appear to affect patient mortality. Luckily, the story does not end here. A new group of incretins with an additional beneficial effect has been discovered; these incretins send a signal to the brain indicating satiety (i.e. that we have had enough to eat).

Satiety increases

In the past year, CHDR has tested several of these new compounds, focusing on their effects on caloric intake and insulin action. Specifically, researchers studied the subjects' subjective feeling of satiety and objective effects on satiety centres in the brain following a mixed meal challenge. 'We used resting-state functional magnetic resonance imaging (RS-fMRI), a technique originally developed at CHDR for CNS research,' says De Visser-Kamerling. 'This technique can be used to visualise changes in relevant networks within the brain. We investigated how the new compounds boost the fMRI signal in the brain areas associated with satiety. Subjectively, our subjects reported that they wanted to eat less. At higher dosages, the compound induced mild nausea, which is basically the same signal telling you that you've had enough to eat. So our results indicate that these new compounds can affect caloric intake, which is an important factor in controlling type 2 diabetes.'

Increasing insulin sensitivity

The studies also revealed that the new compounds affect insulin resistance. Burggraaf explains: 'We have years of experience studying compounds that work on glucose metabolism and other processes. This is difficult to study in healthy subjects because a healthy body maintains blood glucose levels and other values within a narrow range. When glucose levels go outside this range, homeostatic processes involving insulin and glucagon quickly return glucose level to normal. To test the compound's effect in a healthy subject, we use a clever trick known as a pharmacological challenge in which we intentionally disrupt glucose homeostasis, for example by continuously infusing glucose to maintain high blood glucose levels. This temporarily induces a physiological state similar to a patient with diabetes. In this context, we can then measure the compound's effects on glucose uptake, insulin, and glucagon levels in this healthy subject.'

Using a pharmacological challenge, De Visser-Kamerling and her colleagues demonstrated that the new compounds have a potent effect on insulin sensitivity. 'This is quite an exciting discovery. There's an urgent need for this type of treatment for patients with type 2 diabetes, and so far these compounds are highly promising. It's a privilege to be able to contribute to bringing us one step closer to developing an effective treatment for these patients.'

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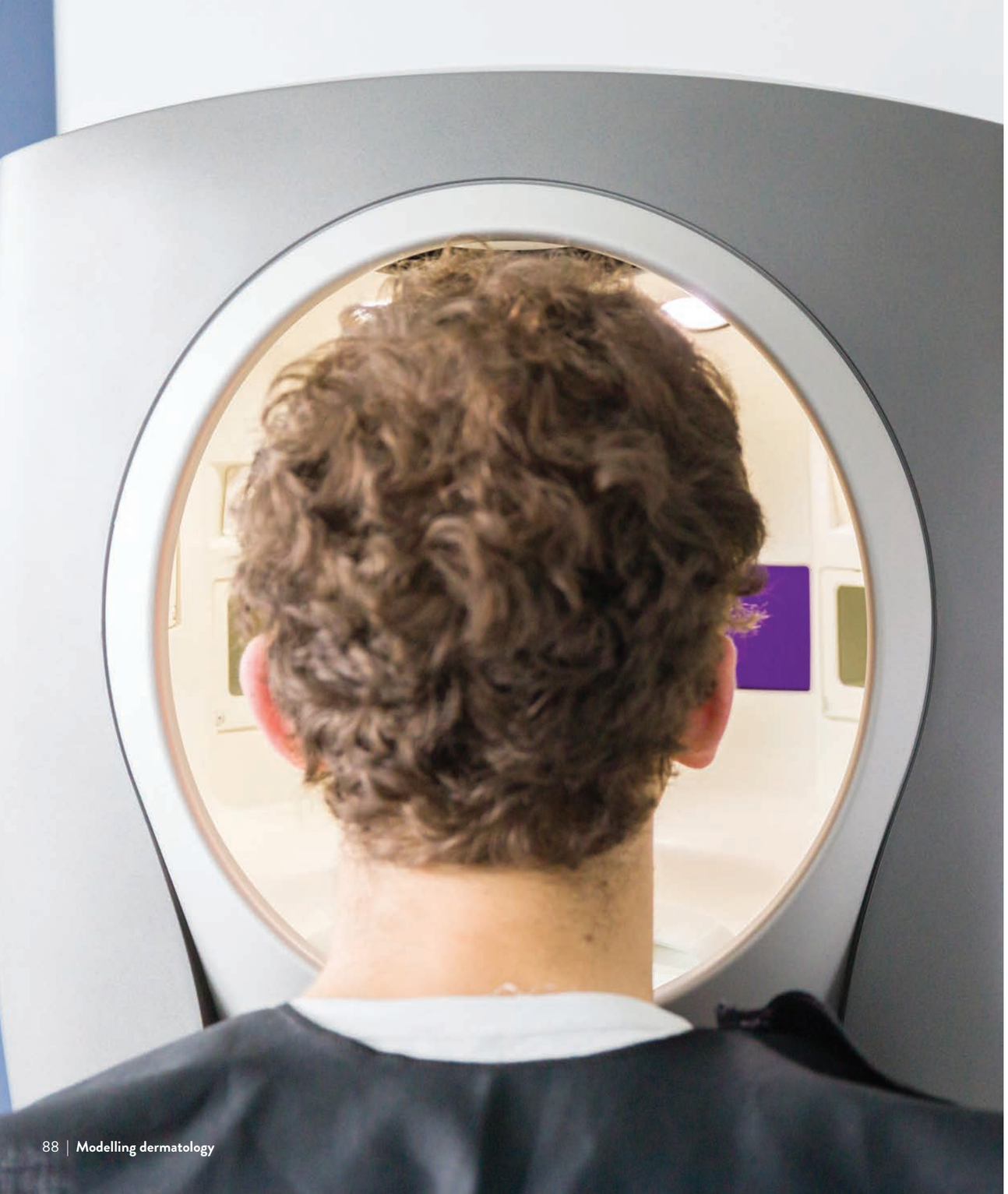
‘CHDR goes beyond other CROs’

‘CHDR is both a CRO and a research partner, since they provide a considerable amount of scientific input and have vast experience with Phase 1 studies. The close working relationship with CHDR is quite different than with other CROs, which simply provide a service, with little input. CHDR always adheres to the established timelines, and they’re both flexible and reasonable. In addition, despite the 9-hour time difference between the Netherlands and the west coast of America, communicating with CHDR is seldom an issue, and our working relationship has gone quite well.’

Medical Expert,
Biotech Company*

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



Modelling dermatology

Developing a dermatology model with psoriasis-like lesions

At CHDR, we can study the pharmacology of CNS drugs using functional test batteries such as NeuroCart, PainCart, and driving simulators, as well as imaging techniques such as resting-state fMRI and PET. Using these tools, CHDR researchers investigate how the target systems function both in healthy subjects and in patients.

At CHDR, researchers are performing increasing numbers of studies in the field of dermatology. To gain the most information from first-in-human trials using compounds for treating skin conditions, CHDR also developed and validated DermaToolbox, which offers researchers a wide array of tests. Dr Robert Rissmann, who coordinates the dermatology trials at CHDR, explains. 'DermaToolbox includes a variety of objective measurements, including clinical photography, multispectral imaging and 3D photography, colorimetry, laser Doppler imaging, transepidermal water loss measurements, Raman spectroscopy, and cutaneous microbiome measurements. In addition, subjective symptoms such as pain and itching can be systematically evaluated. To keep up with the times, we are always looking for new tools to add when the need arises.'

The challenge model

To obtain 'proof-of-pharmacology' for a candidate drug in healthy subjects, CHDR often uses our so-called 'challenge' model. Using a standardised intervention, the subject's physiology can be changed temporarily; in this context, the compound's ability to restore function and/or reduce symptoms is then tested. It is even possible to induce different levels of change on different areas of the skin. 'If these patches of skin do not influence each other,' says Rissmann, 'you eliminate the need for a control group. Each subject serves as his/her own control.'

Of course, before a challenge model can be used in a clinical trial, it must be optimised and thoroughly evaluated. The subject's safety and comfort must be monitored closely, and all objective methods used to measure changes must be validated.

Imiquimod-induced inflammation

The challenge model, which was developed by CHDR in collaboration with researchers at Erasmus Medical Centre in Rotterdam, is based on imiquimod's well-documented effect on the skin. Imiquimod activates the body's innate immune system via Toll-like receptor 7, a protein commonly involved in pathogen recognition. Sold under the brand name Aldara®, imiquimod is used for the topical treatment of genital warts, superficial basal cell carcinoma, and actinic keratosis.

Proof-of-concept

Rissmann describes how he and his colleagues in Rotterdam systematically examined the effects of applying increasing doses of imiquimod to the skin of healthy volunteers. Using several tests available in DermaToolbox, as well as small skin biopsies and blood samples, they studied the cytokine/chemokine cascades activated by imiquimod and the resulting histological changes. Importantly, they also found that topical imiquimod does not reach relevant systemic levels, even at the highest dose tested. These results provided proof-of-concept that the challenge model was safe, well tolerated, and fully reversible. Furthermore, the changes induced by imiquimod appeared to share several key biochemical characteristics with psoriasis. 'Of course,' says Rissmann, 'it's not exactly the same as psoriasis. But I feel confident that the model can be useful for obtaining clinically relevant information regarding candidate immunomodulatory drugs for treating many conditions, including psoriasis.'

Applying the model

In the development phase, subjects were asked to spend three days at the CHDR facility. This allowed researchers to continuously monitoring the subjects' comfort and safety and collect measurements at regular intervals. In the future, for example when the model is used to study new psoriasis treatments, subjects may be able to participate on an outpatient basis. Several concentrations of imiquimod and/or the investigational compound will be applied to the subject's skin. After four days, we will measure the compound's effects. Rissmann: 'Now that the challenge model has been developed and validated, we look forward to using it to investigate mechanisms of action and functional activity in a relatively simple, well-characterised context.'

Biomarkers

A closer look at drug targets

To support research using biomarkers, CHDR invested in a cell sorter and cytometry techniques, allowing us to study cellular drug targets in detail, particularly in immunology. These new techniques are used to measure direct drug-target interactions, thereby complementing indirect measurements such as cytokine production.

Basic research in immunology in recent decades has led to a large number of candidate drugs for use in a wide variety of indications. To learn as much as possible about these compounds in early clinical development, CHDR has designed and validated several tests and functional challenges. In many cases, it is now possible to learn more about the pharmacology of an immunologically active compound by studying its effects on white blood cells using an in vitro assay. Additional information can then be obtained by studying the *ex vivo* effects using white blood cells obtained from subjects who received the compound. Using this innovative approach, CHDR has contributed to the early clinical development of many drugs.

Research Director Dr Matthijs Moerland explains why an additional step is sometimes needed. 'In some cases,' says Moerland, 'the drug targets only a small subpopulation of leucocytes, for example specific T cell subsets. Because there are so few of these cells, it's nearly impossible to study the compound's activity in these cells in the context of the entire white blood cell pool. That's why we purchased a cell sorter, which enables us to enrich these subpopulations, providing a more direct measure of the compound's activity.'

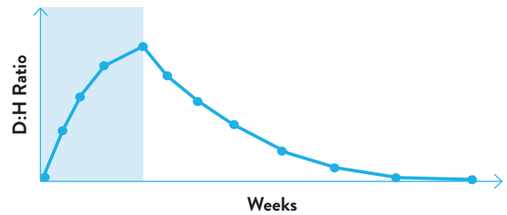
A cell sorter is considered standard equipment in most basic immunology research facilities, but not in most CROs. Moerland: 'Having immediate access to cell sorting and cytometry gives us a clear advantage. We're quite enthusiastic about the possibilities these techniques offer, and we've already begun to benefit from having them available.'

Drug-induced lymphopenia

Recently, Moerland and his colleagues used cell sorting and cytometry to solve a difficult clinical problem. A drug that is currently used to treat an autoimmune disease was found to cause a transient decrease in the number of lymphocytes (i.e. mild lymphopenia). However, a small percentage of patients develop severe lymphopenia; although this is reversible, these patients have a higher risk of infection, causing a fatal outcome in a few cases. Now that this rare complication has been identified, guidelines call for routine monitoring of patients on this drug. However, to identify the problem and determine how it might be prevented, the manufacturer turned to CHDR.

Two explanations

First, Moerland and his colleagues met with scientists from the pharmaceutical company to discuss possible causes of the lymphopenia. 'They really wanted to understand what was happening,' explains Moerland. 'For example, did the drug interfere with lymphocyte production in the bone marrow, or did it affect only circulating lymphocytes? We developed a method to investigate these possibilities in healthy volunteers. So in a way, we went back to the earliest stage of clinical drug development in order to answer a question that arose after the drug had already reached the market.'



Plot showing the increase in the deuterium:hydrogen ratio in the DNA of white blood cells while the subject drinks D_2O (indicated by the shaded blue area), followed by a decrease in the ratio.

Using 'heavy water' to label lymphocytes

Moerland's team developed a technique to determine the age of white blood cells by labelling all newly formed cells for a specific period of time. In the study, healthy subjects received 'heavy water', in which the hydrogen atoms are replaced with deuterium (^2H), a stable isotope of hydrogen, yielding D_2O. Because each deuterium atom contains both a proton and a neutron, it has twice the mass of a hydrogen atom. Both chemically and physiologically, deuterium is identical to hydrogen and is taken up by the tissues and incorporated into the subject's molecules. Using mass spectrometry, deuterium-enriched DNA can be separated from DNA that lacks deuterium. Moerland: 'We took blood samples from our subjects at regular intervals and used our cell sorter to isolate specific lymphocyte subsets, which were then characterised for cell surface markers and analysed at Utrecht University using mass spectrometry. Using this approach, we can identify the lymphocytes that formed after the subjects drank heavy water.'

Plotting the ratio of D_2O content to H_2O content in the DNA of white blood cells yields the graph shown above. Such a graph illustrates the dynamics of lymphocyte production (the rise in this ratio when the subject drinks D_2O), as well as the half-life of these cells (the decrease in ratio when D_2O is no longer given to the subject). Using this approach, CHDR researchers are hoping to gain novel insight into the mechanisms that underlie drug-induced lymphopenia.

Measuring cell stress as an additional tool

Suppose subjects taking the drug have decreased numbers of circulating lymphocytes, but a normal lymphocyte production rate. This may be due to accelerated cell death. Alternatively, the lymphocytes could simply be 'hiding' in the subject's tissues. To

Using antibodies against surface markers to differentiate among different cell types

CHDR recently purchased a magnetic-activated cell sorter (MACS), which uses antibodies labelled with magnetic nanoparticles to sort cells based on their surface proteins. Our new cytometry facility also uses antibodies to identify specific changes at the cell's surface.

Bringing preclinical research to CHDR

Historically, CHDR has always focused on the clinical phase of drug development. Now, with our new laboratory equipment and our growing expertise in biomarkers, we can offer preclinical research. 'Working with human subjects and human materials will always be our main focus,' says Moerland. 'Nevertheless, one of our long-standing mottos is also to use questions as a starting point, not to blindly follow an arbitrary series of phases. So we're now involved in 'preclinical' research projects designed to answer several mechanistic questions, particularly in the field of dermatology. In the future, we hope to perform even more research that lies at the boundary between preclinical and clinical drug development. Alternatively, if basic questions arise during the clinical phase, we can easily go back to the preclinical stage. In this respect, we view drug development as a continuum, and our mission is to facilitate a smooth transition from bench side to bedside.'

investigate these possibilities, CHDR researchers can measure cellular stress in leucocytes obtained from drug-treated volunteers. By measuring markers of apoptosis and mitochondrial membrane potential, researchers can look for a possible correlation between cell stress and lifespan.

Looking towards the future: using monocytes as a model for microglia

In the near future, CHDR will expand our toolbox of biomarkers using cytometry, cell sorting, and other technological approaches. To further exploit these available technologies and data, CHDR recently hired a researcher who specialises in bio-analytics. Moerland explains: 'The clinical development of drugs that affect the CNS has always been one of the major research lines at CHDR, and cell-based biomarkers have increasing importance in CNS research. A growing number of CNS drugs actually act on inflammatory processes within the brain. Specifically, these immunomodulatory CNS drugs target the microglia, rather than targeting the neurons and synapses that have been the main focus of classic drugs in neurology and psychiatry. Many of these immunomodulatory CNS drugs also have effects that can be measured outside of the CNS, and circulating monocytes express many receptors that are also expressed in microglia. To capitalise on these similarities, we're developing methods to measure the pharmacology of drugs that target the microglia by measuring the drug's effect on circulating monocytes. Of course, this approach goes beyond simply modelling the drug's intended effect; it's also interesting to study the peripheral effects of CNS drugs in order to identify any beneficial and/or adverse effects that can occur throughout the entire body. So some of what we'll do is actually exploratory in nature, reaching beyond the physiological pathways that have already been charted.'

Finding the most suitable target

Moerland cites another important reason to increase dialogue between preclinical researchers and clinical pharmacologists early in the drug-development process. 'Usually, a company chooses a clinical condition to target. And after that early step, everything becomes set in stone, and the company – and perhaps their investors – will cling to the idea that either the compound will treat that specific condition or it won't. I think that much can be gained by adopting a more open approach. The first step should be to investigate what the compound does in subjects. Then, using this knowledge regarding its pharmacological effects, you can choose a suitable condition to target. Using this approach, you'll have a much better match between the compound and the patients it may ultimately help.'

Education

Taking ‘blended learning’ to the next level

At CHDR, one of our key strategic goals is to provide innovative education to healthcare professionals. Together with our partners at Leiden University, Leiden University Medical Centre, and University of Applied Sciences Leiden, we are investing in the development of new teaching materials and teaching methods. The overall goal is to fundamentally improve the ways in which students gain the basic knowledge and skills required in clinical pharmacology.

CHDR teaches basic and clinical pharmacology to students at various levels, including medical students, students in biomedical and biopharmaceutical sciences, pharmacy students, and nurse practitioners-in-training. In addition to providing this essential basic education, CHDR is also involved in training other healthcare professionals; for example, we teach clinical pharmacology to medical residents, nurse practitioners, pharmacists-in-training, and clinical pharmacologists. Director of Education Dr Robert Rissmann explains: ‘Educating future healthcare professionals is a key part of our mission and is essential for promoting safe and effective pharmacotherapies. It is also an effective way of keeping in touch with the younger generation and identifying talented students, including students who may contribute to CHDR’s research later in their career.’

A novel integrative approach

‘Our plans for education are always ambitious. We feel the time has come to centralise and integrate all of our pharmacology education programmes. Such an integrated curriculum will combine all of our current blended learning tools, including video animations and online lectures,’ Rissmann says. ‘This will naturally require collaboration between CHDR and our partners.’ In addition to helping raise the necessary funds, such a collaborative approach is also essential for integrating pharmacology into the rest of the curriculum. Rissmann: ‘After all, both a pulmonologist lecturing on asthma and a psychiatrist teaching students how to treat patients with depression will discuss pharmacotherapeutics. If we can encourage these teachers and lecturers to use the same teaching resources that we use, pharmacology education will become more consistent and more recognisable across the board. For students, this makes it easier to learn basic clinical pharmacology skills.’

Making better use of face-to-face contact

In recent years, several universities have been experimenting with massive online open courses (also known as ‘MOOCs’) and other forms of e-based learning. CHDR is hoping to learn from these pioneers and to implement the strategies that have been successful, while avoiding known pitfalls. Rissmann: ‘We’ve noticed that e-learning alone doesn’t necessarily work well for most students, and the dropout rates for MOOCs are still quite high. Students need the element of personal interaction. But students shouldn’t need to attend a lecture just for the basic transfer of information. It’s far more efficient to watch a short video at home, where they can take the time to look up books and articles online, or watch animations of complicated processes such as drug-receptor interactions. Time in the classroom can then be used for reflection, discussing how to apply the knowledge learned in the video, and answering any questions the students might have.’

Inspiring people

Rissmann stresses that online educational resources will never fully replace traditional teaching methods. ‘That’s why we believe in a blended approach. Education isn’t just about facts; it’s also about context and learning how to apply what you’ve learned in a specific situation. Feedback is an essential component in all of this, and interactive teaching is still the most effective approach. And,’ Rissman adds, ‘let’s not forget the importance of teachers as a source of inspiration. Watching an online video is usually much less inspiring than forming a personal connection with the teacher. You can compare it with patient compliance; if you want patients to take their medicine, it’s better to establish a trusting relationship between doctor and patient, rather than simply handing out informational pamphlets.’

What to memorise versus what you can look up

Revising pharmacology education will take time. Given the vast amount of information provided to students during their education, experts in both pharmacology and didactic education will have to come up with a comprehensive plan of how to present it all. These experts will also need to distinguish between the elements that students should memorise versus elements that they can simply look up when needed. Rissmann explains: ‘Students need to have a basic frame of reference, a general approach to

pharmacology and pharmacotherapy. These days, there's no need for students to cram facts into their heads. Rather, students need to be taught how to use the resources available, such as our own Teaching Resource Centre (TRC) Pharmacology app. In fact, in some cases it's even better to look it up, as the information will likely be more up-to-date. Some facts learned in medical school will become outdated before the students graduate.'

'Time in the classroom can be used for reflection and interaction, not just for the basic transfer of information.'

Heading towards the future

CHDR has already established a basic framework for modernising pharmacology education. The next logical step is to build upon this foundation in collaboration with our partners. Rissmann: 'This client-centred approach is of course nothing new for CHDR, thanks to open contact with our sponsors, and we believe this is also the way to approach students. Although our partners may need some time to get used to the idea, we believe in our vision of education, and we'll continue to work towards achieving our goals. Because we all feel that it's important to invest in high-quality education, I'm confident that we will reach these goals.'

Scientific output

Bibliometric analysis

This year, CHDR commissioned the Centre of Science and Technology Studies in Leiden to perform a bibliometric analysis for 2016 and previous years. This analysis provides an objective evaluation of CHDR's publication rate and the scientific impact of our research. The table below summarises the indicators used to measure CHDR's research output over the past 15 years.

Publication output (P)

Although many activities can be quantified for a research institute, the simplest and most common measure of scientific output is the number of publications in peer-reviewed journals.

Ranking an institution based solely on the number of publications makes it possible to compare research output among institutions. However, the number of researchers at each institution can affect the number of publications. Therefore, measuring the average impact of the publications can provide a more appropriate measure of scientific impact.

Citation impact (MNCS)

Citations are provided in research articles to refer to previously published research. Tracking how frequently an institution's publications are cited – excluding self-citations – can provide a useful measure institution's scientific impact and their influence on future research. Mean Normalised Citation Score (MNCS) is commonly measured over a four-year window.

Table 1: Overview of publication indicators

Indicator	Dimension	Definition
P	Output	Total number of publications
MNCS	Impact	Average normalised number of citations per publication
PP (top 10%)	Impact	Proportion of papers that are in the top 10% of their respective field
MNJS	Journal impact	Average normalised citation score for the journals in which the papers were published

PP(top10%)

This score provides the measure of an oeuvre in the top 10% of the most frequently cited papers. A value of 10% or higher indicates a relatively high proportion of frequently cited papers. Importantly, unlike MNCS, PP(top10%) is less sensitive to outliers (i.e. papers cited an extremely high number of times).

Journal impact (MNJS)

The Mean Normalized Journal Score (MNJS) reflects the impact of the scientific journals in which the institution has published. Generally, MNJS is used as a measure of the relative importance of the journals within a field.

Summary

CHDR's bibliometric analysis reflects a steady increase over the past several years, stabilising at an average of 25 papers per year. This increase in the number of publications likely reflects CHDR's increase in the number of clinical studies conducted each year. With respect to the impact of CHDR's publications, the current publication impact score (MNCS) is 0.8, which is close to the world average (1.0); thus, CHDR – a full-service CRO – is competitive with research-driven institutes and academic departments. In addition, CHDR's publications are cited by research groups around the globe, and currently more than 10% of CHDR's publications are among the top 10% most-cited publications in their respective fields.

Figure 1: Number of publications from 2002 through 2016.

Figure 2: Citation impact (MNCS) for CHDR from 2001 through 2015.

Figure 3: PP(top10%) of high-impact papers for CHDR from 2001 through 2015.

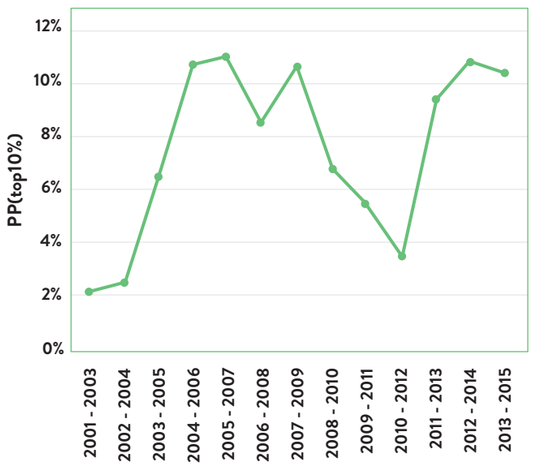
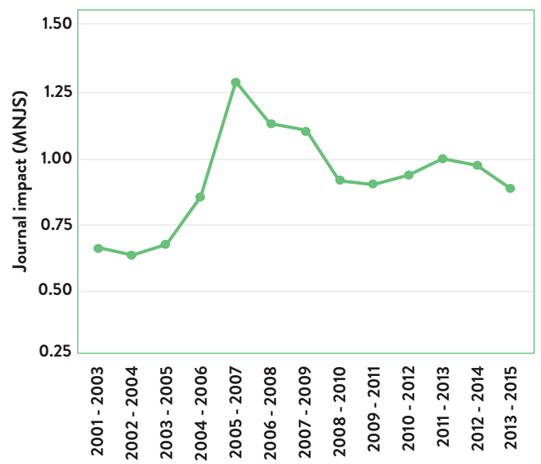


Figure 4: Journal impact (MNJS) for CHDR from 2001 through 2015.



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